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INTERCONTINENTAL PARIS LE GRAND HOTEL
For the historic 48th meeting of the Retina Society, we travel very appropriately to a city famed for its history, art, and style as well as for its many contributions to medicine! As with our meeting in Rome a few years ago, we have stretched our schedule to allow for free time to explore the City of Lights, and have expanded our social offerings with a special *soupçon français*! The program and evening events are sprinkled with a liberal selection of tastes and sounds and sights that we hope will send you home filled with scientific inspiration, and reflecting happily on the art of medicine and the medicinal power of art!

From our opening *soirée* on the canopied terrace overlooking the original courtyard, to our final banquet in the recently restored and opulent ballroom designed by Garnier, architect of the world famous Opéra, we will be based at the fabled InterContinental Paris Le Grand Hotel, scene of so many elegant evenings since the *dix-neuvième siècle*. The subtext of our meeting is the art and artists of Paris, and we will sample avidly from the painting, sculpture and architecture of this most beautiful and romantic of the world’s cities. Michael Marmor, colleague and author of *The Artist’s Eye*, will give a very special lecture Thursday after the scientific session closes entitled *Monet and the Orangerie: Art, Politics, Eye Disease and Color*, perfectly setting the stage for a not-to-be-missed evening which begins with cocktails and délices at the museum itself, exclusively our own for the night. Then we stroll across the Place de la Concorde to the Pavillon Gabriel for a memorable evening of dining and music — and the art of conversation! — on one of the most storied boulevards of the world, *l’Avenue des Champs Elysées*! Continuing our immersion, Friday afternoon, for those whose imagination has been fired by *Les Nymphéas* and the tale of Monet and his inspiration, we will tour his famous gardens and home at Giverny.

Champagne glasses lift this year to toast Dr. Gisèle Soubrane and Dr. Pat Wilkinson as our guests of honor, recognized for their remarkable careers in our field, full of signal contributions and leadership of special distinction. Drs. Evangelos Gragoudas and Thomas Gardner are our worthy distinguished award recipients and we look forward to their featured presentations, as well of those of our junior prize winners, Dr. Yoshihiro Yonekawa and Dr. Devron Ghandasra, who will give the Fellowship and Margherio Award talks. *Félicitations aux tous les honorés*!

Many thanks go to our wonderful Program Committee that this year includes Bernie Doft, Charlie Barr, Allen Ho, and myself, chaired by Mark Johnson. From fascinating cases to late-breaking showstopper presentations, the program is simply terrific. And of course to Judy Cerone Keenan go our very most heartfelt *merci* — what a loyal and gracious and able partner for our society!

*The Retina Society à Paris: vraiment un tour-de-force!* A very special treat for the mind and the senses — we hope you find all your faculties fully engaged. I look forward to savoring and relishing every aspect of our 48th annual meeting with you, *mes chers amis*!

Warmest regards,

Julia A. Haller, MD
President, The Retina Society
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LE JARDIN LUXEMBOURG
INTRODUCTION

This annual meeting is intended to increase the physician’s knowledge, skills and performance to provide services for patients. Topics for discussion will include but are not limited to age-related macular degeneration, diabetic retinopathy, imaging, inflammation, tumors, retinal vascular disease, macular disease, pediatrics and surgery. At the Interesting Retinal Cases Session and Video Conference, physicians will be able to participate in discussion and reach a conclusion on treatment of various vitreoretinal cases presented by participants. The attendee’s basic knowledge and treatment skills will be enhanced by the information presented and subsequent discussions.

OBJECTIVES

Upon completion of this conference, attendees should be able to achieve the following overall program objectives:

1) Utilize evidence based information to improve patient outcomes in retinal vascular disease (for example, diabetic retinopathy and retinal vein obstruction) and macular disease (for example, age-related macular degeneration and central serous retinopathy) and to help guide a clinician to best individualized therapy for a particular patient.

2) Apply data and information from new imaging technologies (for example, OCT-angiography, intraoperative and en face OCT, wide field angiography) to achieve an understanding of the pathogenesis and improved treatments for macular diseases.

3) Implement new surgical technology and consider the potential value of vitreoretinal surgical pharmacology (micro incision vitrectomy surgery, intraoperative endoscopy, chemotherapeutics for proliferative vitreoretinopathy, retinal patch, apoptotic inhibitors for retinal detachment) to improve surgical techniques and outcomes of vitreoretinal surgery.

CME ACCREDITATION AND CREDIT DESIGNATION*

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of William Beaumont Hospital and The Retina Society. William Beaumont Hospital is accredited by the ACCME to provide continuing medical education for physicians.

William Beaumont Hospital designates this live activity for a maximum of 21.75 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

*Number of credits subject to change; final credits will be determined based on the final agenda and will be listed on the final CME handout provided in advance of the seminar.

(CME Credit Breakdown: Wed 2.75, Thurs 6.25, Fri 4.0, Sat 4.25, Sun 4.5)

STAFF AND CONTENT VALIDATION REVIEWER DISCLOSURE

The CME Committee members and CME staff involved with this activity as content validation reviewers have reported no relevant financial relationships with commercial interests.

continued on next page
RESOLUTION OF CONFLICTS OF INTEREST

In accordance with the ACCME Standards for Commercial Support of CME, William Beaumont Hospital implemented mechanisms, prior to the planning and implementation of this CME activity, to identify and resolve conflicts of interest for all individuals in a position to control content of this CME activity.

HOW TO CLAIM CREDIT

Please see separate CME handout for instructions on how to claim CME credits and Conflicts of Interest information.
Wednesday, October 7

12:00 Noon Exhibit Set-up — Salon Berlioz
1:00 pm Speaker Ready Room Open — Saint Saens Room
12:00 - 3:00 pm The Retina Society Executive Committee Meeting — Debussy Room
3:00 - 7:00 pm Meeting Registration — Salon Opéra Lobby
4:00 - 6:35 pm Interesting Retinal Cases/Video Presentations — Opéra Ballroom
7:00 - 10:00 pm Welcoming Reception — Salon Ravel

Thursday, October 8

7:00 am Meeting Registration — Salon Opéra Lobby
Exhibits/Continental Breakfast — Salon Berlioz
7:30 - 10:00 am Spouses/Guests Hospitality and Breakfast — Salon Ravel
9:30 am - 3:30 pm Spouses Tours — Meet in Salon Ravel at 9:15 am for Buses
7:30 am - 12:30 pm Scientific Session — Opéra Ballroom
12:37 - 1:30 pm Scientific Session Meeting Attendees Lunch — Salon Ravel
1:30 - 2:30 pm Dessert and Poster Viewing — Salons Bizet-Gounod
2:30 - 5:00 pm Scientific Session — Opéra Ballroom
5:05 - 5:30 pm Special Lecture — family and friends invited — Opéra Ballroom
Michael Marmor — Monet and the Orangerie: Art, Politics, Eye Disease and Color
6:30 - 10:00 pm Reception/Dinner — Musee de L’Orangerie and Pavillon Gabriel
Meet at 6:00 pm in Lobby for Buses

Friday, October 9

7:00 am Meeting Registration — Salon Opéra Lobby
Continental Breakfast/Exhibits — Salon Berlioz
7:30 - 10:00 am Spouses/Guests Hospitality and Breakfast — Salon Ravel
7:30 am - 12:30 pm Scientific Session — Opéra Ballroom
1:00 - 6:00 pm Trip to Giverny with Boxed Lunch — Meet in Lobby at 12:45 pm for Buses

Evening FREE

Saturday, October 10

7:00 am Meeting Registration — Salon Opéra Lobby
Continental Breakfast/Exhibits — Salon Berlioz
7:30 - 10:00 am Spouses/Guests Hospitality and Breakfast — Salon Ravel
7:30 am - 12:00 Noon Scientific Session — Opéra Ballroom
12:15 - 1:00 pm Annual Business Meeting — Retina Society Members only — Opéra Ballroom
Afternoon FREE
7:00 - 11:00 pm Banquet and Dancing — Opéra Ballroom

Sunday, October 11

7:00 am Meeting Registration — Salon Opéra Lobby
Continental Breakfast/Exhibits (Spouses & Guests Welcome) — Salon Berlioz
7:30 am - 12:20 pm Scientific Session — Opéra Ballroom
Adjourn
WEDNESDAY, OCTOBER 7
7:00 – 10:00 PM
WELCOMING RECEPTION
InterContinental Paris Le Grand, Salon Ravel
Enjoy classic French cuisine and refreshments while greeting old friends and new. Join us in the Salon Ravel located on the Ground Floor of the InterContinental Paris Le Grand, a registered French historic landmark hotel.

THURSDAY, OCTOBER 8 TO SATURDAY, OCTOBER 10
7:30 – 10:00 AM
HOSPITALITY SUITE — Salon Ravel
Spouse and guest hospitality suite will be available for coffee, tea, and breakfast, as well as a place to meet friends. On Sunday, spouses and guests are welcome to continental breakfast in the Berlioz Room.

THURSDAY, OCTOBER 8 — SPOUSES & GUESTS
FULL DAY: 9:15 AM MEET IN LOBBY FOR BUSES — PLEASE HAVE TICKET
HISTORY & SOUL OF PARIS — Jacquemart-André Museum, Lunch and Passage Tour

Step into the Jacquemart-André Museum and at once you realize you are entering not only an art museum, but an opulent treasure of a private residence. Heir to a banking family, Edouard André spent his fortune acquiring works of art which he exhibited in his mansion, completed in 1875. In 1881, André married Nélie Jacquemart, a well-known artist. Together Edouard and Nélie travelled Europe, including the Middle East—Cairo, Luxor and Aswan—returning via Beirut, Constantinople and Athens.

Wherever they roamed, they visited auction rooms and antique dealers, and to accommodate their many acquisitions—panels, fireplaces, tapestries, frescos and ceiling paintings, in addition to paintings and sculpture—the couple continued to expand the mansion. Discover the grandeur of the state Apartments, informal Apartments, the Winter Garden, the Italian Museum and the intimate Private Apartments. Like the Frick in New York, and the Gardner in Boston, this museum and home transports the visitor into a special, private, elite world.
THURSDAY, OCTOBER 8, CONTINUED — SPOUSE & GUEST TOUR

12:15 PM — GATHER FOR LUNCH
BUSES WILL LEAVE MUSEUM AT 11:45 AM — IF LEAVING FROM HOTEL, PLEASE MEET IN THE LOBBY BY 12:30 PM FOR A SHORT WALK TO THE RESTAURANT

LE GRAND COLBERT
Just behind the Palais-Royal, we will gather at Le Grand Colbert, the renowned brasserie serving French dishes with original and exotic touches. Listed as an historic monument, the restaurant’s opulent atmosphere provides an old world touch with exquisite French service.

1:30 – 3:30 PM
PASSAGES TOUR: FROM THE PALAIS-ROYAL TO THE SOUL OF THE SECRET CITY
Walk in the footstep of Coco Chanel, The Sun King Louis XIV, and Marie-Antoinette, among others, that have passed through the prestigious Place Vendôme and the secret garden of the Palais-Royal. It is here that you will discover the soul of Paris. You will hear the legend of the Ritz, explore the hidden arcades, and uncover the best secrets of the Parisian chic. Our guide is a luminary in the field of art history, and one of the best known in Paris.
THURSDAY, OCTOBER 8

5:05 – 5:30 PM
SPECIAL LECTURE: MICHAEL MARMOR, MD — MONET AND THE ORANGERIE: ART, POLITICS, EYE DISEASE AND COLOR
Opéra Ballroom
The Retina Society’s distinguished expert and author of “The Artist’s Eyes” deftly sets the stage for our evening’s visit to the Musée de l’Orangerie and tomorrow’s journey to Giverny and Monet’s garden.

6:30 – 10:00 PM
MEET IN LOBBY AT 6:00 FOR BUSES MUST HAVE TICKET
RECEPTION/DINNER
Musée de l’Orangerie and Pavillon Gabriel
The Musée de l’Orangerie will be ours alone for a visit with Monet’s Nymphéas and other treasures in the collections, followed by a stroll to The Pavillon Gabriel for an extraordinary evening of fine dining and special entertainment as only Paris can provide.
Wear comfortable shoes for a magnificent walk through the world of Monet. Having settled in Giverny in 1883, Monet transformed an abandoned property into a floral masterpiece, strategically planting a palette of color that would be the inspiration for many of his greatest works of art. Monet’s passion for gardening combined with his pictorial knowledge yields a display of color and form that, thanks to the talent of current gardeners, is in full display today.

We will tour Monet’s pink stucco house, his studios, and collection of Japanese prints, then venture along the garden path lined with cypress and spruce, and colorful flowerbeds bordered by trimmed box trees.

The passion Monet felt for Japan led him to introduce, in an unexpected way, various Japanese touches into his completely original universe. Japanese art and gardens inspired the transformation of the spectacular “water garden” including his nymphaeas flowers. The footbridge spanning this vast stretch of flower-covered water is reminiscent of the bridges found in many of his Japanese prints. You are sure to come home inspired, informed, and invigorated by our October afternoon immersed in the imagination and life of one of the world’s most influential artists.

“I perhaps owe having become a painter to flowers.”

CLAUDE MONET
SATURDAY, OCTOBER 10
7:00 – 11:00 PM

BANQUET AND DANCING — BLACK TIE OPTIONAL

Opéra Ballroom

A hotel worthy of its name, the InterContinental Paris Le Grand, opened in 1862. It was regarded as one of the great hotels of France, and still represents the ultimate grandeur of 19th Century Paris. Join us for our traditional black-tie-optional Banquet in gilded splendour. The Opéra Ballroom, designed during the reign of Napoleon III, is an appropriately elegant setting for haute cuisine and an evening of celebratory music and dancing.
Gisèle Soubrane, respected and admired icon of international ophthalmology, is honored with gratitude by The Retina Society, at our 48th annual meeting in her home city of Paris.

Gisèle’s passion for medical retina, in particular for the study of age-related macular degeneration, drove her choices from very early in her illustrious career, a pioneering course especially for a woman in the rarified world of European academia. In addition to her medical degree, she took a PhD degree in Biology of Aging in the University Pierre et Marie Curie in Paris. Based throughout her medical career at the University of Paris East-Creteil, Dr. Soubrane’s leadership, scholarship, and clinical acumen propelled her through the professorial ranks to the chairmanship of the department of Ophthalmology, following her mentor Gabriel Coscas.

Dr. Soubrane’s scientific contributions are legion, particularly in clinical research where not only did she participate in all the voluminous publications of the Department of Ophthalmology of Créteil but also independently described Occult CNV (1987), Pseudo Reticular Drusen (1990) and the gene involvement in AMD (1998). Her research focuses on innovations in the diagnosis of retinal diseases, especially AMD, on physio pathogenesis and experimental models of AMD, and on new therapeutic approaches. Collaborating with basic and clinical scientists worldwide, she has been a signal contributor to our modern understanding and treatment of retinal disease. She has taught a generation of medical students, residents, and fellows with generosity and flair; her faithful and numerous mentees are spread all over the world.

Dr. Soubrane is a member of many key French, European and International associations, including the French Ophthalmology Society, where she served as General Secretary, the European Board of Ophthalmology, where she served as General Secretary and President, and the European societies for Vision and Eye Research for which she is past President and Honorary Member. She was elected member of the Academia Ophthalmologica Internationalis and of the Academia Europea Ophthalmologica, and has been a member of the executive committees of both The Macula Society and Club Jules Gonin. She holds advisory positions for several national and international ophthalmology journals.

Mme. le Professeur Gisèle has delivered a host of named lectures including the Bjerrum, the Belfast fellows lecture, the Maebashi, the AOI lecture, and the Kreissig, and has been awarded the Paul Chibret, Michaelson, Gass, and Coscas medals. Other awards include the Honor Award of the American Academy, the Herman Waker prize of the Gonin Club, the Junius Kuhnt prize, the Jules François medal from the from the International Council of Ophthalmology, and the European distinction for Excellence in Teaching from the EBO. Professor Soubrane has a Doctor Honoris Causa degree of the University of Ulm, is an Honorary member of the Finish Society of Ophthalmology and owns the ne plus ultra distinction of the “Légion d’Honneur” from the French State.

continued on next page
Dr. Soubrane’s newest challenge is the position of Professor Emeritus in the oldest department of Ophthalmology in Paris, the Hotel Dieu, University of Paris V, where she is appropriately enough, just adjacent to Notre Dame!

Renaissance woman of the world, Gisèle is a gourmet cook, has a magnificent garden, and is an avid traveller and explorer, ever knowledgeable about history and ever curious about new discoveries. She is a warm and energetic cheerleader for her two daughters (including an ophthalmologist), two sons and growing number of grandchildren who love spending time with their grande-mère, especially at her home on the Côte d’Azur!

The Retina Society salutes the inimitable Professor Gisèle Soubrane, clinician scientist, leader, mentor, and woman of many parts, whose style and substance have graced our specialty so notably over her storied and pioneering career.

— Julia Haller, MD
Dr. Charles Patton “Pat” Wilkinson, master surgeon, diplomat, scholar, author, and one of the key leaders of Ophthalmology in our time, is very gratefully honored by the Retina Society, an organization, like many, that he has served so ably in his illustrious career.

Pat grew up in Oklahoma where his father, the legendary football coach Bud Wilkinson, instilled in him the team leadership skills that have characterized him lifelong. Early surgery for collegiate injuries to knees and shoulders became football’s loss and medicine’s gain. Tackling academics at Stanford University, he was admitted to Johns Hopkins University’s School of Medicine, and was thereby set on a course that intersected many of the bright stars of his generation. After an internship and residency under Ed Maumenee’s tutelage with luminaries who became lifelong friends including Steve Ryan, Ron Smith, and Ron Michels, he went on to fellowship training at the Bascom Palmer Eye Institute, where the exciting world of vitreoretinal surgery was developing and close personal and professional friendships were nurtured. He then followed his Sooner roots back to join the faculty at the University of Oklahoma, where he held the rank of Professor of Ophthalmology for over 15 years prior to recruitment back to Baltimore. He has served as the Chairman of the Department of Ophthalmology, Greater Baltimore Medical Center, since 1992, as well as Professor, Department of Ophthalmology, at The Johns Hopkins University.

Dr. Wilkinson’s service to our specialty is simply staggering. He was President of the American Ophthalmological Society in 2010 and President of the American Academy of Ophthalmology (AAO) in 2007. He served as a Director of the American Board of Ophthalmology (ABO) from 1997 – 2004 and was Chairman of the organization during the last year. From 1998 through 2001 he was a member of the Board of Trustees of the AAO, a position he resumed from 2006 – 2008. He has served as a member and subsequent Chair of the FDA Ophthalmic Devices Panel. He was Chairman of the Preferred Practice Patterns Retina Panel of the AAO for 10 years and was Chairman of the Diabetes Section of the AAO’s Eye Care America project for a decade ending in 2010. He has been actively involved in several specialty and subspecialty societies, including serving as President of the Retina Society and a member of the Board of Trustees of the ASRS from 2002 – 2006.

He has received the American Academy’s Honor Award, Senior Honor Award and Life Honor Achievement Award, and in 2003 he received a Secretariat Award.

Dr. Wilkinson’s research interests include retinal detachment, diabetic retinopathy, and macular degeneration. He has published extensively on a variety of vitreoretinal topics, including very notably his authorship with Tom Rice of the magnum opus *Michels Retinal Detachment.*
Pat and his beautiful and formidable wife Alice are among the best-loved as well as the most respected and admired members of our retinal community. With professional obligations and their extended family now growing past three daughters and a son to include a raft of grandchildren, they have many demands on their time! It is a special honor to have them with us in Paris as we recognize C. Pat Wilkinson, MD for his extraordinary career of leadership in our field.

— Julia Haller, MD
The Retina Society Fellowship Research Award was established in 1996 to encourage academic pursuit in young vitreoretinal surgeons and to acquaint them with the scientific and social aspects of the Society. The applicant must be sponsored by an active member of The Retina Society. Each paper is judged on originality, quality of investigation methods, and merit of scientific contribution.

RECIPIENT OF THE 19TH FELLOWSHIP RESEARCH AWARD

YOSHIHIRO YONEKAWA, MD
Birmingham, MI
Sponsor: Antonio Capone Jr, MD

CONGRATULATIONS!

PRIOR RECIPIENTS OF THE AWARD

2014  Francisco Folgar, MD, sponsored by Emily Chew
2013  Glenn Yiu, MD, PhD, sponsored by Glenn Jaffe
2012  Lejia Vajzovic, MD, sponsored by David Abramson
2011  Cagri Besirli, MD, sponsored by David Zacks
2010  Brian L. VanderBeek, MD, PhD, sponsored by David Zacks
2009  Sandra Rocio Montezuma, MD, sponsored by Joan Miller
2008  Mehran Taban, MD, sponsored by Peter Kaiser
2007  Sai Chavala, MD, sponsored by Thomas Lee
2006  Polly A. Quiram, MD, sponsored by George Williams
2005  Francisco Max Damico, MD, sponsored by Lucy Young
2004  Sean S. Ko, MD, sponsored by Shizuo Mukai
2003  Seenu M. Hariprasad, MD, sponsored by William Mieler
2002  Franco M. Recchia, MD, sponsored by Allen C. Ho
2001  David N. Zacks, MD, sponsored by Joan Miller
2000  Magdalena Krzystolik, MD, sponsored by Evangelos Gragoudas, and Enrique Garcia-Valenzuela, MD, PhD, sponsored by James Puklin
1999  Thomas C. Lee, MD, sponsored by Shizuo Mukai
1998  Ingrid U. Scott, MD, sponsored by Timothy Murray
1997  Andrew Chang, MD, sponsored by Lawrence Morse

AWARD SELECTION COMMITTEE
David Zacks, MD, Chair; Emily Chew, MD, Timothy Murray, MD, Lucy Young, MD

WE WOULD LIKE TO THANK ALL MEMBERS WHO HAVE SPONSORED APPLICANTS AND ASK THAT ALL MEMBERS CONTINUE TO SUPPORT THIS AWARD.
In 2006, The Retina Society inaugurated the J. Donald M. Gass lectureship. Dr. Gass was a peerless observer of the fundus. His unique and repeated ability to identify fundamental patterns of disease from the mass of seemingly chaotic details invites sincere comparison to Michelangelo working in marble. With this lectureship, we honor his memory as a warm and cherished member and friend as well as his inestimable importance to our patients and our field.

**PRIOR RECIPIENTS OF THE AWARD**

- 2014 **Alexander J. Brucker, MD**, Philadelphia, PA
- 2013 **Michael T. Trese, MD**, Royal Oak, MI
- 2012 **Harry W. Flynn Jr., MD**, Miami, FL
- 2011 **Mario Stirpe, MD**, Rome, Italy
- 2010 **Ursula Schmidt-Erfurth, Prof Dr**, Vienna, Austria
- 2009 **Philip J. Rosenfeld, MD**, Miami, FL
- 2008 **Lawrence A. Yannuzzi, MD**, New York, NY
- 2007 **Lee M. Jampol, MD**, Chicago, IL
- 2006 **Carmen A. Puliafito, MD**, Los Angeles, CA

**AWARD SELECTION COMMITTEE**

Charles Barr, MD, Chair
Bailey Freund, MD
Joan Miller, MD
SriniVas Sadda, MD
Marco Zarbin, MD
Dr. Evangelos Gragoudas is, most deservedly, internationally famous in every aspect of the tripartite academic mission. His remarkable clinical practice in retinal diseases and intraocular melanoma provides definitive treatment and comfort for patients around the world, his innovative translational research has brought several important new therapies into our field, and his generous teaching and insightful mentorship have nurtured hundreds of physicians-in-training including many who have become highly accomplished and famous. Visibly Greek (and, as some fondly tease him, audibly so, despite living for decades in the U.S.), he is extremely proud of his classical roots and traditions. His extraordinary but initially terrifying for the uninitiated fluorescein conferences are legendary for his use of the Socratic teaching method. In particular, he delights when the clinical discussion can be turned toward larger questions regarding life, truth, and other fundamental issues. At this point he becomes most probing and engaging, helping his students to see the parallels to the clinical situation at hand and to understand that all truly important questions have already been explored and settled by the ancient Greek philosophers: (“You need to read more!”) His iconic life journey from a childhood in the countryside of Lesbos, with its beautiful olive groves and stubborn mules, to a noted professorship at Harvard has endowed him with unmatched cultural sensitivity and no doubt inspired him to develop one of the earliest international research fellow programs, providing a much-needed pathway for state-of-the-art training for scores of fellows from every continent. Indeed, the Retina Society wishes to recognize, with the J. Donald M. Gass Award, not only the profound depth but also the remarkable reach of the diverse academic contributions of Dr. Gragoudas, a widely beloved mentor and truly cosmopolitan expert in our field.

He completed his medical training in Athens, Greece and his ophthalmology Residency at Boston University School of Medicine. He was a Clinical Fellow in Diabetic Retinopathy at the Elliot P. Joslin Research Laboratory at Harvard Medical School (HMS) and subsequently a Retinal Fellow under Dr. Charles Schepens at the Massachusetts Eye and Ear Infirmary. In 1975, Dr. Gragoudas joined the full-time faculty at the Massachusetts Eye and Ear/Harvard Medical School, and was promoted to Professor of Ophthalmology in 1994. He has been Director of the Retina Service at Massachusetts Eye and Ear since 1985. A prolific clinician-scientist, Dr. Gragoudas has published more than 250 articles in peer-reviewed journals and written or authored more than 100 chapters, reviews, and books.

Dr. Gragoudas is considered a pinnacle authority on the diagnosis and management of intraocular tumors, and his expertise has made the MEEI Retina Service a major center for all aspects of ocular oncology. He pioneered the use of proton beam therapy in eye tumors, and early on he generously assisted in the development of other charged particle centers with many collaborators, most notably with his colleague and dear friend Dr. Leonidas Zografos of Lausanne. Presently, with more than 30 years of follow-up, proton beam therapy has proven to be extremely successful. In a single morning, continued on next page
Dr. Gragoudas sees more patients with ocular melanoma than most retina specialists will see in a lifetime.

Dr. Gragoudas’ second major contribution to ophthalmology stems from his long-standing interest in photodynamic therapy (PDT) for the treatment of ocular tumors and ocular neovascularization. He collaborated with Dr. Joan Miller on preclinical studies of PDT using the light-sensitive dye, Verteporfin, for the treatment of choroidal neovascularization. Dr. Gragoudas was instrumental in designing and executing the early clinical studies and was an integral member of the study group and writing group for the large clinical trials. Based on these large clinical trials, photodynamic therapy using Verteporfin was approved by the health authorities throughout the world and became the first widely used treatment for neovascular retinal disease that effectively slowed disease progression.

Dr. Gragoudas’ third major contribution has been his work on ocular angiogenesis and anti-angiogenesis therapy. He worked with a group of ophthalmologists, including Drs. Joan Miller, Tony Adamis, Pat D’Amore and others in collaboration with the laboratory of noted angiogenesis discoverer, Dr. Judah Folkman. This team first demonstrated the critical role of vascular endothelial growth factor (VEGF) in ocular neovascularization and went on to develop therapies targeting VEGF. Pegaptanib, the first compound based on this approach effectively slowed the progression of age-related macular degeneration (AMD), the most frequent cause of blindness in patients over age 60. A second-generation pharmaceutical, ranibizumab, was found to result in vision improvement for the first time in approximately one-third of patients with neovascular AMD who underwent treatment.

He has received numerous honors and awards including: Academy Honor Award of American Academy of Ophthalmology; Retina Research Foundation prize of the Jules Gonin Lectureship; Research to Prevent Blindness Senior Scientific Investigators Award; Senior Achievement Award of American Academy of Ophthalmology; J. Donald M.Gass Medal of the Macula Society; HMS Distinguished Alumni Award; the Arnall Patz Medal of the Macula Society; Mildred Weisenfeld Award for Excellence in Ophthalmology from ARVO; and the Charles Edward Whidden Professorship in Ophthalmology at Harvard Medical School. In 2014 Harvard Medical School established the Gragoudas Professorship in Ophthalmology. In 2014 Dr. Gragoudas and his colleagues received the Champalimaud Vision Award for their work on using anti-angiogenesis drug therapy for the treatment of age-related macular degeneration. This award is considered the “Nobel Prize” in Vision Research.

Through our society meetings and many social gatherings (N.B. the social program of his Aegean Retina meeting has no equal) we have come to know his secret for continued happiness and success—his wonderful wife Lea and their two sons Stelios and Nicholas. We also thank them most sincerely for sharing Evan so generously with all of us as the Retina Society bestows the J. Donald M. Gass Award.

— Donald D’Amico, MD
The Raymond R. Margherio Endowed Memorial Fund was established to support research into macular disease and development of new techniques of macular surgery. The Fund supports an award presented annually to a vitreoretinal fellow of an Active Member of The Retina Society. The fellow will present his work at the Annual Meeting of The Retina Society. The winner is selected by the Research Award Committee.

RECIPIENT OF THE 14TH MARGHERIO AWARD

DEVON GHODASRA, MD
Ann Arbor, MI
Sponsor: Thomas Gardner, MD

CONGRATULATIONS!

PRIOR RECIPIENTS OF THE AWARD

2014  John B. Miller, MD, sponsored by Evangelos S. Gragoudas, MD
2013  Dimitra Skondra, MD, sponsored by Joan Miller
2012  Anthony B. Daniels, MD, sponsored by Ivana Kim
2011  Marc-Andre Rheaume, MD, sponsored by Shizuo Mukai
2010  Daniel F. Kiernan, MD, sponsored by William Mieler
2009  Catherine Cukras, MD, PhD, sponsored by Frederick Ferris
2008  Edward F. Hall, MD, sponsored by David Zacks
2007  Stephen J. Kim, MD, sponsored by Baker Hubbard
2006  Jasmine R. Elison, MD, sponsored by D. Jackson Coleman
2005  Michael D. Ober, MD, sponsored by Lawrence Yannuzzi
2004  Howard S. Ying, MD, sponsored by Morton Goldberg
2003  Antonio P. Ciardella, MD, sponsored by Stanley Chang
2002  Eugene S. Lit, MD, sponsored by Donald J. D’Amico

Raymond R. Margherio, MD
1939 – 2000
President,
The Retina Society
1996 – 1997
THE AWARD OF MERIT IN RETINA RESEARCH

Presented in conjunction with the Charles L. Schepens Lecture

The Award of Merit in Retina Research

was created in 1978 by Retina Research Foundation, Houston, Texas, to recognize outstanding vision scientists whose work contributes to knowledge about the retina and retinal diseases. Each year, the Awardee is invited to give the Charles L. Schepens Lecture, a highlight of The Retina Society annual meeting that was established in honor of the founder of the Society.

The award offers a $50,000 cash prize that includes a $5,000 honorarium and a $45,000 research grant. The recipient is chosen by the Awards Committee of The Retina Society.

Funding for the Award of Merit is provided by the Retina Research Foundation through a series of endowed gifts that are dedicated to the Award. The Retina Research Foundation of Houston, Texas presents the Award of Merit in Retina Research to a vision scientist whose work represents: 1. A single outstanding achievement in retina research, or; 2. A potentially significant contribution to new knowledge about the retina, its role in the visual process and/or vitreoretinal diseases or disorders.

Prior Recipients of the Award

<table>
<thead>
<tr>
<th>Year</th>
<th>Recipient</th>
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<tbody>
<tr>
<td>1978</td>
<td>Charles L. Schepens, MD, Boston, MA</td>
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<td>1979</td>
<td>Richard W. Young, PhD, Los Angeles, CA</td>
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<td>1980</td>
<td>Robert Machemer, MD, Durham, NC</td>
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<td>1981</td>
<td>John E. Dowling, PhD, Boston, MA</td>
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<td>1982</td>
<td>Harry G. Sperling, PhD, Houston, TX</td>
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<td>1983</td>
<td>Arnall Patz, MD, Baltimore, MD</td>
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<td>1984</td>
<td>Werner K. Noell, MD, Kansas City, MO</td>
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<td>1985</td>
<td>Oleg Pomerantzef, Dipl. Eng., Boston, MA</td>
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<td>1986</td>
<td>J. Donald M. Gass, MD, Miami, FL</td>
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<td>1987</td>
<td>Harris Ripps, PhD, Chicago, IL</td>
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<td>1988</td>
<td>Harvey A. Lincoff, MD, New York, NY</td>
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<td>1989</td>
<td>Matthew D. Davis, MD, Madison WI</td>
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<td>1990</td>
<td>Matthew M. LaVail, PhD, San Francisco, CA</td>
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<td>1991</td>
<td>Ronald Michels, MD and Bert Glaser, MD, Baltimore, MD</td>
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<td>1992</td>
<td>Ingrid Kreissig, MD, Tubingen, Germany</td>
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<td>1993</td>
<td>W. Richard Green, MD, Baltimore, MD</td>
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<td>1994</td>
<td>Dr. Kathleen Dorey and Dr. Francois Delori, Boston, MA</td>
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<td>1995</td>
<td>D. Jackson Coleman, MD, New York, NY</td>
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<td>1996</td>
<td>Gabriel Coscas, MD, Paris, France</td>
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<td>1997</td>
<td>Stuart L. Fine, MD, Philadelphia, PA</td>
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<td>1998</td>
<td>Joe G. Hollyfield, PhD, Cleveland, OH</td>
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<td>1999</td>
<td>Lawrence A. Yannuzzi, MD, New York, NY</td>
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<td>2000</td>
<td>Barbara E. K. Klein, MD, MPH, and Robert Klein, MD, MPH, Madison, WI</td>
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<td>2002</td>
<td>Bradley R. Straatsma, MD, Los Angeles, CA</td>
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<td>2003</td>
<td>Stephen J. Ryan, MD, Los Angeles, CA</td>
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<td>2004</td>
<td>Emily Y. Chew, MD, Bethesda, MD and Frederick L. Ferris III, MD, Bethesda, MD</td>
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<td>2005</td>
<td>Anthony P. Adamis, MD, Boston, MA</td>
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<td>2006</td>
<td>Carol Shields, MD, Philadelphia, PA</td>
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<td>2007</td>
<td>Lloyd Paul Aiello, MD, Boston, MA</td>
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<td>2008</td>
<td>William S. Tasman, MD, Philadelphia, PA</td>
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<td>2009</td>
<td>Mark S. Humayun, MD, PhD, Los Angeles, CA</td>
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<td>2010</td>
<td>Eliot L. Berson, MD, Boston, MA</td>
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<td>2011</td>
<td>Michael F. Marmor, MD, Stanford, CA</td>
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<td>2012</td>
<td>Richard F. Spaide, MD, New York, NY</td>
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<td>2013</td>
<td>Cynthia A. Toth, MD, Durham, NC</td>
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<td>2014</td>
<td>Peter Campochiaro, MD, Baltimore, MD</td>
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Award Selection Committee

Charles Barr, MD, Chair
Bailey Freund, MD
Joan Miller, MD
SriNivas Sadda, MD
Marco Zarbin, MD
Thomas W. Gardner, MD, MS, is Professor of Ophthalmology and Visual Sciences, Molecular and Integrative Physiology, and Internal Medicine, at the University of Michigan Medical School. He graduated from Penn State University and Jefferson Medical College in Philadelphia. He completed his ophthalmology residency at Northwestern University Medical Center and his vitreoretinal fellowship at the Bascom Palmer Eye Institute in Miami. Following his fellowship, he returned to his home town of Franklin, Pennsylvania (population 8000), where he practiced comprehensive ophthalmology while obtaining an MS degree in Physiology at Penn State College of Medicine.

In 1991, Dr. Gardner joined the faculty at Penn State, where he established the Penn State Retina Research Group, was awarded the Jack and Nancy Turner Professorship of Ophthalmology, and served as Vice-Chair for Research in the Department of Ophthalmology. In 2010, Dr. Gardner and his research team were recruited to the University of Michigan, where he currently serves as Associate Chair for Research in the Department of Ophthalmology and Visual Sciences.

Tom grew up with two younger brothers who have type 1 diabetes mellitus, a fact that likely ignited his passionate and lifelong interest in clinical and experimental diabetic retinopathy. He and his research group have been responsible for numerous seminal contributions to our understanding of clinical and experimental diabetic retinopathy. Their integrative research program encompasses the full spectrum of diabetic retinopathy pathogenesis and treatment, with particular emphasis on the pathophysiology and pharmacologic modulation of diabetic macular edema, molecular mechanisms of vascular permeability, mechanisms of diabetic retinal neurodegeneration, structure/function relationships in the diabetic retina, angiogenesis, and identification of potential cell-specific targets for new therapeutic agents. Dr. Gardner has published over 160 peer-reviewed papers and book chapters, delivered over 200 presentations nationally and internationally, secured four patents, and received numerous research and teaching awards.

Dr. Gardner has reviewed grants and served on study sections and scientific advisory committees for a wide variety of organizations, including the National Institutes of Health, National Society to Prevent Blindness, U.S. Food and Drug Administration, American Diabetes Association, JDRF, Diabetic Retinopathy Clinical Research Network, and Diabetes UK, to name just a few. He has organized and chaired numerous symposia and workshops on diabetic retinopathy around the world. He serves on the editorial board of five scientific journals and performs manuscript reviews for nearly 50 journals. A beloved and nurturing teacher, he has served as research or clinical mentor to over 50 medical students, graduate students, postdoctoral fellows, faculty members, and vitreoretinal fellows, and currently directs the Michigan Vision Clinician Scientist Development (K12) Program.
Tom and his wife Maureen have raised a wonderful family of three children, Aisling, Colin, and Corinne. Aside from work he enjoys family time, tennis, running, and friends. He grew up in the woods of Pennsylvania and has enjoyed hunting deer and turkeys for many years, although he says that “they’re pretty safe when I’m around”.

— Mark Johnson, MD
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INTERESTING RETINAL CASES/VIDEO CONFERENCE

WEDNESDAY, OCTOBER 7

opiéra ballroom

Moderators: Anita Agarwal, MD | Carl Regillo, MD

4:00 pm Multifocal Vitelliform Lesions
Anita Agarwal, MD

4:05 pm Adaptive Optics Imaging in Cancer Associated Retinopathy
Khushboo Agrawal, MD; presented by Richard Rosen, MD

4:10 pm One in a Million
Audina Berrocal, MD

4:15 pm Severe Visual Loss in Two Cases of Flammer Syndrome
Claude Boscher, MD

4:20 pm Mystery Case
Marcelo Casella, MD, PhD

4:25 pm A New Old Dilemma
Itay Chowers, MD

4:30 pm Young Woman with Mysterious Vision Loss
Antonio Ciardella, MD

4:35 pm Mystery Maculopathy
Mark Johnson, MD

4:40 pm 75-year-old Gentleman with Waldenström’s Macroglobulinemia
Presents with Choroiditis
Rahul Khurana, MD

4:45 pm Exudation and Calcification
Ajay Kuriyan, MD, MS

4:50 pm Atypical Ischemic Vasculopathy
Luiz Lima, MD

4:55 pm When Tests Don’t Jibe: Discordance Between Optical Coherence
Tomography, Electroretinogram and Visual Function
Michael Marmor, MD

5:00 pm Detection of Choroidal Neovascularization with Optical Coherence
Tomography Angiography in a Case of Ampiginous Chorioretinitis
Scott McClintic, MD

5:05 pm Not in a 46 Year Old
Carlos Medina, MD

5:10 pm Acute Monocular Visual Loss in a Healthy 55-year-old Female
William Mieler, MD

5:15 pm Concurrent Anterior Segment Ischemia and Endophthalmitis
After Strabismus Surgery
Jeffrey Olson, MD

5:20 pm Optical Coherence Tomography of Two Unusual Retinal Lesions
Stephen Schwartz, MD, MBA
5:25 pm  The Case of the Intermittent, Painful White Spot  
Michael Stewart, MD

5:30  Metastatic Carcinoma to the Retina and Vitreous  
Tamara Vrabec, MD

5:35  Unilateral Posterior Retinoschisis  
John Wells III, MD

5:40  Progressive Bilateral Visual Loss Following Blunt Trauma to the Head  
Lihteh Wu, MD

5:45  Macular Drusen?  
Lucy Young, MD, PhD

5:50  Drusen in a Young Woman... But are they Really Drusen?  
David Zacks, MD, PhD

5:55  Post Operative Cystoid Macular Edema  
Michael Ober, MD, FACS

VIDEOS

MODERATORS: William Mieler, MD | Shlomit Schaal, MD, PhD

6:00  Active Closure of Macular Hole Using a Specially Designed Needle  
Florian Balta, MD

6:05  Removal of Silicone Oil Droplets Adherent to Silicone Intraocular Lens Implants  
Raymond Iezzi, MD, MS

6:10  Single-layered Inverted Internal Limiting Membrane Flap Technique for Macular Hole in Highly Myopic Eyes  
Ji Eun Lee, MD, PhD

6:15  Intraoperative Volcano Eruption  
Tamer Mahmoud, MD, PhD

6:20  Novel Intraocular Macular Lenses to Restore Reading Vision in Age-related Macular Degeneration Patients with Poor Vision  
Carsten Meyer III, MD, FEBO

6:25  Surgical Management of Dislocated Intraocular Lens in a Chronic Uveitis Patient  
Shlomit Schaal, MD, PhD

6:30  Pars Plana Lensectomy in the Era of Small Incision  
Demetrios Vavvas, MD, PhD

6:35  Endoscopic Exploration and Treatment in a Patient with Recurrent Vitreous Hemorrhage Subsequent to Scleral-sutured Intraocular Lens  
Christina Weng, MD, MBA

6:40  ADJOURN
**THURSDAY, OCTOBER 8**

7:00 am  **REGISTRATION — SALON OPÉRA LOBBY**
CONTINENTAL BREAKFAST/EXHIBITS — SALON BERLIOZ

7:25  **WELCOME**
Julia Haller, MD

**DIABETIC RETINOPATHY**
PRESIDING OFFICER: Julia Haller, MD
MODERATOR: Craig Greven, MD

7:30  The Impact of Written Physician Communication on Diabetic Eye Examination Adherence: Results from a Retrospective Cohort Analysis
Philip Storey, MD

7:35  Novel Quantitative Biomarkers for Early Detection of Diabetic Retinopathy
Jennifer Kang-Mieler, PhD

7:40  Aflibercept for Diabetic Macular Edema in Eyes Previously Treated with Ranibizumab and/or Bevacizumab may Improve Visual Acuity and Macular Thickness
Chirag Shah, MD

7:45  Contralateral Eye-to-Eye Comparison of Intravitreal Injection of Ranibizumab and a Dexamethasone Implant in Chronic Diabetic Macular Edema
Tarek Hassan, MD

7:50  Intravitreal Aflibercept Injection (IAI) for Diabetic Macular Edema (DME): 148-week Results from VISTA and VIVID
David Brown, MD

7:55  Intravitreal Aflibercept Injection (IAI) in Patients with Prior Therapy for Diabetic Macular Edema (DME): 148-week Outcomes from VISTA
Peter Kaiser, MD

8:01  Discussion

8:04  Outcomes from Diabetic Macular Edema Eyes with a Limited Initial Anatomic Response to Intravitreal Aflibercept Injection (IAI) in VISTA/ VIVID Studies
David Boyer, MD

8:10  Discussion

8:13  Diabetic Retinopathy Improvements with Ranibizumab: The Fate of Patients with Moderately Severe or Severe Non-proliferative Diabetic Retinopathy (NPDR)
Charles Wykoff, MD

8:19  Discussion

8:22  Neuroretinal Loss Precedes Microvascular Damage from Diabetes Mellitus
Elliott Sohn, MD

8:28  Discussion
8:31 am  Diabetic Macular Edema and Müller Cell Biomarkers: An In Vivo Study  
Edoardo Midena, MD

8:37  Discussion

8:40  MicroRNAs in the Retina and Vitreous: New Targets for Diabetic Retinopathy  
Donald D’Amico, MD

8:46  Discussion

8:49  Utilization of Anti-Vascular Endothelial Growth Factors (VEGFs) for Diabetic Macular Edema in U.S. Clinical Practice Using the Vestrum Health™ Database  
Nancy Holekamp, MD

8:55  Discussion

8:58  Lack of Longitudinal Association between Thiazolidinedione Use and Incidence of Diabetic Macular Edema: The ACCORD EYE Study Four-year Results  
Craig Greven, MD

9:04  Discussion

9:07  Comparative Effectiveness of Intravitreous Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema in a Randomized Trial: One-year Treatment and Safety Outcomes  
Robert Hampton, MD

9:13  Discussion

9:16  DRCR.net Comparative Effectiveness Randomized Clinical Trial of Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema (One-year Results)  
John Wells III, MD

9:22  Discussion

9:25  Diabetic Macular Edema Outcomes with Anti-VEGF Treatments: Comparison of Randomized Controlled Clinical Studies  
Marco Zarbin, MD

9:31  Discussion

9:34  Randomized Trial of Prompt Panretinal Photocoagulation vs. Ranibizumab and Deferred Panretinal Photocoagulation for Proliferative Diabetic Retinopathy  
Scott Friedman, MD

9:40  Discussion

9:43  Panretinal Photocoagulation for Diabetic Retinopathy: One and Done?  
Victor Gonzalez, MD

9:49  Discussion

9:52  REFRESHMENT BREAK/EXHIBITS — Salon Berlioz
PUBLIC SESSION 1 – CLINICAL \& TECHNICAL ASPECTS OF IMAGING

THURSDAY, OCTOBER 8, 2015

10:22 am
Assessment of Macular Circulation with Retinal Vasculitis Using Optical Coherence Tomography Angiography
Phoebe Lin, MD

10:28
Discussion

10:31
Ultra-high Speed Swept Source Optical Coherence Tomography Angiography Compared with Fluorescein Angiography in Diabetic Retinopathy
Nadia Waheed, MD

10:37
Discussion

10:40
Quantitative Retinal Vascular Perfusion Density Mapping of Diabetic and Normal Subjects Utilizing Optical Coherence Tomography Angiography
Richard Rosen, MD

10:46
Discussion

10:49
En-face Adaptive Optics Optical Coherence Tomography
Ursula Schmidt-Erfurth, Prof Dr

10:55
Discussion

10:58
Outer Retinal Analysis with Automated Ellipsoid Zone Mapping and Layer-based Volumetric Assessment
Justis Ehlers, MD

11:04
Discussion

11:07
Posterior Chamber Imaging via Real Time, High Resolution Ultrasound for the Vitreoretinal Clinician
Yale Fisher, MD

11:13
Discussion

11:16
Ultra-Wide Field Spectral Domain Optical Coherence Tomography of the Retinal Periphery
Netan Choudhry, MD

11:22
Discussion

11:25
Non-diabetic Ocular Abnormalities Detected by Telemedicine Diabetic Retinopathy Assessment Technology in Safety-net Medical Clinics
Ingrid Zimmer-Galler, MD

11:31
Discussion

11:34
Telemedicine for Retinal Disease
Michael Trese, MD

11:40
Discussion

11:43
FDA Regulation of Ophthalmic Medical Devices
Sam Dahr, MD

11:49
Discussion
FELLOWSHIP RESEARCH AWARD PRESENTATION

INTRODUCTION: David Zacks, MD

Familial Exudative Vitreoretinopathy: Microstructural Phenotyping of the Vitreoretinal Interface, Retina, and Choroid with Functional Correlations
Yoshihiro Yonekawa, MD

J. DONALD M. GASS AWARD

INTRODUCTION: Donald D’Amico, MD

Proton Beam Irradiation of Uveal Melanomas — The First Forty Years
Evangelos Gragoudas, MD

LUNCH — SALON RAVEL & VERRIERE

POSTER VIEWING AND DESSERT — SALON BIZET-GOUNOD

INFLAMMATION

PRESIDING OFFICER: Bernard Doft, MD
MODERATOR: Brian VanderBeek, MD

11:52 am

2:30 Sustained InTravitreal DexAmetHasone Implant fOr Uveitic Macular Edema: Results from the TAHOE Study
Rahul Khurana, MD

2:35 Sympathetic Ophthalmia: Clinicopathologic Correlation in a Consecutive Case Series
Sander Dubovy, MD

2:40 Treatment of Cytomegalovirus (CMV) Retinitis with Systemic Infusion of Third Party Donor-derived CMV-specific Cytotoxic T-lymphocytes
Szilárd Kiss, MD

2:45 The Impact of Intravitreal Drugs on Rates of Post-intravitreal Injection Endophthalmitis
Brian VanderBeek, MD

2:51 Discussion

2:54 Endophthalmitis After Intravitreal VEGF Inhibitor Injection
Bernard Doft, MD

3:00 Discussion

3:03 Current Endophthalmitis Incidence Rates After Intravitreal Anti-VEGF Injections and Outcome of Treatment
Harry Flynn Jr, MD

3:09 Discussion

3:12 Topical NSAID Does Not Prevent Post-Operative Cystoid Macular Edema (CME)
Donald Fong, MD

3:18 Discussion

12:07 pm

12:37 – 1:30 LUNCH — SALON RAVEL & VERRIERE

1:30 – 2:30 POSTER VIEWING AND DESSERT — SALON BIZET-GOUNOD
3:21 pm  Intravitreal Sirolimus Improves Inflammation and Visual Acuity in Subjects with Non-infectious Uveitis (NIU) for the Posterior Segment: Results from SAKURA Study  
Thomas Albini, MD

3:27 pm  Discussion

3:30 - 4:00  REFRESHMENT BREAK/EXHIBITS — SALON BERLIOZ

TUMORS

PRESIDING OFFICER: Timothy Murray, MD
MODERATOR: Prithvi Mruthyunjaya, MD

4:00 pm  Intravitreal Bevacizumab (2.5 mg) and Aflibercept (2.0 mg) as Rescue Therapy for Persistent Post-radiation Cystoid Macular Edema  
Mohammed Khan, MD

4:05 pm  Exome Sequencing of Primary and Metastatic Uveal Melanoma  
Ivana Kim, MD

4:11 pm  Discussion

4:14 pm  Personalized Medicine in Ocular Oncology: The Future is NOW  
Timothy Murray, MD

4:20 pm  Discussion

4:23 pm  A New Look at Tumor Size Classification of Primary Posterior Uveal Melanomas  
James Augsburger, MD

4:29 pm  Discussion

4:32 pm  Intravitreal Dexamethasone for Recalcitrant Cystoid Macular Edema Following Brachytherapy Treatment of Uveal Melanoma  
William Mieler, MD

4:38 pm  Discussion

4:41 pm  Peripheral Retinal Perfusion Status Correlates with Radiation Toxicity Following I-125 Brachytherapy for Uveal Melanoma  
Prithvi Mruthyunjaya, MD

4:47 pm  Discussion

4:50 pm  Does Ophthalmic Artery Chemosurgery Increase the Chance of Orbital Disease, Metastasis or Death in Children with Advanced Intraocular Retinoblastoma?  
David Abramson, MD

4:56 pm  Discussion

4:59 pm  ADJOURN

5:00 pm  MICHAEL MARMOR LECTURE — Monet and the Orangerie: Art, Politics, Eye Disease and Color
REGISTRATION — SALON OPÉRA LOBBY
CONTINENTAL BREAKFAST/EXHIBITS — SALON BERLIOZ

AGE-RELATED MACULAR DEGENERATION I
PRESIDING OFFICER: Mark Blumenkranz, MD
MODERATOR: Glenn Jaffe, MD

7:30 Interim Safety Outcomes from a Phase 4 Study of Intravitreal Aflibercept Injection (IAI) in Patients with Neovascular Age-related Macular Degeneration
Michael Singer, MD

7:35 Evaluation of Long-term Treatment with Intravitreal Aflibercept Injection (IAI) in Patients Completing the VIEW 1 and VIEW Extension Studies: One-year Results of the RANGE Study
Lloyd Clark, MD

7:40 Understanding Geographic Atrophy Disease Progression through Visual Function Endpoints: The Lampalizumab Clinical Trial Program
Lawrence Singerman, MD

7:45 Systemic Treatment of Dry Age-related Macular Degeneration
Jackson Coleman, MD

7:50 Predictors of Response to Intravitreal Anti-VEGF Treatment of Age-related Macular Degeneration
Anjali Shah, MD

7:55 Evidence Implicating Role of Circulating MicroRNAs in Resistance to Anti-VEGF Therapy in Exudative Age-related Macular Degeneration
Lawrence Morse, MD

8:01 Discussion

8:04 Pavingstone Degeneration: Evidence of an Association with the ARMS2 Risk Allele
Thomas Friberg, MD

8:10 Discussion

8:13 Increased Prevalence of Intermediate-stage Age-related Macular Degeneration in Persons with the Acquired Immunodeficiency Syndrome
Douglas Jabs, MD

8:19 Discussion

8:22 Encapsulated Cell Therapy for the Long-term Treatment of Neovascular Age-related Macular Degeneration
Glenn Jaffe, MD

8:28 Discussion

8:31 AVA-101 Gene Therapy Trial for Exudative Age-related Macular Degeneration: Results of a Phase 2a Trial
Ian Constable, MD

8:37 Discussion
8:40 am  Final Results from a Phase 2 Study of Squalamine Lactate Ophthalmic Solution 0.2% (OHR-102) in Neovascular Age-related Macular Degeneration
  Thomas Ciulla, MD

8:46  Discussion

8:49  Safety and Efficacy of RTH258, a Single-chain Anti-VEGF Antibody Fragment, in Patients with Neovascular Age-related Macular Degeneration: Results from Two Phase II Studies
  Pravin Dugel, MD

8:55  Discussion

8:58  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
  Susanna Park, MD

9:04  Discussion

9:07  Microvolume Drug Delivery: A Novel Therapeutic Strategy for Patients with Neovascular Age-related Macular Degeneration
  Brian Berger, MD

9:13  Discussion

9:16  Lamp-2 Deficiency Associated with Dysfunctional Autophagosomes and Phagosomes in Age-related Macular Degeneration
  Joan Miller, MD

9:22  Discussion

9:25  Active Rap1 Inhibits TNFx-induced Choroidal Endothelial Migration via NADPH Oxidase and Nuclear Factor Kappa B Dependent Activation of Rac1
  Mary Elizabeth Hartnett, MD

9:31  Discussion

9:34  REFRESHMENT BREAK/EXHIBITS — SALON BERLIOZ

RETINAL VASCULAR DISEASE
PRESIDING OFFICER: Jeffrey Heier, MD
MODERATOR: Amani Fawzi, MD

10:04  Anti-VEGF Treatment of Macular Edema Secondary to Retinal Vein Occlusion in Clinical Practice: A Retrospective Study of Effectiveness and Patterns of Use
  Arthur Fu, MD

10:09  Evaluation of Macular Microvasculature and Blood Flow Velocities by Non-invasive, High-resolution Functional Imaging in Central Retinal Vein Occlusion
  William Smiddy, MD

10:15  Discussion
10:18 am  Retinal Metabolic Imaging Using Visible Optical Coherence Tomography in Animal Models of Retinal Ischemia  
Amani Fawzi, MD

10:24  Discussion

10:27  Evaluation of Rescue Treatment with Intravitreal Aflibercept Injection (IAI) in Eyes Randomized to the Laser Control Arm in the VIBRANT Study  
Elias Reichel, MD

10:33  Discussion

10:36  The Effect of Intravitreal Aflibercept on Capillary Non-perfusion in Patients with Proliferative Retinopathy and/or Macular Edema Secondary to Proliferative Diabetic Retinopathy and Central Retinal Venous Occlusive Disease (ANDROID Study)  
Jeffrey Heier, MD

10:42  Discussion

10:45  Higher Red Cell Distribution Width Values are Associated with Worse Vision in Retinal Vein Occlusion  
Shlomit Schaal, MD

10:51  Discussion

10:54  Laser Chorioretinal Anastomosis for Central Retinal Vein Occlusion: Success Rates and Technique with a New Photocoagulator System  
Ian McAllister, MD

11:00  Discussion

11:03  Encapsulated Cell Technology Implant to Reverse Retinal Ischemia  
Jeffrey Olson, MD

11:09  Discussion

11:12  PRN Dexamethasone Implant for Macular Edema for the Pan-American Collaborative Retina Study Group  
Michel Farah, MD

11:18  Discussion

11:21  Correlation between Optical Coherence Tomographic Hyper-reflective Foci and Visual Outcomes After Intravitreal Bevacizumab for Macular Edema in Branch Retinal Vein Occlusion  
Hyung Chan Kim, MD

11:27  Discussion

11:30  Sickle Cell Microangiopathy and Biomarkers  
Anita Agarwal, MD

11:36  Discussion

11:39  RAYMOND R. MARGHERIO AWARD PRESENTATION

INTRODUCTION: David Zacks, MD, PhD
The Safety and Feasibility of Office-based Vitreous Aspiration  
Devon Ghodasra, MD
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<td>RETINA RESEARCH FOUNDATION AWARD OF MERIT — Charles L. Schepens Lecture</td>
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<td>INTRODUCTION: Mark Johnson, MD</td>
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<td>Clinical Implications of Translational Research in Diabetic Retinopathy</td>
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<td>Thomas Gardner, MD</td>
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<td>12:24 pm</td>
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<td>1:00</td>
<td>BUSSES TO GIVERNY WITH BOX LUNCH</td>
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**SATURDAY, OCTOBER 10**

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<td>REGISTRATION — Salon Opéra Lobby CONTINENTAL BREAKFAST/EXHIBITS — Salon Berlioz</td>
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<td>7:30</td>
<td>Pars Plana Vitrectomy After Intravitreal Ocriplasmin for Symptomatic Vitreomacular Adhesion Tanuj Banker, MD</td>
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<td>7:35</td>
<td>Real-life Experience After Intravitreal Ocriplasmin for Vitreomacular Traction and Macular Hole: A Spectral-domain Optical Coherence Tomography Prospective Study Panagiotis Theodossiadis, MD</td>
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<td>7:40</td>
<td>Macular Neurosensory Retinal Detachment Associated with MEK Inhibitor Use for Cancer: A Case Series and Review of the Literature Seenu Hariprasad, MD</td>
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<td>7:45</td>
<td>How do Large Retinal Pigment Epithelial Detachments Respond to Ranibizumab Treatment in HARBOR? David Williams, MD</td>
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<td>7:50</td>
<td>Change of Choroidal Structure in Central Serous Chorioretinopathy Analyzed by Binarization Technique on Optical Coherence Tomography Taiji Sakamoto, MD</td>
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<td>7:55</td>
<td>Detection of Choroidal Neovascularization (CNV) in Chronic Central Serous Chorioretinopathy (CSCR) with Optic Coherence Tomography Angiography (OCTA) Caroline Baumal, MD</td>
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<td>En Face Imaging of Pachychoroid Spectrum Disorders with Swept-source Optical Coherence Tomography Bailey Freund, MD</td>
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<td>8:10</td>
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8:13 am  Increased Inward Deflection (ID) of Cone Photoreceptors is the Earliest Sign of Traction on the Fovea
Tongalp Tezel, MD

8:19  Discussion

8:22  Pneumatic Vitreolysis for Vitreomacular Traction: A Case Series and Meta-analysis of the Literature
Jorge Arroyo, MD

8:28  Discussion

8:31  Formation of an Intraretinal Fluid Barrier in Eyes with Cavitary Optic Disc Maculopathy
Mark Johnson, MD

8:37  Discussion

8:40  Inner and Outer Retinal Damage in Hydroxychloroquine Toxicity
Michael Marmor, MD

8:46  Discussion

8:49  Volume Rendering Optical Coherence Tomography Angiography of Macular Telangiectasia Type 2
Richard Spaide, MD

8:55  Discussion

8:58  Fundus Tessellation: Prevalence and Associated Factors: The Beijing Eye Study 2011
Jost Jonas, MD

9:04  Discussion

9:07  Intravitreal Aflibercept for Neovascular Polypoidal Choroidal Vasculopathy (PCV) in a Predominantly Non-Asian Population
Dennis Marcus, MD

9:13  Discussion

9:16  Effects of Intravitreal Aflibercept on Patients with Polypoidal Choroidal Vasculopathy: Results of VAULT Study
Ji Eun Lee, MD

9:22  Discussion

9:25  Effect of Paracentesis on Retinal Nerve Fiber Layer Thickness During Intravitreal Anti-VEGF Therapy
Tamara Vrabec, MD

9:31  Discussion

9:34  INTRODUCTION OF GUESTS OF HONOR
Julia Haller, MD
Gisèle Soubrane, MD, PhD | C. Pat Wilkinson, MD

9:44  REFRESHMENT BREAK/EXHIBITS — SALON BERLIOZ
SCIENTIFIC PROGRAM

PEDIATRICS
PRESIDING OFFICER: Charles Barr, MD
MODERATOR: Antonio Capone Jr, MD

10:14 am  Genotype-Phenotype Correlation of Mutations Occurring in Wnt-associated Vitreoretinopathies (WAVR): A Basis for Genetically Tailored Management
Kimberly Drenser, MD

10:20  Discussion

10:23  Scleral Buckle Surgery for Primary Retinal Detachment without Posterior Vitreous Detachment
Andrew Eller, MD

10:29  Discussion

10:32  Fundus Pigmentation as a Risk Factor for Development of Retinopathy of Prematurity
Audina Berrocal, MD

10:38  Discussion

10:41  Development, Implementation, and Evaluation of a Novel Retinopathy of Prematurity (ROP) Tele-education System
Paul Chan, MD

10:47  Discussion

10:50  Eye Exam vs. Photographic Screening Validation Testing in Newborn Infants
Darius Moshfeghi, MD

10:56  Discussion

10:59  A Retrospective Comparison of Retinopathy of Prematurity Treated with Bevacizumab vs. Laser
Michael Blair, MD

11:05  Discussion

11:08  Changes in Retinopathy of Prematurity from 1986 – 2013: Comparison of Three U.S. Studies
Charles Barr, MD

11:14  Discussion

11:17  Retinal Detachments After Intravitreal Anti-VEGF Injections for Retinopathy of Prematurity Characterize Retinal Detachments that Developed After Intravitreal Anti-VEGF Treatment for Retinopathy of Prematurity (ROP)
Antonio Capone Jr, MD

11:23  Discussion

11:26  A Natural History Study of Subjects with X-linked Retinoschisis in Anticipation of a Phase I/II Gene Therapy Trial
Mark Pennesi, MD

11:32  Discussion
11:35 am  **LATE BREAKING PRESENTATION**  
Phase 3 Trial of AAV2-hRPE65v2 (SPK-RPE65) to Treat RPE65 Mutation-Associated Inherited Retinal Dystrophies: Mobility Testing and Surgical Experience  
**Stephen Russell, MD**

11:41  Discussion

11:44  **LATE BREAKING PRESENTATION**  
Recommendations to Optimize Patient Outcomes from the 2015 Argus II Investigator Meeting  
**Thiran Jayasundera, MD, FACS**

11:50  Discussion

11:53  **LATE BREAKING PRESENTATION**  
Risk of Myocardial Infarction and Stroke with Single or Repeated Doses of Intravitreal Bevacizumab  
**David Maberley, MD, MSc**

11:59  Discussion

12:02 pm  **LATE BREAKING PRESENTATION**  
Randomized Trial of Prompt Panretinal Photocoagulation vs. Ranibizumab for Proliferative Diabetic Retinopathy: Secondary Outcomes, Safety Assessment, and Clinical Applications  
**Jeffrey Gross, MD**

12:08  Discussion

12:15  **ANNUAL BUSINESS MEETING — THE RETINA SOCIETY**

1:00  ADJOURN

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**SUNDAY, OCTOBER 11**

7:00 am  **REGISTRATION — SALON OPÉRA LOBBY**  
**CONTINENTAL BREAKFAST/EXHIBITS — SALON BERLIOZ**

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**AGE-RELATED MACULAR DEGENERATION II**

**PRESIDING OFFICER:** SriniVas Sadda, MD  
**MODERATOR:** Dennis Han, MD

7:30  Development of an International Standard Set of Patient-centric Outcomes Measures for Macular Degeneration  
**Christina Weng, MD**

7:35  Clinical Utilization of Anti-vascular Endothelial Growth Factor (VEGF) Therapy for Neovascular Age-related Macular Degeneration—Analysis of Electronic Medical Records from a Large Integrated U.S. Health System Database  
**Arghavan Almony, MD**
7:40 am Ranibizumab Use, Patterns of Care and Clinical Outcomes in Real-life Settings in Asia-Pacific, the Middle East, and North Africa: Results of The UNCOVER Study
Timothy Lai, MD

7:45 Long-term Outcomes in Eyes Receiving Fixed-interval Dosing of Anti-vascular Endothelial Growth Factor Agents for Wet Age-related Macular Degeneration
Ivan Suner, MD

7:51 Discussion

7:54 Aflibercept as a Second Line Therapy for Neovascular Age-related Macular Degeneration Following Initial Bevacizumab Therapy
Itay Chowers, MD

8:00 Discussion

8:03 A Single Arm, Investigator-initiated Study of the Efficacy, Safety and Tolerability of Intravitreal Aflibercept Injection in Subjects with Exudative Age-related Macular Degeneration Previously Treated with Ranibizumab or Bevacizumab: 24-month Outcomes
Rishi Singh, MD

8:09 Discussion

8:12 Prospective, Multicenter Investigation of Aflibercept Treat and Extend Therapy for Neovascular Age-related Macular Degeneration (ATLAS Study): One-year Results
Carl Regillo, MD

8:18 Discussion

8:21 The EVEN Study: An In-depth Prospective Multimodal Analysis of Aflibercept Therapy for Pigment Epithelial Detachment in Neovascular Age-related Macular Degeneration
Clement Chan, MD

8:27 Discussion

8:30 Pharmacodynamic Profile of Intraocular Aflibercept in Patients with Neovascular Age-related Macular Degeneration
Carsten Meyer, MD

8:36 Discussion

8:39 Anti-VEGF Therapy in Neovascular Age-related Macular Degeneration with Advanced Visual Loss: Prognostic Indicators for Visual Outcomes
Dennis Han, MD

8:45 Discussion

8:48 Geographic Atrophy and Visual Acuity Following Anti-VEGF Therapy in the Comparison of Age-related Macular Degeneration Treatments Trial
SriniVas Sadda, MD

8:54 Discussion
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<td>Subretinal Fluid and the Development of Macular Atrophy in Neovascular Age-related Macular Degeneration Treated with Ranibizumab in HARBOR</td>
<td>Giovanni Staurenghi, MD</td>
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<td>9:03</td>
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<td>9:06</td>
<td>Intravitreal Bevacizumab for Choroidal Neovascularization in Age-related Macular Degeneration: Five-year Results of the Pan-American Collaborative Retina Study Group</td>
<td>Fernando Arevalo, MD</td>
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<td>Mineralocorticoid Antagonists as Adjuncts in Neovascular Age-related Macular Degeneration</td>
<td>Kapil Kapoor, MD</td>
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<td>9:21</td>
<td>Discussion</td>
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<td>9:24</td>
<td>REFRESHMENT BREAK/EXHIBITS — Salon Berlioz</td>
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<td>9:54</td>
<td>Translimbal Sutureless Intravitreal Fragmentation</td>
<td>Periklis Brazitikos, MD</td>
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<td>9:59</td>
<td>Chandelier-assisted External Subretinal Drainage in Primary Scleral Buckling for Treatment of Rhegmatogenous Retinal Detachment</td>
<td>Sara Haug, MD</td>
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<td>10:04</td>
<td>Long-term Follow-up and Outcomes in Traumatic Macular Holes</td>
<td>John Miller, MD</td>
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<td>10:09</td>
<td>Long-term Results of Macular Hole Surgery Using Indocyanine Green to Peel Internal Limiting Membrane</td>
<td>John Thompson, MD</td>
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<td>10:14</td>
<td>Brilliant Blue G versus Indocyanine Green in Macular Hole Surgery</td>
<td>Christiane Falkner-Radler, MD</td>
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<td>10:20</td>
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<td>10:23</td>
<td>Rates of Reoperation and Retinal Detachment Repair Following Macular Hole Surgery</td>
<td>Stephen Schwartz, MD</td>
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<td>10:32</td>
<td>The Depth of the Epiretinal Traction</td>
<td>Mario Romano, MD</td>
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Preoperative and Intraoperative Prognostic Factors of Epiretinal Membrane (ERM) Surgery After Internal Limiting Membrane (ILM) Peeling Using Brilliant Blue (BB)

Mauricio Maia, MD

Can Reading Speed Testing (MNREAD) or Video Scanning Laser Ophthalmoscopy Analysis Objectively Account for the Subjective Visual Improvement After Surgery for Vitreous Opacities?

Edwin Ryan, MD

Photopsias: A Key to Diagnosis

Gary Brown, MD

Pars Plana Vitrectomy Alone for the Management of Pseudophakic Rhegmatogenous Retinal Detachment with Inferior Breaks

Vicente Martinez-Castillo, MD

The Use of Intraoperative Methotrexate Infusion to Prevent Proliferative Vitreoretinopathy

Christopher Riemann, MD

Unexplained Visual Loss Following Silicone Oil Removal. Results of the Pan American Collaborative Retina Study Group

Lihteh Wu, MD

Evaluation of a Retinal Patch Biopolymer for the Treatment of Retinal Detachment in Pig Eyes

Jean-Pierre Hubschman, MD

Intraocular Foreign Bodies without Endophthalmitis Following Combat Ocular Trauma: A Review of 163 Cases

Marcus Colyer, MD

Autophagy and Control of Photoreceptor Cell Death

David Zacks, MD, PhD

The Role of the Complement System in Photoreceptor Cell Death During Retinal Detachment

Deeba Husain, MD
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<td>12:11 pm</td>
<td>Macrophage Inflammation Exacerbates Photoreceptor Cell Death</td>
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<td>Demetrios Vavvas, MD</td>
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<td>12:17</td>
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Robert Morris, MD |
| POSTER 2 | Pre- and Post-Vitrectomy Choroidal Thickness in Eyes with Epiretinal Membrane and Macular Hole  
Bryan Hong, MD |
| POSTER 3 | Outcomes of Pars Plana Vitrectomy for Retinal Detachment Complicated by Proliferative Vitreoretinopathy  
Nora Khatib, MD |
| POSTER 4 | HC-HA/PTX₃, a Soluble, Active Matrix Component of Amniotic Membrane, Inhibits Proliferation and Epithelial Mesenchymal Transition of Retinal Pigment Epithelial Cells: A Potential Novel Therapy for Proliferative Vitreoretinopathy  
Ajay Kuriyan, MD |
| POSTER 5 | Sealing Retina Break with Polyethylene Glycol-based Synthetic Sealant in Rhegmatogenous Retinal Detachment  
Mikki Arai, MD |
| POSTER 6 | The Effects of Diabetic Retinopathy and Panretinal Photocoagulation on Photoreceptor Cell Function as Assessed by Dark Adaptometry  
Thomas Gardner, MD |
| POSTER 7 | Alteration of N-glycan Profiles in Diabetic Retinopathy  
Kousuke Noda, MD |
| POSTER 8 | The Role of Carotenoids in Skin and Eye Protection from Ultraviolet and Visible Light Stress  
Julian Nussbaum, MD |
| POSTER 9 | Is the Subconjunctival Bleb that Forms at the Injection Site After Intravitreal Injection Drug or Vitreous?  
John Christoforidis, MD |
| POSTER 10 | Anatomical Characteristics and Treatment Outcomes of Pediatric Choroidal Neovascular Membranes  
Dilraj Grewal, MD |
| POSTER 11 | Foveal Development After Use of Bevacizumab for Aggressive Posterior Retinopathy of Prematurity (APROP)  
Jose Maria Garcia-Gonzales, MD |
| POSTER 12 | Persistent Vitreofoveal Traction in a Patient with Ocular Toxoplasmosis: A Case Report  
Alvaro Rodriguez, MD |
| POSTER 13 | Ocular Alterations in Patients with Helicobacter Pylori  
Antonio Casella, MD |
| POSTER 14 | Funduscropy in Cerebral Malaria Diagnosis: An International Survey of Practice Patterns  
Tamer Mahmoud, MD |
| POSTER 15 | Endophthalmitis Associated with Glaucoma Drainage Implants  
Carlos Medina, MD |
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<td>Aprotinin Reduces Intraocular Inflammation in Endotoxin Induced Uveitis</td>
<td>Dimitra Skondra, MD</td>
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<td>POSTER 17</td>
<td>Clinical Presentation, Microbiologic Spectrum, and Visual Outcomes of Acute Infectious Endophthalmitis Undergoing Therapeutic Pars Plana Vitrectomy</td>
<td>Jayanth Sridhar, MD</td>
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<td>Oral Fluoroquinolone Use and the Risk of Uveitis</td>
<td>Harpal Sandhu, MD</td>
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<td>Mycobacterium Chelonae Endophthalmitis Management with Dual Antibiotic Therapy and Complete Surgical Debridement</td>
<td>Andrew Barkmeier, MD</td>
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<td>Spectral-domain Optical Coherence Tomography is Superior for Detecting Epiretinal Membranes in Macular Holes Preoperatively Compared to Time-domain Optical Coherence Tomography: Implications for Pharmacological Vitreolysis</td>
<td>Prethy Rao, MD</td>
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<td>POSTER 21</td>
<td>High-resolution Imaging by Adaptive Optics Scanning Laser Ophthalmoscopy Reveals Two Types of Retinal Hard Exudates</td>
<td>Shintaro Nakao, MD</td>
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<td>Swept Source Optical Coherence Tomography Measurements of Parafoveal Retinal Nerve Fiber Layer/Ganglion Cell Layer and Inner Plexiform Layer/Inner Nuclear Layer</td>
<td>Sonia Hernandez, MD</td>
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<td>Quantification of Retinal Vascular Density and Foveal Avascular Zone in Healthy Subjects using Optic Coherence Tomography Angiography</td>
<td>Abtin Shahlae, MD</td>
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<td>POSTER 24</td>
<td>Optical Coherence Tomography Angiography of Pigment Epithelial Detachment</td>
<td>Antonio Ciardella, MD</td>
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<td>Near-infrared Reflectance Bull’s Eye Maculopathy may be an Early Indication of Hydroxychloroquine Toxicity</td>
<td>Keye Wong, MD</td>
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<td>In-vivo Feasibility Study of a Novel Intraocular Drug Delivery System</td>
<td>Adiel Barak, MD</td>
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<td>POSTER 28</td>
<td>Effect of Intracameral Carbachol on Macular and Choroidal Thickness following Phacoemulsification Surgery</td>
<td>Luiz Lima, MD</td>
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<td>POSTER 29</td>
<td>Microcystic Macular Degeneration in Late-stage Optic Neuropathy</td>
<td>Stefano Piermarocchi, MD</td>
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POSTER PROGRAM

POSTER 30  Nationwide Incidence of Ocular Melanoma and Survival Rate of Ocular Melanoma Patients in Korea, 1999 – 2011: The Korea National Cancer Registry Database Study
Kyu Hyung Park, MD

POSTER 31  Tri-modality Planning Study for Ocular Melanoma
Amanda Deisher, MD

POSTER 32  Preclinical Acute Safety Study of Combined Intravitreal Carboplatin and Etoposide Phosphate for Retinoblastoma with Vitreous Seeding
Stephen Smith, MD
The Impact of Written Physician Communication on Diabetic Eye Examination Adherence: Results from a Retrospective Cohort Analysis

Philip Storey, MD, MPH
Los Angeles, CA

Ann Murchison, MD, MPH, Laura Pizzi, PharmD, MPH, Lisa Hark, PhD, RD, Yang Dai, MS, Benjamin Leiby, PhD, Julia Haller, MD

PURPOSE: To evaluate the effect of written communication between an ophthalmologist and a primary care physician (PCP) on patient adherence to diabetic eye examination recommendations.

METHODS: In a retrospective cohort study of a multi-ethnic population at an urban academic ophthalmology center, billing records were used to identify all patients with diabetes and an initial visit with dilated fundus examination (DFE) from 1/1/2007 to 12/31/2010. Patient charts were reviewed and data collected included demographics, severity of diabetic retinopathy, follow-up eye examinations, and written communication between a patient’s ophthalmologist and PCP. Patients were considered adherent to follow-up if they obtained a DFE within study definitions adapted from American Academy of Ophthalmology recommendations: within 15 months for mild diabetic retinopathy, within 12 months for moderate diabetic retinopathy, and within 4 months for severe diabetic retinopathy. Statistical analyses were performed to examine the relationship between physician communication and diabetic eye examination adherence.

RESULTS: A total of 1,968 people with diabetes were included. Factors associated with increased examination adherence in multivariable analysis were written communication from an ophthalmologist to a PCP (p=0.0071), written communication from a PCP to an ophthalmologist (p=0.036), severity of diabetic retinopathy (p<0.0001), age > 65 years (p=0.027), smoking status (p<0.0001), insulin use (p=0.0061), hemoglobin A1C documented in chart (p=0.0002), and blood glucose documented in chart (p<0.0001). After controlling for other variables, patients with written communication from an ophthalmologist to a PCP had 1.47 times (95% Confidence Interval 1.11-1.94) higher odds of adhering to follow-up recommendations. Patients with written communication from a PCP to an ophthalmologist had 1.53 times (95% Confidence Interval 1.03-2.29) higher odds of adhering to the follow-up recommendations.

CONCLUSIONS: Patients with written communication between ophthalmologists and PCPs are more likely to adhere to diabetic eye examination recommendations. The impact of interventions to improve communication between providers deserves further exploration.
Novel Quantitative Biomarkers for Early Detection of Diabetic Retinopathy

Jennifer Kang-Mieler, PhD
Chicago, IL

Christian Osswald, BS, Emma Dosmar, BS, Micah Guthrie, PhD, William Mieler, MD, Kenneth Tichauer, PhD

PURPOSE: The purpose of this study was to demonstrate the early detection potential of our imaging-based biomarkers for diabetic retinopathy (DR). Utilizing tracer kinetic modeling and conventional fluorescein video-angiography (FVA), quantitative retinal blood flow and vascular permeability can be obtained and used to predict early changes of DR.

METHODS: Long-Evans rats were randomly separated into two groups: a control group and a diabetic group. Diabetes was induced by streptozotocin (STZ, 80 mg/kg) injection into the tail vein. Weekly FVA were recorded using a scanning laser ophthalmoscope. By 4 weeks post-STZ injection, the average blood glucose in the diabetic rats was 406 ± 121 mg/dL. Under ketamine (80 mg/kg BW) and xylazine (10 mg/kg BW) anesthesia, a bolus of fluorescein dye (0.1 mL of 10%) was injected via tail vein to obtain FVA (30 sec, 20 fps, 256x256). The fluorescein images were loaded into MATLAB and “plug flow” tracer kinetic model was applied to obtain retinal blood flow maps and vascular permeability.

RESULTS: The blood flow maps for control rat retinas exhibited the highest volumetric blood flow in the large arteries and veins, with substantially lower tissue flows. In contrast, the blood flow maps in the diabetic rat retinas showed a high tissue flow. The tissue blood flow was significantly higher (P<0.01) in the diabetic rats compared to the controls: 7.6±1.7 ml/min/100g in the control rats and 25.6±13.9 ml/min/100g in the diabetic rats. Tissue blood volumes were also significantly larger (P<0.05) in the diabetic rats compared to controls: 0.13±0.08 ml/100g in the control rats and 0.29±0.14 ml/100g in the diabetic rats. No clinical signs of DR were observed in all animals.

CONCLUSIONS: The current data showed an increase in blood flow in diabetic animals similar to previous studies suggesting that the dynamic fluorescein enhanced fluorescent imaging method can detect changes in blood as well other hemodynamic parameters. The proposed technique is a novel, non-invasive technique to extract hemodynamic parameters and may be powerful biomarkers to detect early changes in DR.
Afiblercept for Diabetic Macular Edema in Eyes Previously Treated with Ranibizumab and/or Bevacizumab may Improve Visual Acuity and Macular Thickness

Chirag Shah, MD, MPH
Boston, MA

Jeffrey Heier, MD

PURPOSE: To evaluate the short-term visual and anatomic outcomes after afiblercept in eyes with diabetic macular edema (DME) previously treated with ranibizumab and/or bevacizumab.

METHODS: This is a retrospective, non-comparative study conducted at Ophthalmic Consultants of Boston. Billing data were used to identify eyes with DME previously treated with ranibizumab and/or bevacizumab, and switched to afiblercept. Included eyes had an injection 4-8 weeks before switching to afiblercept; eyes were excluded if their next follow-up occurred at a shorter interval. Central subfoveal thickness (CST) was collected from the OCT viewing software, and eyes were imaged on the same OCT machine pre- and post-afiblercept injection. The best available visual acuity (e.g., pinhole) was collected and converted to LogMAR. Two-tailed paired t-test was used to compare outcomes.

RESULTS: This study included 16 eyes in 13 patients. The average age at the time of afiblercept injection was 65 (range 27-84, median 70). Eyes received an average of 16 prior injections (range 2-35, median 17). Four eyes (25%) had prior focal laser. Eyes received their last ranibizumab/bevacizumab injection 41 days prior to switching to afiblercept (range 28-56 days, median 39). The follow-up interval after switching to afiblercept increased to 45 days (range 28-59, median 42, p = 0.018). Visual acuity improved after switching to afiblercept at the first follow-up visit, from 20/50 (logMAR 0.40) to 20/46 (logMAR 0.36), p = 0.027). Correspondingly, the mean CST improved from 360 microns (range 271-547, median 358) to 316 microns (range 242-545, median 299, p = 0.004).

CONCLUSIONS: In eyes with DME treated with ranibizumab and/or bevacizumab, switching to afiblercept may further improve visual acuity and macular thickness. A larger sample size with longer follow-up will be presented at Retina Society 2015.
Contralateral Eye-to-Eye Comparison of Intravitreal Injections of Ranibizumab and a Dexamethasone Implant in Chronic Diabetic Macular Edema

Tarek Hassan, MD
Royal Oak, MI

Yoshihiro Yonekawa, MD, Benjamin Thomas, MD

PURPOSE: To directly compare the visual and anatomic effects of intravitreal injections of ranibizumab with those of an intravitreal dexamethasone implant in chronic diabetic macular edema (DME) by treating visually- and anatomically-matched contralateral eyes in the same patient.

METHODS: This retrospective interventional study examined patients with bilateral, symmetrical center-involved DME previously treated with intravitreal anti-VEGF injections (ranibizumab and/or bevacizumab) that demonstrated either (a) persistent DME after multiple injections or (b) minimal response to existing therapy. Patients were transitioned in one eye to receive a dexamethasone intravitreal implant while the contralateral eye continued to receive intravitreal anti-VEGF injections q4-5 weeks. Paired eyes had roughly equivalent baseline CMT (±55µm) and VA (±1 Snellen line). VA, CMT, and intraocular pressure (IOP) were evaluated at baseline and at all follow-up visits.

RESULTS: Ten patients with Type 2 diabetes met the inclusion criteria. All patients had been treated for bilateral DME for a mean duration of 21 months (range 5-50). Eyes receiving the dexamethasone intravitreal implant previously received a mean of 9.5 anti-VEGF injections (range 1-25); eyes continuing anti-VEGF therapy previously received a mean of 9.7 (range 1-20). Eyes receiving dexamethasone had a mean LogMAR VA of 0.396 (SD ±0.16) at baseline and improved to 0.295 (SD ±0.23) at final evaluation. Mean CMT in these eyes improved from 495µm (SD ±152) at baseline to 353µm (SD ±79) at final evaluation (net decrease: 142µm, p=0.0180, Wilcoxon signed-rank test). In the anti-VEGF arm, mean LogMAR VA at baseline was 0.303 (SD ±0.09), and this improved to 0.255 (SD ±0.12) at final evaluation. Mean CMT improved from 479µm (SD ±106) to 381µm (SD ±127; net reduction: 98µm, p=0.0280). Two dexamethasone eyes experienced IOP elevation >30mmHg, compared to 0 anti-VEGF eyes.

CONCLUSIONS: A subset of DME patients demonstrating minimal or incomplete responses to anti-VEGF agents had greater net reduction of CMT and greater net improvement of VA in one eye after a single dexamethasone intravitreal implant, as compared to contralateral eyes receiving multiple anti-VEGF injections.
Intravitreal Aflibercept Injection (IAI) for Diabetic Macular Edema (DME): 148-Week Results from VISTA and VIVID

David Brown, MD
Houston, TX

Jean-François Korobelnik, MD

PURPOSE: To compare efficacy and safety of IAI with macular laser photocoagulation in DME.

METHODS: VISTA and VIVID were two similarly designed phase 3 trials that treated 461 and 404 DME patients, respectively, with IAI 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks following 5 monthly doses (2q8), or laser with monthly follow-up through week 148. Patients continued with the same dosing regimen in the IAI groups through end of study. Starting at week 24, if rescue treatment criteria were met, patients in the IAI groups received laser, and patients in the laser group received IAI 2q8. Patients in the laser group who had not already qualified for rescue treatment, received IAI as needed per retreatment criteria beginning at week 100. The primary efficacy endpoint was mean change from baseline in best-corrected visual acuity (BCVA) at week 52.

RESULTS: In VISTA, mean BCVA gain from baseline in the 2q4, 2q8, and laser groups was 12.5, 10.7, and 0.2 letters (P<.0001) at week 52, and 11.5, 11.1, and 0.9 letters (P<.0001) at week 100, respectively. In VIVID, mean BCVA gain from baseline in the 2q4, 2q8, and laser groups was 10.5, 10.7, and 1.2 letters (P<.0001) at week 52, and 11.4, 9.4, and 0.7 letters (P<0.0001) at week 100. The most frequent ocular serious adverse event from baseline to week 100 was cataract (2.4%, 1.0%, and 0.3% for the 2q4, 2q8, and laser groups, respectively) in a pooled analysis of VISTA and VIVID. In VISTA, BCVA gains from baseline in the 2q4 and 2q8 groups were 10.4 and 10.5 letters at week 148, respectively. Safety outcomes at week 148 in VISTA were consistent with those through week 100 in VISTA and VIVID. The 148-week results of VISTA/VIVID are expected by the time of presentation.

CONCLUSIONS: In both trials, IAI demonstrated significant superiority in visual outcomes over laser at week 52, with similar efficacy in the 2q4 and 2q8 groups. BCVA gains from baseline with both IAI regimens were sustained at week 100 in VISTA and VIVID, and at week 148 in VISTA. IAI was generally well tolerated.
Intravitreal Afiblercept Injection (IAI) in Patients with Prior Therapy for Diabetic Macular Edema (DME): 148-Week Outcomes from VISTA

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PURPOSE: To evaluate visual and anatomic outcomes following IAI and laser in subgroups of DME patients with and without prior anti-VEGF therapy for DME.

METHODS: Two phase 3 studies, VISTA and VIVID, treated 461 and 404 DME patients, respectively, with either IAI 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks following 5 initial monthly doses (2q8), or laser with sham injections. The primary endpoint was the mean change from baseline in best-corrected visual acuity (BCVA) at week 52. An exploratory analysis examined the improvements in BCVA and central retinal thickness (CRT) through week 148 in patients with and without prior anti-VEGF therapy for DME. The analysis focused only on the VISTA study as it enrolled more patients with prior anti-VEGF therapy than did VIVID (42.9% vs 8.9%, respectively).

RESULTS: Of patients that received prior anti-VEGF therapy in VISTA, 83.3%-92.6% received ≥1 prior bevacizumab, and 71.4%-82.4% received only bevacizumab as a prior treatment for a duration ranging from 28 days to 3.9 years. In patients with prior anti-VEGF therapy, the mean change form baseline BCVA in the 2q4, 2q8, and laser groups was +10.4, +10.5 and -0.7 letters at week 52, and +10.9, +10.8 and -0.8 letters at week 100. The corresponding changes in patients without prior anti-VEGF therapy were +14.1, +11.0, and +0.9 letters at week 52, and +12.0, +11.3, and +2.1 letters at week 100, respectively. In patients with prior anti-VEGF therapy, the mean reduction from baseline CRT was 180.2, 192.2, and 90.9 mm at week 52, and 180.1, 196.4, and 94.1 mm at week 100, respectively. The corresponding reductions in patients without prior anti-VEGF therapy were 190.3, 175.7, and 61.0 mm at week 52, and 200.0, 186.7, and 76.9 mm at week 100, respectively. Overall incidence of Anti-Platelet Trialists’ Collaboration-defined arterial thromboembolic events was 8.4%, 7.2%, and 5.8% in the 2q4, 2q8, and laser groups, respectively, at week 100. Results through week 148 will be presented.

CONCLUSIONS: Visual and anatomic improvements over laser with both IAI regimens were similar through week 100 in subgroups of patients with and without prior anti-VEGF therapy for DME.
Outcomes from Diabetic Macular Edema (DME) Eyes with a Limited Initial Anatomic Response to Intravitreal Afibercept Injection (IAI) in VISTA/VIVID Studies

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PURPOSE: To determine outcomes through week 100 in DME eyes that demonstrated a limited initial anatomic response (≤10% reduction in central retinal thickness [CRT]) from baseline [BL] through week 12 in VISTA and VIVID.

METHODS: VISTA and VIVID were two similarly designed, phase 3 trials that treated 461 and 404 DME patients, respectively, with IAI 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks following 5 monthly doses (2q8), or laser. From week 24, patients could receive rescue treatment (active laser for IAI groups and IAI 2q8 for laser group). A subgroup of eyes with limited initial CRT response as evaluated by spectral domain optical coherence tomography and defined as ≤10% CRT reduction from BL at every visit through week 12 were evaluated.

RESULTS: The proportion of eyes with limited initial CRT response in 2q4, 2q8, and laser groups, respectively, was 20.8%, 14.6%, and 48.7%, in VISTA, and 14.1%, 13.3%, and 45.5% in VIVID. The corresponding BL Best-corrected visual acuity (BCVA) letter score was 61.5, 62.5 and 62.1 in VISTA, and 63.5, 63.2, and 63.0 in VIVID, which was slightly greater than BL BCVA across all treatment groups in the overall VISTA/VIVID population. In eyes with limited initial CRT response, the mean BCVA gains at week 52 from BL in the 2q4, 2q8, and laser groups was +8.2, +10.5, and -2.6 letters in VISTA, and +7.4, +10.9, and +0.8 letters in VIVID, and corresponding gains at week 100 were +6.6, +7.6 and -2.0 in VISTA, and +9.6, +8.1, and -0.1 letters in VIVID, respectively. The most frequent ocular serious adverse event in an integrated analysis of VISTA/VIVID was cataract (2.4%, 1.0%, and 0.3% for the 2q4, 2q8, and laser groups, respectively).

CONCLUSIONS: Compared to laser, IAI demonstrated significant BCVA gains at weeks 52 and 100 in a subgroup of eyes with a limited initial CRT decrease. The benefits of IAI in this sub-group were maintained with continued IAI dosing despite a limited initial CRT response. IAI was generally well tolerated and safety profile was similar to laser control.
Diabetic Retinopathy (DR) Improvements with Ranibizumab: The Fate of Patients with Moderately Severe or Severe Non-Proliferative Diabetic Retinopathy (NPDR)

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**PURPOSE:** Patients with moderately severe or severe NPDR (ETDRS-DR Severity Scale [DRSS] levels 47 and 53, respectively) are at high risk of progression to early proliferative DR (PDR) or high-risk PDR within 1 year (ETDRS Report 12, Ophthalmology, 1991). Here we evaluated the effect of ranibizumab on DR specifically in patients with DM at high risk of worsening to PDR.

**METHODS:** In the randomized phase III RIDE/RISE studies, patients with DME (N=759) received monthly ranibizumab (0.3 mg or 0.5 mg) or sham injections for 24 months. Sham-arm patients crossed over to monthly 0.5 mg ranibizumab from month 24 to 36. DR severity was graded on the ETDRS-DRSS by masked evaluators using 7-field fundus photographs.

**RESULTS:** Baseline ETDRS-DRSS ranged from 10-75; 29% of patients had mild or moderate NPDR (ETDRS-DRSS 35/43), 33% had moderately severe or severe NPDR (ETDRS-DRSS 47/53), 31% had PDR (ETDRS-DRSS 60-75), 2% had absent or questionable DR, and in 5% DR could not be graded. Among patients with baseline ETDRS-DRSS 47/53, rates of ≥2-step DR improvement were significantly greater for ranibizumab-treated patients vs sham at months 12 (76.1%, 75.7%, and 2.3% for 0.3 mg ranibizumab, 0.5 mg ranibizumab, and sham, respectively) and 24 (78.4%, 81.1%, and 11.6%) (all ranibizumab vs sham comparisons, P<0.0001). Respective rates of ≥3-step DR improvement at month 24 were 22.7%, 28.4%, and 1.2% (each ranibizumab arm vs sham, P<0.0001). Rates of ≥2-step DR worsening from baseline at month 24 were significantly lower for 0.3 mg ranibizumab (0%) and 0.5 mg ranibizumab (2.7%) vs sham (15.1%; P=0.0001 for 0.3 mg ranibizumab and P=0.008 for 0.5 mg ranibizumab), as were rates of ≥3-step worsening (0% for both 0.3 mg and 0.5 mg ranibizumab and 5.8% for sham; P=0.02 for 0.3 mg ranibizumab vs sham; P=0.0365 for 0.5 mg ranibizumab vs sham).

**CONCLUSIONS:** More than 75% of ranibizumab-treated patients with moderately severe or severe NPDR (ETDRS-DRSS 47/53) experienced ≥2-step DR improvements at 12 and 24 months, and almost none had ≥2-step DR worsening at month 24. Ranibizumab treatment resulted in clinically relevant DR improvements in this population of patients at high risk of progression to PDR.
Neuroretinal Loss Precedes Microvascular Damage from Diabetes Mellitus

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PURPOSE: Diabetic retinopathy is commonly characterized as a microvasculopathy but recent cross-sectional studies suggest that ganglion cell (GC) and nerve fiber layer (NFL) loss is progressive in diabetic eyes with little to no detectable diabetic retinopathy on fundoscopy. We sought to determine whether neurodegeneration or vascular changes occur first in humans and mice with diabetes.

METHODS: Donor eyes (5 diabetic with no-to-minimal retinopathy, mean age 80; 5 control, mean age 75) obtained from the Iowa Lions Eye Bank had a macular punch immunostained to label retinal vessels, NFL and GCs. No eyes had history of glaucoma, uveitis, DME, PDR, laser, injection or other retinal condition. Capillary density was measured in whole mount sections using automated segmentation with manual removal of large vessels. NFL thickness and GC density were determined by two masked graders.

To control for inherent variability in humans we examined inner retinal structures and vascular changes in diabetic mice. We compared NFL-GC thickness on SD-OCT and immunolabeled retinal tissue for GC density, pericyte, and capillary analysis in streptozotocin-induced (STZ) mice at 6 and 20 weeks of diabetes (n=21) to age-matched control (n=15) C57BL/6 mice.

RESULTS: NFL was significantly thinner in the diabetic donors (17.3 microns) compared to controls (30.4; p=0.03). Though GC density was less in the diabetics, this was not significantly different from controls. Capillary density was not different between the two groups.

In STZ mice, GC density was reduced at week 20 compared to controls (44.1% vs. 50.2%, respectively, p<0.05) but not at week 6 (p=0.85). Automated OCT analysis found that NFL-GC thickness in STZ mice was thinner compared to controls at 6 (8.97um vs 10.54um, p<0.05) and 20 weeks (6.45um vs 8.98um, p<0.001). At 6 weeks, there was no difference between pericyte density or number of acellular capillaries. At 20 weeks, pericyte density was not statistically different in the superficial, inner or outer vascular plexi.

CONCLUSIONS: Diabetes causes progressive neuroretinal loss which is not preceded by, and thus cannot be mediated by, microvascular retinopathy. These results suggest that diabetic neural retinopathy is neurotoxic, rather than ischemic, in origin, imputing a paradigm shift when considering visual loss from diabetes.
Diabetic Macular Edema and Müller Cells Biomarkers: An In Vivo Study

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PURPOSE: To evaluate, in human diabetic eyes, the relationship between regressing versus persistent diabetic macular edema (DME) and the biomarkers of Müller cells activation.

METHODS: Twenty-six diabetic eyes with regressing diabetic macular edema (DME) were compared with 26 persistent DME eyes, and 20 diabetic eyes without DME. Aqueous humor was sampled in all eyes using a 30 gauge needle through a peripheral clear cornea approach. Each subject underwent full ophthalmic examination, and SD-OCT retinal layers segmentation, before aqueous humor sampling. Each sample was analyzed to quantify: glial fibrillary acidic protein (GFAP), AQP4 and Kir 4.1 as biomarkers of Müller cells activation (by ELISA).

RESULTS: Mean concentration of GFAP, Kir 4.1 and AQP4 significantly decreased in DME eyes versus non DME eyes (p<0.002, for each comparison). Regressing DME eyes showed a significant increase of Müller cells biomarkers compared to persistent DME eyes (p<0.005), never reaching the values of non DME eyes (p< 0.002). AQP4 and Kir 4.1 better represented Müller cells activity (p< 0.001 and < 0.002, in all comparison).

CONCLUSIONS: The activation of Müller cells in diabetic retina has been confirmed by the increase of specific biomarkers, even in the aqueous humor. The decrease of Müller cells specific biomarkers in eyes with DME, associated with cystic changes in the middle retina, is a sign of Müller cells degeneration, as previously reported. This study shows that when DME regresses Müller cells activity may be, at least partially, restored, providing the opportunity for retinal recovery in both metabolic and functional activity. These results show that Müller cells activity is critical in the pathophysiology and management of DME.
MicroRNAs in the Retina and Vitreous: New Targets for Diabetic Retinopathy

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PURPOSE: MicroRNAs (miRNAs) are major regulators of gene expression and are important modulators for physiologic processes and diseases. There are few studies characterizing miRNA profiles of the vitreous and retina, and no studies demonstrating whether vitreous miRNA levels are reflective of retinal gene expression. We hypothesize that retinal diseases such as diabetic retinopathy are associated with alterations of miRNA, and that vitreous biopsy may permit detection of abnormal miRNA activity. We studied human vitreous biopsy specimens as well as animal models of hyperglycemia to further define disease-specific miRNA activity in the eye.

METHODS: For our IRB-approved human study, we obtained vitreous biopsies collected at vitrectomy from diabetic patients and nondiabetic controls and processed these specimens for miRNA. For the mouse models, we used Ins2Akita mice, C57BL6/J mice, and wild-type mice and processed tissues for cell-specific miRNAs, in addition to examining the eyes by fundus photography, fluorescein angiography, and OCT.

RESULTS: Our preliminary human data revealed that miRNAs are present in human vitreous, and there is differential miRNA expression in patients with diabetic retinopathy compared to nondiabetic patients. The detailed examination of tissues from the hyperglycemic mouse models displayed substantial down regulation of several miRNAs including angiogenesis-associated miR-126 and miR-143 in the retina and choroid/RPE, when compared to controls; intravitreal injection with custom-designed anti-miR-126 and miR-143 molecules substantially increased vascular permeability in these animals compared to the controls, and these changes were specific to cellular layers within the retina.

CONCLUSIONS: Our pilot studies on human vitreous are encouraging, showing a differential expression of miRNAs between the diabetics and controls; detailed miRNA profiling of these precious human specimens is ongoing. In the hyperglycemic mouse studies, blocking miR-126 and miR-143 produced striking changes in the fundus with an increase in retinal vascular permeability. The miRNAs identified by our screening techniques offer potential new targets and may open the way for novel miRNA therapeutics for diseases such as diabetic retinopathy.
Utilization of Anti-vascular Endothelial Growth Factors (VEGFs) for Diabetic Macular Edema in U.S. Clinical Practice Using the Vestrum Health® Database

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PURPOSE: First-time analysis of the Vestrum Health® database to evaluate the annual frequency of intravitreal injections (IVIs) of anti-vascular endothelial growth factors (anti-VEGFs) in community retina specialty practices among eyes treated for diabetic macular edema (DME) during 2011 to 2014.

METHODS: The Vestrum Health® database of EHRs from 173 community retina specialists in the US was retrospectively analyzed. Individually-identifiable eyes with a diagnosis of DME any time in their history and no diagnoses of retinal vein occlusion (RVO) or age-related macular degeneration (AMD) were selected from among the 353,466 patients who had at least one encounter in the database prior to 10/01/2014. Eyes with an IVI of anti-VEGF (bevacizumab, ranibizumab, aflibercept) on or after the initial diagnosis and between 01/01/2011 and 09/30/2014 were selected. Patients were required to be from physician practices that submitted data for ≥6 months prior to and ≥12 months after the initial IVI. The number of injections per eye were evaluated for the index anti-VEGF and for all anti-VEGFs among the selected eyes. The number of injections per eye were also evaluated for a subset of drug initiators, defined as eyes that had not had any IVIs of the index anti-VEGF during the prior 6 months.

RESULTS: Of 58,037 eyes with DME, 54,072 remained after excluding those with RVO or AMD. Of these, 17,454 had an anti-VEGF injection, 9,646 met the physician data inclusion criteria and 8,971 were drug initiators (6,002 bevacizumab, 2,953 ranibizumab, and 16 aflibercept). Mean and median injections per patient during 12 months following drug initiation were bevacizumab (2.90, 2) ranibizumab (4.42, 4), and any anti-VEGF (3.84, 3).

CONCLUSIONS: Compared with clinical trials of anti-VEGFs, where typically 7 to 12 injections during the first year of treatment provided maximal visual acuity benefit, the volume of injections in US retina specialty practice is low and maximal visual acuity benefit is unlikely.
Lack of Longitudinal Association between Thiazolidinedione Use and Incidence of Diabetic Macular Edema: The ACCORD EYE Study Four-year Results

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**PURPOSE:** To report the longitudinal association between use of thiazolidinediones (TZDs) and visual acuity (VA) change, diabetic retinopathy (DR) incidence and progression, and diabetic macular edema (DME) incidence and progression in the ACCORD Eye Study.

**METHODS:** We analyzed baseline and four-year follow up examination data and centrally-graded fundus photographs in 2856 patients. We defined DME progression as a 2-step change on the Early Treatment Diabetic Retinopathy Study (ETDRS) DME scale and DR progression based on 3-step progression on the ETDRS person-scale for retinopathy, surgery or laser treatment. We evaluated 10 and 15 letter change on the ETDRS distance acuity chart.

**RESULTS:** After adjusting for age, sex, race and diabetes duration, TZD use was not associated with increased DME incidence at four-years of follow up in both the analysis of any use (Adjusted odds ratio (95% CI): 1.22 (0.72 to 2.05)) and adjusting for TZD duration of use (aOR: 1.02 (0.99 to 1.04)). DR incidence/progression was more common in patients with no or mild DR at baseline ever treated with TZDs vs. never (aOR: 1.68 (1.11 to 2.55)), but this association disappeared when adjusting for the proportion of time on TZD (aOR: 1.02 (1.00 to 1.04)). Additionally, DR progression among those with moderate or severe DR at baseline was no different between TZD users and non-users. TZD usage had no effect on the ultimate visual acuity outcome, regardless of whether we analyzed 10 or 15 letter change.

**CONCLUSIONS:** In this longitudinal study of patients with type 2 diabetes, there was no association between the utilization of TZDs and visual acuity outcomes or DME progression.
Comparative Effectiveness of Intravitreous Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema in a Randomized Trial: One-year Treatment and Safety Outcomes

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PURPOSE: To evaluate the safety of anti-vascular endothelial growth factor (anti-VEGF) aflibercept, bevacizumab, or ranibizumab, as well as focal/grid laser photocoagulation for treating diabetic macular edema (DME) involving the center of the macula and to evaluate the number of intravitreous injections of anti-VEGF administered within this randomized trial.

METHODS: At 89 sites in the Diabetic Retinopathy Clinical Research Network (DRCR.net), one eye of 660 adults with decreased visual acuity from DME involving the macular center was assigned randomly to a standardized treatment protocol of intravitreous 2.0-mg aflibercept (N = 224), 1.25-mg bevacizumab (N = 218), or 0.3-mg ranibizumab (N = 218). Follow-up visits occurred every 4 weeks in the first year. Retreatment with anti-VEGF was based on visual acuity and/or OCT central subfield thickness (CST) changes. After 6 months, if central-involved DME persisted and was not improving, focal/grid laser, if feasible, was added. If the nonstudy eye needed anti-VEGF treatment, the nonstudy eye received the same agent as the study eye.

RESULTS: Endophthalmitis occurred in 0.02% of injections (2 non-study eyes treated with study drugs) among 2 study participants (0.3%). Two study eyes (1%) from each group reported intraocular inflammation. The study did not identify a difference in the rates of death, hospitalization, serious adverse events, or other pre-specified systemic adverse events, including Anti-Platelet Trialists’ Collaboration (APTC)-defined cardiovascular events. Focal/grid laser photocoagulation was administered at least once (between 24 and 48 weeks) in 37% of eyes treated with aflibercept, 56% of eyes with bevacizumab, and 46% of eyes with ranibizumab (PP=0.045 for overall comparison).

CONCLUSIONS: The median number of injections was 9 to 10 per group. Laser photocoagulation was performed in fewer aflibercept-treated eyes than bevacizumab- or ranibizumab-treated eyes, potentially driven by a protocol requiring fewer lasers in eyes having resolution of central-involved DME. Differences in rates of death, hospitalization, major cardiovascular events or serious adverse events were not identified.
DRCR.net Comparative Effectiveness Randomized Clinical Trial of Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema (One-year Results)

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Diabetic Retinopathy Clinical Research Network

PURPOSE: To evaluate the relative changes in visual acuity and optical coherence tomography (OCT) central subfield thickness (CST) efficacy, at 1-year, of intravitreous injections of anti-vascular endothelial growth factor (anti-VEGF) agents aflibercept, bevacizumab, or ranibizumab for treating diabetic macular edema (DME) involving the center of the macula.

METHODS: At 89 sites in the Diabetic Retinopathy Clinical Research Network (DRCR.net), one eye of 660 adults with decreased visual acuity from DME involving the center of the macula, confirmed with an OCT CST time domain equivalent >250 µm, were assigned randomly to a standardized treatment protocol of intravitreous 2.0-mg aflibercept (N = 224), 1.25-mg bevacizumab (N = 218), or 0.3-mg ranibizumab (N = 218). Follow-up visits occurred every 4 weeks. The primary outcome was change in visual acuity at 1 year. Secondary efficacy outcomes included change in CST on OCT.

RESULTS: The mean change in visual acuity letter score at one year was greater with aflibercept (+13.3) than bevacizumab (+9.7) or ranibizumab (+11.2). The greater overall effect was driven by eyes with initial VA 20/50 or worse (~50% of the cohort). Mean VA letter score improvement in this subgroup was +18.9 aflibercept, +11.8 bevacizumab, +14.2 ranibizumab (P-values: aflibercept-bevacizumab <0.001, aflibercept-ranibizumab=0.003, ranibizumab-bevacizumab=0.21). The mean letter score difference between aflibercept and bevacizumab of +6.5 equates on a patient level to 63% relatively more aflibercept than bevacizumab-treated eyes improving ≥15 letters (improvement 67% vs. 41%); +4.7 letter mean difference between aflibercept and ranibizumab equates to 34% relatively more aflibercept than ranibizumab-treated eyes (improvement 67% vs. 50%). For eyes with initial VA 20/32 to 20/40, mean change was +8.0 (aflibercept), +7.5 (bevacizumab) and +8.3 (ranibizumab). The treatment effect on OCT CSF thickness will be presented. Information regarding safety will be presented separately.

CONCLUSIONS: In eyes with decreased visual acuity from DME, all three agents, on average, substantially improve visual acuity. However, the relative effect depends on initial visual acuity. When initial visual acuity loss is mild, on average, there were no apparent differences between the three treatment groups. However, the worse the initial visual acuity, the greater the relative advantage of aflibercept over the other two agents.

Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services EY14231, EY23207, EY18817.
Diabetic Macular Edema Outcomes with Anti-VEGF Treatments: Comparison of Randomized Controlled Clinical Studies

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**PURPOSE:** Comparing outcomes across trials of ranibizumab (RBZ), aflibercept (AFL), and bevacizumab (BVZ) for the treatment of DME is challenging due to differences in study design and implementation. This exploratory analysis compared outcomes while considering differences in baseline characteristics.

**METHODS:** Study designs, primary endpoints, inclusion/exclusion criteria, baseline characteristics, BCVA outcomes, and safety outcomes were compared for anti-VEGF-treated arms of Protocol-i (RBZ), RIDE/RISE (RBZ), RESOLVE (RBZ), RESTORE (RBZ), VIVID/VISTA (AFL), and Protocol-T (RBZ, AFL, BVZ). Inclusion criteria were similar except for baseline BCVA: Protocol-i/RESTORE/Protocol-T enrolled patients with BCVA up to 20/32, whereas others capped vision at 20/40. A Protocol-i subgroup analysis was also conducted, including only eyes with baseline BCVA 20/40 or worse (n=581, 68%).

**RESULTS:** Mean baseline BCVA was higher in trials including 20/32 vision versus those capping BCVA at 20/40 (63-65 letters in Protocol-i/RESTORE/Protocol-T vs 55-61 letters in RIDE/RISE/RESOLVE/VIVID/VISTA). A ‘ceiling effect,’ where better baseline vision correlated with lower Year-1 BCVA gains, was observed across trials excluding Protocol-T. Mean BCVA gains were -11 letters from baseline in RIDE/RISE/RESOLVE/VIVID/VISTA versus -8 letters in Protocol-i/RESTORE. In Protocol-T, baseline BCVA was 65 letters across arms, and Year-1 mean BCVA gains were +10-13 letters. In the Protocol-i subanalysis, baseline BCVA was -57-58 letters and mean BCVA gains were +11 letters among patients with ≤20/40 baseline vision versus +9 letters among all patients. High inter-arm variability (4.6-8.5 letters) was observed among patients with the worst baseline vision (<39 letters) in RIDE vs RISE and VIVID vs VISTA and within arms in Protocol-T (for baseline BCVA 20/100-20/320, interquartile range [IQR]: -13-16 letters) compared with better-seeing patients (inter-arm difference <2 letters; IQR -8-10 letters, respectively). In Year-1, patients received 7-10 injections in trials with as-needed regimens, with no differences evident among drugs. One-year APTC event rates were similar across trials (1.5-4.6% in RIDE/RISE/VIVID/VISTA/Protocol-i/Protocol-T).

**CONCLUSIONS:** Anti-VEGF therapy has been demonstrated to effectively treat DME across clinical trials. While BCVA gains correlated with baseline BCVA in earlier trials, this ceiling effect appears to be confounded by Protocol-T. Among patients with poor baseline BCVA, vision gains between identical treatment arms can vary by >1 line. APTC safety was similar across trials.
Randomized Trial of Prompt Panretinal Photocoagulation vs. Ranibizumab and Deferred Panretinal Photocoagulation for Proliferative Diabetic Retinopathy

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PURPOSE: To determine if visual acuity outcomes at 2 years in eyes with proliferative diabetic retinopathy that receive intravitreous ranibizumab with deferred panretinal photocoagulation (PRP), if needed, are non-inferior to those in eyes that receive standard prompt PRP therapy.

METHODS: At 56 sites in the Diabetic Retinopathy Clinical Research Network (DRCR.net), 394 eyes of 305 adults with proliferative diabetic retinopathy and no prior PRP were assigned randomly to prompt PRP or a standardized treatment protocol of 0.5-mg intravitreous ranibizumab with deferred PRP if needed. Eligible eyes had visual acuity approximately equivalent to Snellen of 20/320 or better. Eyes with or without diabetic macular edema could be eligible, but could not have had intravitreous anti-vascular endothelial growth factor within 2 months or intravitreous or peribulbar steroids within 4 months of enrollment. Follow-up visits occurred every 4 weeks to 16 weeks depending on treatment group and treatment course.

RESULTS: The primary outcome of this non-inferiority study was change in visual acuity at 2 years. The secondary outcomes evaluate proportion of eyes in the deferred PRP group requiring PRP treatment, changes in Humphrey visual field, NEI VFQ-25 assessment, need for supplemental PRP after completion of initial PRP, need for vitrectomy, and frequency of vitreous hemorrhage. The results of this clinical trial will be presented; however because of the potential public health impact of these results, the DCRR.net requests that the results be presented only after the 2-year primary manuscript is published, which is expected to occur prior to the 2015 Retina Society Annual Meeting.

CONCLUSIONS: Conclusions will follow from the results presented.
Pan-Retinal Photocoagulation for Diabetic Retinopathy: One and Done?

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PURPOSE: Although pan-retinal photocoagulation (PRP) is the standard of care for proliferative diabetic retinopathy, it may be associated with reduced visual field, iatrogenic macular edema, and vitreous hemorrhage. This analysis explores the impact of prior PRP laser and ranibizumab treatment on the need for additional PRP and on new proliferative events in diabetic retinopathy (DR) patients with diabetic macular edema (DME) in RIDE/RISE.

METHODS: RIDE/RISE were 2 parallel, randomized, 3-year core phase III trials that evaluated intravitreal ranibizumab in DR patients with DME. Prior PRP was permitted if given at least 3 months prior to screening. Patients were randomized to monthly ranibizumab 0.3 mg (n=250), ranibizumab 0.5 mg (n=252), or sham injections (n=257) for 24 months. At month 24, sham-treated patients crossed over to monthly ranibizumab 0.5 mg. Patients could receive PRP during the study when clinically indicated per investigator discretion and protocol guidelines.

RESULTS: Of 759 patients enrolled in RIDE/RISE, 61 (24.4%), 64 (25.4%), and 57 (22.2%) patients in the ranibizumab 0.3 mg, ranibizumab 0.5 mg, and sham arms, respectively, received PRP prior to the study. Over 36 months of the core studies, patients in the ranibizumab arms required less PRP than those in the sham/crossover arm (4 [1.6%), 6 [2.4%], and 34 [13.2%] patients in the ranibizumab 0.3 mg, ranibizumab 0.5 mg, and sham/crossover arms, respectively, received PRP). Almost twice as many patients in the sham/crossover arm with prior PRP received additional PRP during the study compared with those without prior PRP at baseline (21.1% vs 11.0%, respectively); <5% of ranibizumab-treated patients received PRP during the study (in patients with or without prior PRP, respectively: 1.6% vs 1.6% in 0.3 mg arm; 4.7% vs 1.6% in 0.5 mg arm). In patients with prior PRP, ranibizumab delayed the time to a new proliferative event over 36 months.

CONCLUSIONS: 21% of patients with prior PRP in the sham/crossover arm received additional PRP during the first three years of RIDE/RISE in contrast to 2-5% of patients with prior PRP in the ranibizumab arms.
Assessment of Macular Circulation with Retinal Vasculitis Using Optical Coherence Tomography (OCT) Angiography

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PURPOSE: A feature of OCT angiography is its ability to provide a quantitative estimate of retinal blood flow by calculating vessel density. This study examines the macular blood flow, as measured by OCT angiography, in eyes with angiographically active retinal vasculitis compared to normal eyes.

METHODS: Adult patients with retinal vasculitis were imaged with fluorescein angiography (FA) and OCT angiography with commercially available 70 kHz OCT using the split-spectrum amplitude decorrelation angiography algorithm (SSADA). A 3 x 3 mm angiogram centered at the fovea was obtained by projecting the flow signal internal to the retinal pigment epithelium in the en face orientation. Parafoveal vessel density was defined as percentage of pixels with detectable flow signal in a 1mm ring surrounding the fovea (Fig. 1A). The choriocapillaris vessel density was calculated as a percentage of pixels with detectable flow signal within 10 microns external to the RP in the 3x3mm area.

RESULTS: Five patients (7 eyes) with angiographically active retinal vasculitis were included in the study. Their diagnoses included lupus retinal vasculitis with choroiditis, Bechet’s disease, TINU with retinal vasculitis, sarcoidosis, and idiopathic retinal vasculitis. Data from 11 normal eyes were drawn from a previously compiled database. The average vessel density in normal eyes, in a 1mm wide parafoveal ring (Figure 1A), was 87.1% (95% CI 83.9-90.2). In eyes with retinal vasculitis, the average parafoveal vessel density (Figure 1B) was significantly lower, at 79.8% (95% CI 76.3-83.4, p=0.006). We also imaged choroidal blood flow in the patient with lupus vasculitis and choroiditis. The choriocapillaris vessel densities were 83.3% and 83.6% in the right and left eyes, respectively, compared to 96.3% (95%CI 94.0%-98.5%) in normal eyes (n=7).

CONCLUSIONS: Patients with retinal vasculitis have significantly lower parafoveal vessel density compared to normal eyes, as measured by OCT angiography. Lower parafoveal vessel density was noted even in patients who had only peripheral vasculitis on FA. This technique shows promise as a possible biomarker for determining disease activity, and gauging treatment response in patients with retinal vasculitis.
Ultra-High Speed Swept Source Optical Coherence Tomography Angiography Compared with Fluorescein Angiography in Diabetic Retinopathy

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PURPOSE: To evaluate the clinical utility of optical coherence tomography angiography (OCTA) using a prototype ultra-high speed, swept source OCT (SS-OCT) device and compare it with intravenous fluorescein angiography (FA) for analysis of the retinal microvasculature in diabetic retinopathy.

METHODS: This prospective, observational cross-sectional study evaluates a series of diabetic eyes and normal controls with a prototype ultra-high speed SS-OCT system operating at a 1060 nm wavelength and 400,000 A scans per second imaging speed. Stage of diabetic retinopathy was determined by clinical examination. Imaging was performed using the angiographic 3x3mm and 6x6mm SS-OCT scan patterns to generate enface OCT angiograms for each eye. Two masked Boston Image Reading Center (BIRC) trained readers reviewed FA and OCTA images independently to identify microaneurysms, vascular loops, and capillary dropout. Size of the foveal avascular zone (FAZ) and the perifoveal intercapillary area on OCTA were measured in both normal and diabetic eyes.

RESULTS: Forty-three diabetic and 11 normal eyes were evaluated with OCTA, and FA was performed in 17 of 43 diabetic eyes within 8 weeks of the OCTA. OCTA was able to identify a majority of microaneurysms noted on FA, with the added benefit of localizing their exact intraretinal depth. OCTA also revealed retinal vascular abnormalities such as retinal non-perfusion, reduced capillary density, and increased vascular tortuosity and microaneurysms, some of which were not detected on FA. Both the FAZ and perifoveal intercapillary area as measured by OCTA were enlarged in diabetic eyes when compared to normal control eyes (p<0.0001).

CONCLUSIONS: OCTA using an ultra-high speed SS-OCT prototype enables a non-invasive visualization of macular microvascular pathology in eyes with diabetic retinopathy. It can detect a majority of microaneurysms seen on FA, and can also delineate other areas of retinal vascular abnormalities that are not evident on FA. OCTA is also able to more easily delineate the FAZ and perifoveal intercapillary area in comparison to FA. In the future, OCTA may be of clinical utility in the evaluation of diabetic eye disease.
Quantitative Retinal Vascular Perfusion Density Mapping of Diabetic and Normal Subjects Utilizing Optical Coherence Tomography Angiography

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PURPOSE: To describe a new quantitative graphic mapping technique for analyzing and displaying retinal vascular perfusion density utilizing Optical Coherence Tomography Angiography and to demonstrate its ability to discriminate and grade progressive changes in diabetic retinopathy patients compared to normal subjects.

METHODS: Diabetic patients and normal subjects were imaged using a 70 kilohertz SD-OCT system to obtain OCT volumetric images of the macula (3mm x 3mm and 6mm x 6mm). A prototype analysis software was applied to split-spectrum amplitudinal decorrelation angiography (SSADA) images to measure pixel density and color-coded retinal perfusion density maps were generated. Average perfusion density values were compared to clinical stages based on fundus features to evaluate the ability of perfusion density to quantitatively discriminate levels of retinopathy progression.

RESULTS: Eighteen eyes of 10 subjects with nonproliferative diabetic retinopathy, 18 eyes of 9 subjects with proliferative diabetic retinopathy, and 8 eyes of 4 control subjects were imaged. The average perfusion density for the control group was 0.2477 ± 0.0639 (3x3) and 0.2702 ± 0.1006 (6x6), while the average perfusion density for the NPDR group was significantly reduced at 0.2012 ± 0.0694 (3x3) and 0.2474 ± 0.1048 (6x6). The PDR group appeared further reduced at 0.1944 ± 0.0692 (3x3) and 0.2402 ± 0.1047 (6x6). Choroidal perfusion density was significantly reduced in all diseased groups.

CONCLUSIONS: Color-graded perfusion density mapping based upon OCT angiography provides an easily interpretable quantitative picture of retinal vascularity which may be useful for staging diabetic retinopathy. This technique may provide clinicians with a more consistent approach to charting progression of retinal vasculopathy allowing them anticipate the necessity or more aggressive interventions prior to catastrophic visual loss.
En-face Adaptive Optics Optical Coherence Tomography (AO-OCT)

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**PURPOSE:** Adaptive optics (AO) is an essential technology to visualize cellular structures in the human retina. However, only the combination of AO with optical coherence tomography (OCT) provides high isotropic resolution in all 3 dimensions.

**METHODS:** In order to minimize the influence of motion a transverse scanning OCT/scanning laser ophthalmoscope (SLO) instrument is used. For SLO, a resonant scanner at 8kHz (16kHz line rate) and a 20 to 40 Hz frame rate a 3 to 6 seconds recording time is used. The OCT instrument is equipped with an active axial eye tracking at ~1kHz and a dynamic focus scheme which allows the visualization of nearly motion artifact free 3D volumes of the retina with an axial (cellular) resolution of 5.2µm in tissue.

**RESULTS:** A pixel to pixel correspondence between SLO and OCT allows integration of axial and transversal resolution. Focal planes such as ELM, inner/outer photoreceptor segment (IS/OS) layers, photoreceptor end tips and the retinal pigment epithelium (RPE) can be visualized with cellular resolution. Co-registration of rods and cones in combined maps are obtained. In cone imaging inner and outer segments and individual intersegment patterns due to disease are identified. The dynamic focus of the transversal scan mode presents all retinal layers with identical accuracy and simultaneously. Dye-free vascular imaging at high resolution visualizes vessel calibers as well as flow characteristics by detection of individual erythrocytes.

**CONCLUSIONS:** AO-SLO/OCT is capable to visualize the 3D architecture of photoreceptors including foveal cones and perifoveal rods. Depth-resolution of transversal AO-OCT allows differentiation between end tips of rods and cones. Vascular imaging detects flow and structure with improved contrast of individual erythrocytes.
Outer Retinal Analysis with Automated Ellipsoid Zone Mapping and Layer-based Volumetric Assessment

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PURPOSE: The integrity of the outer retina, in particular the ellipsoid zone (EZ), has been described as a key component for visual outcomes in various retinal diseases. Objective metrics for assessment of the EZ remain limited. The purpose of this study was to evaluate a novel analysis tool for EZ mapping with en face visualization and volumetric layer-based assessment in both normal eyes and eyes with pathology.

METHODS: IRB-approval was obtained. An automated OCT mapping tool was developed for segmenting the EZ and additional retinal layers, providing linear, area, and volumetric measurements, as well as en face visualization of relative thicknesses. In addition to normal controls, OCT scans in eyes with age-related macular degeneration with geographic atrophy and hydroxychloroquine toxicity. Dynamic assessment of EZ status following therapeutic interventions, such as following ocriplasmin injection and intraoperative dynamics following membrane peeling, were also evaluated.

RESULTS: Normal eyes (n = 13) exhibited smooth EZ maps without disruption or focal thinning or elevation. Hydroxychloroquine eyes (n = 3) exhibited concentric thinning with foveal sparing on the EZ map. Eyes with geographic atrophy (n = 8) revealed focal areas of thinning or EZ absence in areas correlating with geographic atrophy. In the dynamic assessment, eyes treated with ocriplasmin (n = 13) showed variable attenuation in the EZ that, when present, was diffuse throughout the macular area. The transient nature of the effect was able to be demonstrated with longitudinal EZ mapping. Following membrane peeling (n = 3), intraoperative OCT assessment, with EZ mapping demonstrated an increase in EZ-RPE height and area that were well-represented in the en face visualization.

CONCLUSIONS: In this study, automated EZ mapping provides in-depth visualization of alterations in retinal architecture with both en face and volumetric assessments. This technology provides a unique opportunity for assessing disease burden and longitudinal EZ dynamics. This analysis tool was able to be utilized in multiple disease conditions and provided rich visual feedback on the status of the relative retinal layer relationships. This tool may be useful for evaluating additional retinal diseases and improving our understanding of the status of the EZ in retinal pathologies.
Posterior Chamber Imaging via Real Time, High Resolution Ultrasound for the Vitreoretinal Clinician

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PURPOSE: Real time imaging is critical to all diagnostic B-scan imaging, recent improvements in technique, hardware and software for high resolution anterior ultrasound provide invaluable diagnostic information for the posterior segment surgeon. Simplified methodology with movie segment capture permit surgeon controlled review of the Posterior Chamber-pars plana area. Relevant cases will demonstrate this expanded technology.

METHODS: High Resolution, Real time B-scan Images are created utilizing a hand held 40 MHz transducer equipped with a water-filled, sterile transducer cover. Topical anesthesia and lubricant gel provide direct contact of the compliant, soft water bag enclosing the sector scan high resolution transducer. Axial, radial and coronal real time images of the anterior segment are reviewed and captured. Bench measurement of resolution is 23 X 35 microns.

RESULTS: Real Time, High Resolution ultrasound imaging of the posterior chamber is extremely useful to the vitreoretinal clinician prior to possible surgical intervention. Diagnostic information in movie segment format provides additional understanding of pathologic anatomy in this usually “non-visible” but critical area. Coupled with posterior segment ultrasound, high resolution anterior real time B-scan expands the surgeons knowledge often changing surgical approach.

CONCLUSIONS: Improvements in technique, hardware and software make real time, anterior segment, high resolution ultrasound easily available to the vitreoretinal surgeon. Posterior chamber pathology can be imaged and evaluated prior to surgery.
Ultra-Wide Field Spectral Domain Optical Coherence Tomography of the Retinal Periphery

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PURPOSE: To describe the Spectral-Domain OCT features of peripheral retinal pathologies using an Ultra-Wide Field (UWF) steering technique to image the retinal periphery.

METHODS: Observational study of 11 patients (11 eyes) with various peripheral retinal pathologies including: senile retinoschisis, retinal tear, retinal detachment, retinal tuft, ora seratta pearl, cobblestone degeneration, ora tooth, peripheral cystoid degeneration, retinal hole, vortex vein and dark without pressure. The area of peripheral pathology was examined using a steering approach with an SD-OCT machine and an Ultra-wide field scanning laser ophthalmoscope. Near Infrared (NIR) SLO-images were registered to the Ultra-wide field color photograph.

RESULTS: Using SD-OCT the anatomic features of all pathologies were clearly visible. Examination of dark without pressure revealed an abrupt transition zone from of the ellipsoid zone (EZ) and cone outer segment tips (COST) line, from normal reflectivity to hyporeflectivity. Peripheral reticular cystoid degeneration was found to possess numerous inter-connecting inner retinal channels/elongated cystic spaces with underlying thin outer retina. Similar features were observed in the retina adjacent to the ora serrata pearl, which also contained an internal inner retinal cystic cavity. Cobblestone degeneration featured the absence of RPE with an intact Bruch’s membrane and overlying atrophic retina. Detached free-floating retina secondary to a retinal tear revealed intact laminar architecture of all retinal layers. Many of the peripheral retinal pathologies such as senile retinoschisis, cobblestone degeneration, ora seratta pearl, peripheral cystoid degeneration and retinal tuft, demonstrated varying degrees of intraretinal cystic changes and internal separation of retinal layers (schisis cavities). Vitreous adhesion was visible in all pathologies with traction observed in several conditions, including retinal hole, senile retinoschisis and retinal tuft. The vitreous adhesion was observed to be in a sunburst pattern on focal pathologies such as the ora seratta pearl, retinal tuft and retinal hole. Finally, enhanced depth imaging (EDI SD-OCT) of a vortex vein revealed dilated hyporeflective tubular structures within the choroid.

CONCLUSIONS: Ultra-wide field SD-OCT provides detailed anatomical information of the peripheral retina and peripheral retinal pathologies not previously imaged. This technique may expand our understanding of these conditions and their clinical significance in routine practice.
Non-diabetic Ocular Abnormalities Detected by Telemedicine Diabetic Retinopathy Assessment Technology in Safety-net Medical Clinics

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PURPOSE: Telemedicine applications have emerged as an effective adjunct strategy to screen patients with diabetes for diabetic retinopathy (DR). In particular, this technology has great public health potential for underserved and minority populations with a low utilization of traditional eye care services. The purpose of this study is to evaluate the utility of a telemedicine DR assessment program to identify nondiabetic eye disease in primary care safety-net medical clinics.

METHODS: Patients with diabetes who presented to one of 8 primary care Federally Qualified Health Centers serving minority and underserved populations were invited for DR surveillance. A telemedicine platform was utilized with a non-mydriatic retinal camera to acquire fundus images and a remote telemedicine reading center to evaluate the retinal images. In addition to evaluation for DR, the images were reviewed for non-DR pathology. The percentage of participants with abnormalities other than DR requiring referral for ophthalmic evaluation was assessed.

RESULTS: From June 2013 to March 2015, a total of 37,090 patients with diabetes were imaged. Non-DR pathology was present in 7,694 (21%) subjects. Abnormalities included retinal vein occlusion (n=74), findings suspicious for exudative age-related macular degeneration (n=28), nonexudative age-related macular degeneration (n=635), findings suspicious for hypertensive retinopathy (n=2,113), epiretinal membrane (n=660), macular hole (n=30), findings suggestive of glaucoma (n=3,291) and cataract (n=863). Any diabetic retinopathy and markers for macular edema were identified in 22,682 (61%) and 3,981 (11%) respectively.

CONCLUSIONS: The percentage of underserved and minority populations with diabetes compliant with recommended annual eye examinations for DR is low. Telemedicine DR assessment programs deployed in medical safety-net settings are an effective screening strategy to evaluate large populations of patients with diabetes. In this study, nondiabetic eye disease was detected at a relatively high rate in approximately 1 in 5 persons screened in safety-net medical clinics. This indicates a possible significant collateral role for telemedicine technology in identifying potentially sight-threatening nondiabetic eye diseases such as glaucoma, macular degeneration and cataracts, which are amenable to vision-preserving treatments if diagnosed and treated in a timely manner.
Telemedicine for Retinal Disease

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PURPOSE: This paper will outline the current state of telemedicine for retinal disease in the United States.

METHODS: A series of validations studies for retinal telemedicine systems for diabetes retinopathy of prematurity and E consults will be presented. In addition, how a telemedicine system is built with hard and software components. Regulatory and licensing issues will be discussed.

RESULTS: Examples of current systems with the pros and cons of these systems and a work-flow sheet for establishing a telemedicine system will be presented given current regulations.

CONCLUSIONS: The future of monitoring disease especially retinal disease can be done remotely as populations’ age and numbers needed monitoring increase. We must know how to effectively use telemedicine for retinal disease.
FDA Regulation of Ophthalmic Medical Devices

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PURPOSE: The past several years have witnessed a dramatic increase in medical device technology applied to medical and surgical retinal diseases. The number of FDA device applications related to retinal diseases has increased. The purpose of this presentation is to add clarity to the FDA medical device approval process for ophthalmic products, with a focus on retina.

METHODS: The presenter has served as the principal clinical reviewer for retina-related device applications since 2007 and will present an overview of that experience. To preserve confidentiality, unapproved products not in the public domain will not be specifically named, but pertinent examples of approval issues will be discussed, as will products in the public domain.

RESULTS: Several hundred device related reviews were performed over several years, within different contexts including pre-IDE, IDE, adverse event report, interim/annual report, labeling amendment, 510 (k), PMA, HDE, and Panel meeting.

CONCLUSIONS: Retinal physicians and surgeons play a critical role in bring new retinal devices to market, collaborating with industry at every stage, from development to clinical trials validation to regulatory approval and post approval surveillance. An understanding of the FDA device approval process will facilitate that role, to the ultimate benefit of patients.
Familial Exudative Vitreoretinopathy: Microstructural Phenotyping of the Vitreoretinal Interface, Retina, and Choroid with Functional Correlations

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PURPOSE: In vivo microstructural analysis of familial exudative vitreoretinopathy (FEVR) has been largely unexplored. We present new anatomic features of FEVR with functional associations.

METHODS: We identified 294 patients with FEVR examined from 2009 - 2014. Those imaged with spectral-domain optical coherence tomography (SD-OCT) with or without enhanced depth imaging (EDI) were included, and images were correlated with best-corrected visual acuity (BCVA), widefield angiography, fundus autofluorescence, and Wnt signaling pathway mutations.

RESULTS: A total of 209 imaging sessions were acquired in 65 eyes from 36 patients. Mean age was 19.3 years. Fifty-nine (91%) eyes had interpretable images, of which 45 (76%) had anomalous structural findings. A broad spectrum of features was identified: vitreous hemorrhage, dysgenic posterior vitreous, posterior hyaloidal organization, subhyaloid hemorrhage, vitreomacular traction, vitreo-papillary traction, vitreo-fold traction, vitreo-laser scar adhesion, persistent foveal inner retinal layers, retinal atrophy, macular edema, intraretinal exudates, dry or edematous radial folds, patchy or broad disruption of the ellipsoid zone and external limiting membrane (ELM), subretinal fluid, and subfoveal lipid aggregation.

Mean foveal thickness was 317 ± 155 um, mean central macular thickness (CMT) was 348 ± 169 um, and mean subfoveal choroidal thickness was 229 ± 64 um, in stages 1 to 3. Greater foveal thickness and CMT (Rho = 0.519, 0.577, respectively; both P < 0.001) correlated with poorer BCVA, but not choroidal thickness (Rho = 0.027; P = 0.897). Univariate regression demonstrated that macular edema (P < 0.001), disruption of the ellipsoid zone and ELM (P < 0.001), exudation (P = 0.001), vitreomacular traction (P < 0.001), and stage (P < 0.001) were associated with poorer BCVA. Distribution of the ellipsoid zone and ELM (β = 0.440; P = 0.004) retained significance in the multivariate modeling (R² = 0.610; P < 0.001), and exudation trended towards significance (β = 0.223; P = 0.059). The sensitivities of SD-OCT detecting angiographic macular edema and hypoautofluorescent outer retinal dysfunction were both 100%. Microstructural-genetic associations were not identified.

CONCLUSIONS: SD-OCT and EDI identified dysgenic microstructural anomalies in the majority of FEVR patients, introducing a new dimension in the diagnosis and treatment of vitreoretinal pathologies associated with FEVR.
Proton Beam Irradiation of Uveal Melanomas—The First Forty Years

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PURPOSE: Proton beam radiotherapy (PBRT) was first used to treat uveal melanomas (UM) at the Massachusetts Eye and Ear Infirmary (MEEI) in 1975. Proton irradiation has highly localized and uniform dose distributions, which may optimize local control and minimize complications. As a result, large tumors and tumors located in close proximity to the optic nerve and fovea can be treated with less visual loss. A large uveal melanoma registry was established at the MEEI to evaluate the efficacy and safety of PBRT. Today, research efforts continue with the goal of improving functional outcomes and survival in these patients.

METHODS: Close to 4000 patients have been treated with proton therapy for uveal melanoma through a collaborative effort of the department of Radiation Oncology at Massachusetts General Hospital and the Retina Service of MEEI. Outcomes of interest include tumor recurrence and melanoma metastasis as well as functional outcomes such as visual acuity, and radiation-induced complications. Cumulative rates of each outcome are calculated using the Kaplan-Meier method, and Cox proportional hazards regression is used to evaluate risk factors associated with these events. Subgroup analyses are completed for patients with tumors located near critical structures, to more closely determine outcomes after treatment.

RESULTS: Local recurrence develops in 3% of cases. The five year rate of vision retention (20/200 or better) is 48% and by 15 years after treatment 29% of patients maintain this level of visual acuity. Proximity of the tumor to the optic disc and macula and tumor size (height and largest tumor diameter) are the strongest predictors of vision loss. Eye loss occurs in less than 10% of cases. Maculopathy and papillopathy are radiation-induced complications contributing to vision loss. Yet, 50% of patients with tumors near the optic disc have visual acuity of counting fingers or better 5 years after PBRT. Overall, 20% of patients die from metastatic melanoma, with the highest annual rates (approximately 4%) observed between 3 and 6 years after diagnosis and treatment.

CONCLUSIONS: These long-term results confirm that proton therapy is very efficacious for the treatment of ocular melanoma. Large tumors and tumors located posteriorly can be successfully treated with protons. However, despite high rates of local control, metastasis can develop, and there are currently no effective treatments for metastatic disease. Presently, there are over 20 centers worldwide, and over 10 proton centers in the United States.
Sustained InTravitreal DexAmetHasone Implant fOr Uveitic Macular Edema: Results from the TAHOE Study.

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PURPOSE: Cystoid macular edema (CME) is the leading cause of visual impairment in eyes with uveitis. It is often difficult to treat and may persist despite adequate control of the uveitis itself. The TAHOE Study is to determine whether a dexamethasone intravitreal (DEX) implant is effective to treat uveitic CME.

METHODS: This is a phase 4, prospective, single arm interventional study. Ten patients with non-infectious uveitic CME were treated with the DEX implant and followed monthly for one year. Re-injections were given with recurrence of CME by spectral domain optical coherence tomography. The primary outcome measure is best corrected visual acuity (BCVA) (using the Early Treatment Diabetic Retinopathy Study protocol) at day 90.

RESULTS: At day 90, the BCVA improved with an average gain of 14 letters (p=0.0008) with DEX treatment. At day 90, 70% (7/10) patients had a >10 letter improvement in BCVA and 50% (5/10) patients had a >15 letter improvement in BCVA. At day 90, there was a decrease in central subfoveal thickness of 140 µm (p=0.003). At day 360, the BCVA improved with an average gain of 19 letters (p=0.0004) with the DEX implant treatment and a decrease in central subfoveal thickness of 172 µm (p=0.0007).

The median time to recurrence of CME after treatment with the DEX implant was 200 days. 60% of the patients required a second injection of the DEX implant during the one year after the initial treatment. At least 1 episode of intraocular pressure > 25 mmHg occurred within one year in 10% of eyes (1/10). 25% (2/8) of patients had worsening of lens opacity requiring cataract extraction.

CONCLUSIONS: The dexamethasone intravitreal implant maybe an effective treatment for patients with uveitic CME. Its therapeutic effects are observed both with visual acuity and retinal thickness at day 90. Patients can maintain excellent visual acuity and anatomical outcomes through 12 months with close monitoring. Further studies comparing the DEX implant with other local steroid therapies for uveitic CME should be pursued.
Sympathetic Ophthalmia: Clinicopathologic Correlation in a Consecutive Case Series

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PURPOSE: To correlate the clinical course of sympathetic ophthalmia with the histological and immunohistochemical characteristics of the enucleated inciting eye.

METHODS: A consecutive case series with baseline clinical features and subsequent histopathologic findings.

RESULTS: Evaluation of the 16 enucleated inciting eyes (blind and painful) disclosed that 9 of the 16 had typical histology, fulfilling the criteria for sympathetic ophthalmia of diffuse granulomatous inflammation. Among the 16, 11 sustained previous penetrating trauma, 4 underwent previous eye surgery, and 1 patient presented with an unknown etiology. Patients with atypical histology (7 of 7) were taking corticosteroids at the time of enucleation. Only 2 of 9 patients with typical histology were taking corticosteroids at the time of enucleation. At 6 months after enucleation of the inciting eye, 4 of the 7 patients with atypical histology had a visual acuity of ≥20/40 compared with 8 of 8 patients (100%) with typical histology. On a 4-point scale (0-3+), the choroidal infiltrate of the 9 histopathologically typical eyes showed an average of 2.5+ CD68 (macrophages), 2.5+ CD20 (B cells), and 1.5+ CD3 (T cells).

CONCLUSIONS: Histopathologic findings had minimal correlation with the clinical course of sympathetic ophthalmia. Corticosteroid treatment before enucleation may influence the pathologic confirmation of sympathetic ophthalmia. The predominance of B lymphocytes and macrophages over T lymphocytes may represent different stages of the disease process.
Treatment of Cytomegalovirus (CMV) Retinitis with Systemic Infusion of Third Party Donor-derived CMV-Specific Cytotoxic T-lymphocytes

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PURPOSE: Cytomegalovirus (CMV) retinitis afflicts immunocompromised patients who are unable to generate an effective T-cell response against the virus. Some patients experience severe vision loss despite maximal systemic and intravitreal therapy. We describe a novel technique of third party donor-derived CMV pp65 cytotoxic T-lymphocytes (CTL) intravenous (IV) infusions for treatment of CMV retinitis.

METHODS: T-cells from 3rd party donor blood samples were isolated and stimulated with autologous dendritic cells loaded with pool of overlapping pentadecapeptides spanning the CMV pp65 protein. For each T-cell line, the specific pp65 peptide eliciting a T-cell response, as well as the HLA allele presenting this epitope, were determined. Patients with CMV retinitis who were resistant to, refractory to, or intolerant of intravitreal/systemic antiviral therapy received 3 weekly IV infusions of 1x10^6 T cells/kg matched with the patient at 2 or more HLA alleles and restricted in their cytotoxicity to CMV pp65 epitopes presented by one of the matched HLA alleles. Data was collected prospectively.

RESULTS: This technique was employed in 3 patients with CMV retinitis. Each patient had a distinct basis for immunosuppression: (1) a leukemic patient status post stem cell transplant; (2) a renal allograft recipient on immunosuppressants for graft rejection; and (3) an AIDS patient with persistently low CD4 count despite anti-retroviral therapy. All three had failed to respond to more than 2 weeks of antiviral drugs. Two patients (1-2) had CMV UL97 or UL54 mutations conferring resistance to antivirals. All three patients exhibited a clinical response to CMV pp65 CTL infusions. One patient (1) developed cystic macular edema after infusions which subsequently cleared. Another patient (3) had cystic macular changes prior to infusions which also cleared. Visual acuity was stable or improved in all 3 cases, with no recurrences over a maximal followup of 18 months. No patients experienced systemic toxicity, exacerbation of graft-versus-host disease, or graft rejection from the CMV pp65 CTLs.

CONCLUSIONS: Third party donor-derived CMV pp65 cytotoxic T-lymphocyte peripheral IV infusions appear efficacious and safe for the long-term treatment of CMV retinitis. These encouraging results warrant further studies for long-term safety, tolerability, and efficacy.
The Impact of Intravitreal Drugs on Rates of Post-intravitreal Injection Endophthalmitis

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PURPOSE: Although rare, endophthalmitis is the most serious ocular complication post intravitreal injection. Previous clusters of endophthalmitis associated with locally compounded bevacizumab have raised concerns at the FDA over the safety of its use for ocular diseases. Steroids have been suggested as one alternative for treating macular edema, yet a comparison between steroids and anti-VEGF agents on rates of endophthalmitis has never been evaluated. The goal of this study is to determine if compounding in a large national sample increases the risk of endophthalmitis post intravitreal injection, and to determine if there is a difference in rates of endophthalmitis after intravitreal steroids vs. anti-VEGF agents.

METHODS: This is a retrospective cohort study using medical claims data from a large, national U.S. insurer. Data were searched for all intravitreal injections (CPT 67028) performed between 2003 and 2012. Cohorts were based on anti-VEGF agents (bevacizumab, ranibizumab, aflibercept and pegaptanib) individually and collectively for comparison to intraocular steroids (triamcinolone and dexamethasone). Cases were defined as having a new endophthalmitis diagnosis (ICD9 360.0x) and either a “tap-and-inject” procedure (CPT67015, 67025), a vitrectomy (67036) or an intravitreal antibiotic injection on the same day, between 1 and 14 days post-injection. Exclusion occurred for any history of endophthalmitis.

RESULTS: Of the 452,762 total injections given to 72,687 patients, 299,000 were bevacizumab and 87,505 were ranibizumab. 50 (rate=0.017%, 1/5980 injections) and 22 (0.025%, 1/3978) cases of endophthalmitis occurred respectively. No significant difference in endophthalmitis rates between the anti-VEGF agents (OR=1.54, 95% CI: 0.93, 2.57; p=0.095) was seen. 390,946 anti-VEGF injections and 18,105 steroid injections were performed which were followed by 74 (0.019%, 1/5283) and 24 (0.13%, 1/754) cases of endophthalmitis respectively. The odds of endophthalmitis were 6.85 (95% CI: 3.75, 12.50; p<0.001) times higher post-steroid injection compared to anti-VEGF injections.

CONCLUSIONS: Nationally, the use of compounded bevacizumab is as safe as ranibizumab with regards to endophthalmitis rates, but intravitreal steroids injections are associated with higher odds of endophthalmitis.
Endophthalmitis After Intravitreal VEGF Inhibitor Injection

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PURPOSE: Review the incidence of endophthalmitis, microbiology, visual presentation, treatment and visual outcome of endophthalmitis after intravitreal injection of VEGF inhibitor over the last 5 years in a single retina group practice.

METHODS: Retrospective review of all newly diagnosed endophthalmitis managed by our group over the past 5 years for cases occurring within 6 weeks after intravitreal VEGF inhibitor injection.

RESULTS: We managed 42 cases of post injection endophthalmitis during the past 5 years. Of 84612 intravitreal injections done by our group there were 22 eyes who developed endophthalmitis, an incidence of 0.0026. The other 20 cases had the inciting injection performed by outside ophthalmologists, and were referred to us once endophthalmitis was diagnosed. The 42 cases represented 1/3 of all cases of endophthalmitis seen by our group. The mean time between inciting injection and diagnosis was 5.3 days. Average follow up was 189 days. Underlying disease for which VEGF inhibitor was administered was AMD in 81%, venous occlusive disease in 7%, and diabetic macular edema in 12%. Cultures were positive in 62% of cases, and of those 65% were coagulase negative staph, 23% were Strep species, 8% S. Aureus. There were no gram negative or fungal cases. Initial treatment was tap & inject in 74%. Mean presenting VA was logMAR 1.92 (CF), and mean final vision logMAR 0.99 (20/200).

CONCLUSIONS: Endophthalmitis after intravitreal injection is a major cause of endophthalmitis, representing about 1/3 of all cases. Organisms are mostly coagulase negative staph, but almost 1/4 of culture positive cases were Strep species. A large proportion of cases were the result of injections done by outside physicians, where the incidence is impossible to calculate as we don't know the total number of injections given by these physicians. In our group, with a fixed injection protocol of betadine, lid speculum, and no talking during injection the incidence of infection was very low.
**Current Endophthalmitis Incidence Rates After Intravitreal Anti-VEGF Injections and Outcomes of Treatment**

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**PURPOSE:** To assess the incidence rates and treatment outcomes of infectious endophthalmitis after intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents.

**METHODS:** Records of patients undergoing intravitreal cultures and antibiotics after anti-VEGF injections from January 1, 2005 through December 31, 2014 at the Bascom Palmer Eye Institute (BPEI) were reviewed. In addition, the 2011-2013 data from the largest commercial Claims and Encounters database in the U.S. (the MarketScan) was utilized to calculate the national population-based endophthalmitis incidence rate.

**RESULTS:** The population based incidence rate after anti-VEGF injections was 391/740,757 (0.053%). The BPEI rate was 20/121,285 (0.016%) during the study period 2005-2014. In the BPEI cases for each anti-VEGF medication, the rates were the following; bevacizumab 8/67,043 (0.012%), ranibizumab 6/33,134 (0.018%) and aflibercept 6/19,103 (0.031%) and pegaptanib 0/2005 (0%). Nine BPEI cases were culture-positive: Streptococcus species(5), coagulase-negative Staphylococcus (3), and Bacillus non-anthracis (1). Final VA varied from 20/25 to NLP. Of the 9 culture positive cases, 5 achieved 20/400 or better but 4 remained light perception or worse. Of the 11 culture negative cases, 9 improved to 20/100 or better (baseline visual acuity), including 7 achieving 20/60 or better. All 6 aflibercept associated cases in the study were culture negative and 5/6 returned to their baseline visual acuity.

**CONCLUSIONS:** The endophthalmitis incidence rates after anti-VEGF injections at BPEI and in the commercial database were low. Treatment outcomes were variable but were generally better in the culture negative cases.
Topical NSAID Does Not Prevent Post-Op Cystoid Macular Edema (CME)

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**PURPOSE:** To investigate the incidence of cystoid macular edema (CME) in patients receiving topical non-steroidal anti-inflammatory drugs (NSAIDs) following cataract surgery.

**METHODS:** Between 2007 and 2014, 117,264 patients had cataract extraction in Kaiser Permanente Southern California. The frequency of CME was determined by the presence of a CME diagnosis in the 90 days postoperative period. Patients with prior vitrectomy or scleral buckle, or a prior diagnosis of macular edema, were excluded. NSAID use was determined by whether the patient filled a prescription for NSAIDs during the 30 days post-operative period.

**RESULTS:** Over 54% of patients were prescribed NSAIDs. The prevalence of CME was 1.7% among those given NSAIDs and 1.4% in those untreated. Compared to the risk among non-Hispanic Whites, the risk of developing CME among non-Hispanic Blacks was 1.46 (95% CI: 1.26, 1.68). After adjusting for age, gender, race, and diabetes status, the relative risk of developing CME among NSAIDs users was 1.19 (95% CI: 1.08, 1.31).

**CONCLUSIONS:** Clinical studies have demonstrated varying results between NSAID use and the risk of CME. Additionally, many studies had small cohorts and short follow-up. In our study of 117,264 patients with 3 months of follow-up, NSAID use did not reduce and might have increased the risk of CME. Physicians should carefully consider the use of post-operative NSAIDs following cataract surgery.
Intravitreal Sirolimus Improves Inflammation and Visual Acuity in Subjects with Non-infectious Uveitis (NIU) of the Posterior Segment: Results from SAKURA Study

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PURPOSE: To determine the efficacy of intravitreal sirolimus, a novel local immunoregulatory therapy, in resolving inflammation and preserving or improving vision in subjects with NIU of the posterior segment.

METHODS: SAKURA Study 1 is a phase 3, double-masked, multinational study in which subjects with active NIU of the posterior segment (baseline vitreous haze [VH] score ≥1.5+ in the study eye) were randomized to receive intravitreal sirolimus 440µg (n=114), 880µg (n=116), or an active control dose of 44µg (n=117). Injections were administered every 2 months. Efficacy was assessed by outcomes including VH and best corrected visual acuity (BCVA) measures at Month 5, with safety assessed through Month 6.

RESULTS: At baseline, the mean VH score was 1.9±0.5, and the median BCVA was 68 ETDRS letters across all 3 dose groups. Efficacy was greatest with the 440µg dose: significantly more subjects achieved the primary endpoint, VH score of 0 without the use of rescue therapy, with 440µg vs the 44µg active control dose (22.8% vs 10.3%; p=.025, adjusted for multiplicity). There was also a higher rate of VH resolution to 0/0.5+ with 440µg vs 44µg (52.6% vs 35.0%; p=.008). BCVA was preserved over the double-masked period: the median BCVA at Month 5 was 75 letters for 440µg vs 71 letters for 44µg. Subjects with worse vision at baseline showed greater visual improvements: the median BCVA improved by 10.5 letters in subjects with baseline BCVA 1% of subjects were ocular inflammation (0.3%-5.2%), cataract (1.7%), increased intraocular pressure (1.2%), and medication residue (transient drug depot in the visual axis; 1.4%). Results with the 880µg dose versus the active control dose of 44µg were not statistically significant.

CONCLUSIONS: Monotherapy with intravitreal sirolimus 440µg significantly improved intraocular inflammation while preserving overall vision in subjects with active NIU of the posterior segment. Improvement in visual acuity was more pronounced in subjects with worse visual acuity at baseline. Intravitreal sirolimus is an effective steroid-sparing alternative to local steroid treatment for NIU.
Intravitreal Bevacizumab (2.5mg) and Aflibercept (2.0mg) as Rescue Therapy for Persistent Post-radiation Cystoid Macular Edema

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**PURPOSE:** To investigate the efficacy of intravitreal aflibercept (2mg) and “double-dose” bevacizumab (2.5mg) as rescue therapy for persistent post-radiation cystoid macular edema (CME) resistant to standard-dose (1.25 mg) bevacizumab (IVB).

**METHODS:** Retrospective, interventional case series. Eyes with post-radiation CME after plaque radiotherapy for uveal melanoma were treated with monthly standard-dose IVB, and if unresponsive, with double-dose IVB. Eyes resistant to the above treatments were then treated with monthly intravitreal aflibercept as rescue therapy. Primary outcomes were change in central macular thickness (CMT) and visual acuity.

**RESULTS:** This study includes 24 eyes of 24 patients with post-radiation CME resistant to a mean of 8 monthly injections of standard-dose IVB. 18/24 eyes (72%) had subclinical macular edema at time of tumor diagnosis. Before radiation, mean tumor basal diameter was 12 mm and mean tumor thickness was 5.8 mm. Mean radiation dose to the macula was 4416 cGy.

All 24 eyes were treated with a mean of 4 monthly injections of double-dose IVB. At a mean of 5 months, mean CMT increased from 430.2 microns (SD 114.3) to 439.4 microns (SD 130.7) (p=0.60) and mean LogMar visual acuity worsened from 0.24 (SD 0.29, Snellen 20/34) to 0.62 (SD 0.34, Snellen 20/80) (p=0.47). Of these eyes, 17/24 (71%) required alternative therapies for persistent CME.

Of the 17 eyes with persistent CME resistant to single and double-dose IVB, five eyes received a mean of 8 monthly injections of intravitreal aflibercept. At a mean of 7 months, mean logMar visual acuity improved from 0.53 (SD 0.15, Snellen 20/70) to 0.35 (SD 0.20, Snellen 20/45) (p=0.05). Mean CMT reduced significantly from 463.4 microns (SD 138.2) to 286.4 microns (SD 71.4) (p=0.038). No patient experienced worsening of CMT or visual acuity while treated with intravitreal aflibercept, and no alternative therapies were necessary. No injection related complication was observed for any patient.

**CONCLUSIONS:** Intravitreal aflibercept is a promising rescue therapy for persistent post-radiation CME in patients with poor response to “standard dose” and “double dose” IVB, with reduction in CMT and improvement in visual acuity. Subclinical macular edema at tumor presentation may help identify patients at risk for persistent CME following plaque radiotherapy.
Exome Sequencing of Primary and Metastatic Uveal Melanoma

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PURPOSE: To improve our understanding of the genetic drivers of uveal melanoma.

METHODS: Tumor samples were obtained from 62 patients with uveal melanoma. Primary tumor samples were from enucleated eye specimens, while metastatic samples were from core biopsies obtained by interventional radiology. We sequenced the exome of 61 primary tumors and 3 liver metastases, each with matched normal DNA. A subset of 52 tumor/normal pairs passed standard quality control metrics, including screening for tumor DNA in normal samples or normal DNA in tumor samples, and were included in the analysis set. Standard methods developed at the Broad were used for data processing and analysis. Targeted resequencing of select mutations was performed using microfluidic PCR. Additionally, the function of mutant EIF1AX was probed using loss of function experiments in melanoma cell lines.

RESULTS: Consistent with prior studies, the majority of uveal melanomas harbored mutually exclusive mutations in GNAQ and GNA11. Co-occurring with GNAQ and GNA11 mutations were inactivating mutations throughout the BAP1 coding region as well as recurrent mutations in the splicing factor SF3B1 and the translation initiation factor EIF1AX. Somatic mutations found only in metastatic tumor samples were also identified.

Functional studies revealed that knockdown of EIF1AX was lethal in both wild type and mutant cells. To identify transcripts regulated by EIF1AX at the level of translation, RNA sequencing of polysome-associated mRNAs was performed. Suppression of wild type, but not mutant EIF1AX expression reduced the efficiency of ribosomal protein translation.

CONCLUSIONS: Uveal melanoma is characterized by recurring mutations in a limited number of genes. EIF1AX is the first translation initiation factor reported as recurrently mutated in cancer. Targeting of protein translation mechanisms may represent a new therapeutic avenue.
Personalized Medicine in Ocular Oncology: The Future is NOW

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PURPOSE: To evaluate the impact of molecular genomic testing on primary and adjunctive therapy for clinical uveal melanoma. Microincisional vitrectomy surgery provided direct tumor access for endolaser ablation, tractional tissue release, fine needle aspiration biopsy and intravitreal triamcinolone acetonide delivery. Fine needle aspiration biopsy was processed for molecular genomics and differential primary treatment was applied for small tumors, while adjunctive screening/treatment strategies were employed for medium/large melanoma tumors.

METHODS: IRB approved, retrospective review of a consecutive case series of patients undergoing fine needle aspiration biopsy for molecular genomics of uveal melanoma. Small tumor patients underwent 23/25 gauge MIVS, membrane peeling, endolaser tumor ablation, 25 gauge multi-pass fine needle aspiration biopsy, and intravitreal steroid. All patients with Class 1 molecular genomics were followed with standard serial screening. Class 2 patients were treated with subsequent 125iodine brachytherapy. All medium/large uveal melanoma patients were treated with 125iodine brachytherapy while Class 1 patients were followed with standard serial screening and Class 2 patients were offered adjunctive systemic therapy AND enhanced metastatic screening. Molecular genomics were standardized using molecular genomic testing through Castle Biosciences including review of all reported results.

RESULTS: One hundred consecutive patients were evaluated. Mean age at entry was 61 years (range 32-87). Mean followup was 24 months (range 12-24). Mean VA was 20/80 (range 20/20-HM). 34 eyes had small tumors, 48 eyes had medium tumors and 18 eyes had large tumors at the time of treatment. For small tumors, 20 eyes were Class 1a, 12 eyes were Class 1b, and 2 eyes were Class 2. For Medium tumors, 18 eyes were Class 1a, 22 were Class 1b and 8 eyes were Class 2. For large tumors, 4 eyes were Class 1a, 6 eyes were Class 1b, and 8 eyes were Class 2. All 34 small tumor patients are alive and well including the 2 Class 2 patients who underwent secondary 125iodine brachytherapy. All Class 1b patients are alive and well for both medium and large tumor patients (22 medium and 6 large). For medium and large melanoma Class 2 patient all medium tumor patients are alive and well while 4/8 large tumor patients have developed metastatic disease (no deaths). Mean followup VA is 20/40 (range 20/20 - 5/200). Radiation retinopathy is present in 92/100 patients and all are undergoing intravitreal pharmacotherapy. Surgical complications included progressive retinal detachment in three patients and persistent macular vascular activity in 26 patients.

CONCLUSIONS: Personalized medicine using molecular genomic screening had identified high risk molecular genomic signatures in 34% of small tumors allowing targeted treatment avoiding radiotherapy in greater than 95% of these patients while allowing early treatment and enhanced followup for highrisk genomic patients. Molecular targeting alters screening followup in over 60% of medium/large tumor eyes AND allows discussion of adjunctive systemic therapy in all Class 2 patients. Complications are associated with fine needle aspiration biopsy and appear acceptable in the spectrum of options to management. At this time, personalized medicine using molecular genomics should be broadly evaluated in the management of uveal melanoma.
A New Look at Tumor Size Classification of Primary Posterior Uveal Melanomas

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PURPOSE: Multiple different tumor size classification systems have been employed by various investigators to categorize primary posterior uveal melanomas into small, medium, large and even extra-large categories over the years. The purpose of this talk will be to explain the different classification systems, comment on the strengths and weaknesses of each system, and propose an alternative approach to size classification.

METHODS: Among the tumor size classification systems that have been used over the years are ones based on the following: (1) largest basal diameter [LBD] of the tumor, (2) maximal thickness [TH] of the tumor, (3) largest linear dimension [LTD] of the tumor; (4) cubic volume [LBD x smallest basal diameter (SBD) x TH] of the tumor; and (5) multiple different LBD x TH categorizations [(a) Warren system, (b) revised Warren system, (c) COMS system, and (d) different TNM systems]. Each of these systems will be explained and illustrated.

RESULTS: Single dimension systems have the advantage of simplicity while systems based on both the basal diameter and thickness of the tumor are substantially more complex to apply. Surprisingly, systems based on cross sectional area or three dimensional volume do not provide significantly better prognostic discrimination than do systems based on single tumor dimensions. The advantages, disadvantages, and inherent weaknesses of the various currently employed size classifications will be addressed.

CONCLUSIONS: An optimal tumor size classification system should be based on measurements that are relatively easy and reproducible to determine, reflect current treatment options, divide tumors into subgroups of similar numbers of cases, and classify a tumor of “average” size into the medium (intermediate) size group but should not have “right angle corners” when plotted as an LBD x TH graph. An alternative tumor size classification system that takes into account these various factors will be presented for discussion.
Intravitreal Dexamethasone for Recalcitrant Cystoid Macular Edema Following Brachytherapy Treatment of Uveal Melanoma

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PURPOSE: To determine the efficacy of intravitreal dexamethasone in the treatment of recalcitrant radiation maculopathy following iodine-125 brachytherapy treatment of uveal melanoma.

METHODS: Consecutive retrospective analysis of patients treated in a University setting between the years of 2010-12 (with minimum of 24 months follow-up).

RESULTS: Fifty-eight patients were diagnosed clinically and echographically with uveal melanoma with a mean base of 12.0 mm and height of 6.5 mm at the time of diagnosis. I-125 brachytherapy, with a mean dosage of 85.5 Gray, was applied over an average of 152 hours. Patients were then followed quarterly for an average of 32.1 months (range 24 – 52 months). Twenty-three patients (40%) developed radiation maculopathy an average of 17.7 months (range 12 – 31 months) post-brachytherapy, correlating with dosage of the radiation and proximity of the tumor to the macula. All patients were initially treated with intravitreal bevacizumab, often times alternating with triamcinolone. Recalcitrant CME remained seven patients, in spite of an average of 16 injections (range of 13-20 injections). These seven patients were switched to intravitreal dexamethasone with resolution of the CME after 1 to 2 injections, and stability for up to one year. Visual results were wide ranging, from 20/25 to 20/400, with five of these seven patients requiring cataract extraction.

CONCLUSIONS: Radiation maculopathy develops quite frequently following I-125 brachytherapy of uveal melanoma. Initial treatment with bevacizumab and/or triamcinolone is variably effective. Recalcitrant CME appears to respond quite readily to intravitreal dexamethasone and perhaps should be considered earlier in the treatment regimen of radiation maculopathy.
Peripheral Retinal Perfusion Status Correlates with Radiation Toxicity Following I-125 Brachytherapy for Uveal Melanoma

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**PURPOSE:** To analyze wide field fluorescein angiography (FA) in patients with uveal melanoma treated with radioactive iodine-125 plaque brachytherapy (PBT).

**METHODS:** Retrospective, consecutive, observational case series of patients with choroidal melanoma treated with PBT with available pre- and post-treatment ultra widefield FA images. Visual acuity, optical coherence tomography (OCT), and FA characteristics were evaluated from baseline to final follow-up. FA images were transformed into standardized projections, and then standardized projections were evaluated for areas of peripheral nonperfusion, which were outlined and saved as binary masks. Area masks were measured by an automated measurement tool to calculate area in mm². Statistical analysis was performed.

**RESULTS:** A total of 65 patients with a mean age of 59 years were included, mean time to final follow-up was 53 months (range, 12.1 to 99.5 months) after PBT. Area of nonperfusion increased from 0 mm² at baseline to 77 mm² at last follow up. There was a statistically significant correlation between greater area of nonperfusion with FA evidence of macular edema at 12 months (P = 0.010) and last follow-up (P = 0.014) after PBT. Greater area of nonperfusion also correlated with OCT evidence of cystoid macular edema at the last follow-up after PBT (P = 0.004). Greater area of nonperfusion correlated with development of radiation retinopathy at 12 months (P = 0.004) and last follow-up (P = 0.041) and last follow-up (P < 0.0001) after PBT. Radiation treatment parameters and impact on perfusion abnormalities will be presented.

**CONCLUSIONS:** Wide field FA is a useful tool to document and quantify the progressive nature of peripheral nonperfusion after PBT in patients with choroidal melanoma. Greater areas of non-perfusion correlate with worsening vision as well as greater rates of macular edema and radiation retinopathy. Targeting the pathophysiology of retinal ischemia may lead to better treatment strategies designed to prevent vision loss.
Does Ophthalmic Artery Chemosurgery Increase the Chance of Orbital Disease, Metastasis or Death in Children with Advanced Intraocular Retinoblastoma?

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PURPOSE: Children with advanced intraocular retinoblastoma are candidates for primary enucleation or ophthalmic artery chemosurgery (OAC). 90% of eyes primarily enucleated just 10 years ago now receive OAC as first line treatment in an attempt to retain the eye with some useful sight. Is the decision to retain and treat the eye increasing the chance of developing either orbital retinoblastoma and/or metastatic retinoblastoma? The purpose of this study is to determine the incidence and timing of orbital retinoblastoma and metastatic retinoblastoma in children treated primarily with OAC at Memorial Sloan Kettering Cancer Center, New York.

METHODS: Retrospective, single Institution IRB approved review of 160 eyes of 147 patients with advanced intraocular retinoblastoma (Reese-Ellsworth Group V or International Classification of Retinoblastoma Group D or E eyes) treated at our Institution with primary enucleation or primary OAC for advanced intraocular retinoblastoma.

RESULTS: Of 86 eyes of 75 patients primarily treated with OAC 1 patient developed orbital retinoblastoma and metastatic disease (and is alive, disease free at 7 years 3 months) and 1 other patient developed metastatic disease (and is alive, disease free at 37 months) without orbital involvement. The incidence of orbital retinoblastoma was 1.2% and metastatic disease 2.7% but no patient died of metastatic retinoblastoma (mean follow-up 37.4 months).

Of similarly staged eyes primarily enucleated 6 (8.3%) developed orbital recurrences and metastases and 2 cases (2.8%) died of metastatic disease. Although the groups were not randomized they were statistically similar in all ways except there were more eyes with rubeosis in the enucleated group but this was not associated with a higher incidence of orbital disease. The 24 month Kaplan Meier estimate for orbital recurrence was significantly worse for the enucleation group with a Log-Rank p value =0.04.

CONCLUSIONS: Children with advanced intraocular retinoblastoma are candidates for primary enucleation or ophthalmic artery chemosurgery. In this single Institution study they had a greater chance of developing orbital disease, metastasis and death in primarily enucleated eyes when compared to eyes primarily treated with OAC. OAC does not increase the chance of developing orbital disease, metastatic retinoblastoma or death from metastatic retinoblastoma. OAC may prevent the development of orbital disease by treating unrecognized sub clinical orbital metastases.
FRIDAY
Interim Safety Outcomes from a Phase 4 Study of Intravitreal Aflibercept Injection (IAI) in Patients with Neovascular Age-related Macular Degeneration

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PURPOSE: To report an interim safety analysis of IAI given every 8 weeks following 3 initial monthly doses for treatment of patients with neovascular age-related macular degeneration (nAMD) in the RE-VIEW study.

METHODS: RE-VIEW is a phase 4, open-label, single arm, multicenter, 100-week study. Patients 50 years of age and older with nAMD and a best-corrected visual acuity (BCVA) of 73 to 24 ETDRS letters in the study eye were eligible if they had no sign of nAMD in the fellow eye. Planned dosing is 2 mg IAI every 8 weeks after 3 monthly doses for 96 weeks. The primary endpoint is the mean BCVA change from baseline at week 100. A planned interim analysis evaluated IAI safety, in particular the change in corneal endothelial cell density (ECD) at week 52. Percentage change in corneal ECD from baseline was assessed by specular microscopy comparing the treated study eye with the untreated fellow eye.

RESULTS: RE-VIEW enrolled and treated 154 patients; 64.9% of patients were ≥75 years old. Patients received a mean (SD) of 7.7 (1.2) IAI injections from baseline through week 52. The mean corneal ECD decreased by 0.2% and 0.3% (P=0.8715) from baseline in the study eye and untreated fellow eye at week 52, respectively, a decrease within the limit of the expected age-related decrease of 0.6%/year. Pre-injection intraocular pressure in the study eye remained unchanged from baseline with a mean change of -0.1 mm Hg at week 52. Serious ocular adverse events occurred in 4 (2.6%) patients during the study. Anti-Platelet Trialists’ Collaboration-defined arterial thromboembolic events occurred in 4 (2.6%) patients from baseline to week 52. The mean BCVA gain from baseline was 5.9 letters at week 52. The mean reduction in central retinal thickness was 169.6 mm, and 53.0% of patients had dry retina at week 52 as evaluated by spectral domain optical coherence tomography.

CONCLUSIONS: This planned interim safety analysis indicates that IAI had a similar safety profile as observed in prior IAI nAMD studies with no effect on corneal ECD at week 52. IAI improved visual and anatomic outcomes in this patient population.
Evaluation of Long-term Treatment with Intravitreal Aflibercept Injection (IAI) in Patients Completing the VIEW 1 and VIEW Extension Studies: One-year Results of the RANGE Study

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PURPOSE: To evaluate the efficacy and safety of long-term treatment with IAI for neovascular age-related macular degeneration (AMD) in patients previously treated in the VIEW 1 study and subsequently in the VIEW extension study.

METHODS: A prospective, open-label, multi-center, nonrandomized study at 5 sites enrolled patients who had successfully completed follow-up in the VIEW 1 study and, subsequently in the VIEW extension study. All patients received mandatory IAI at baseline and week 8, and then were followed utilizing a treat and extend protocol with pre-specified retreatment criteria. The maximum interval between treatments was 12 weeks, but IAI could be administered as frequently as every 4 weeks. Patients were treated at all study visits. The primary outcome variable at week 52 was the proportion of patients that maintained vision defined as loss of ≤5 ETDRS letters from baseline.

RESULTS: A total of 37 patients were enrolled; 35 (94.5%) patients completed the primary outcome visit at week 52. The mean number of IAI treatments through week 52 was 7.9 with a mean treatment interval of 59 days. Mean baseline ETDRS BCVA was 61.5 letters (20/63) and 30 (85.7%) patients maintained vision (loss of <5 letters from baseline) at week 52. 23 patients (67%) maintained visual acuity of 20/70 or better. At baseline, the mean central retinal thickness as measured by a SD-OCT was 216 microns, which was maintained through week 52. There were no ocular serious adverse events associated with IAI during this study. One patient required aortic valve replacement but remained in the study. Two patients withdrew consent due to worsening hypoxia and dementia.

CONCLUSIONS: Following long-term treatment with anti-VEGF agents for AMD, maintenance therapy utilizing a treat and extend approach with IAI was safe and effective in maintaining visual acuity for an additional year. Continued follow-up of these patients through 2 years will give additional insight into the efficacy and safety of longer term treatment with IAI.
Understanding Geographic Atrophy Disease Progression Through Visual Function Endpoints: The Lampalizumab Clinical Trial Program

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PURPOSE: Geographic atrophy (GA) is an advanced form of AMD characterized by RPE/photoreceptor degeneration and progressive, irreversible vision loss. Although the fovea is rarely atrophic in early GA, patients often report visual dysfunction that is not reflected in BCVA measurement. Visual function endpoints that may better capture the visual dysfunction versus standard, high-contrast, black-on-white ETDRS chart letters will be evaluated.

METHODS: Chroma (NCT02247479) and Spectri (NCT02247531) are 2 identically-designed, double-masked, randomized, international, phase 3 (ph3) trials evaluating the efficacy and safety of intravitreal lampalizumab 10 mg administered every 4 or 6 weeks versus sham injections in approximately 1870 patients with bilateral GA secondary to AMD. Each treatment group will include both complement factor I (CFI) genetic biomarker-positive and CFI-negative patients. Proxima A and B are two separate, parallel, prospective, observational studies with a combined enrollment target of 560 patients globally. Proxima A will include patients with inclusion criteria similar to the ph3 population, and Proxima B will include patients with GA phenotypes different from the ph3 population.

RESULTS: The primary efficacy endpoint in Chroma and Spectri is defined as the mean change in GA lesion area of the study eye from baseline at 1 year, as measured by fundus autofluorescence. Secondary endpoints will evaluate the effect of lampalizumab versus sham on visual function, vision-related patient-reported outcomes at 2 years, and both high-contrast best-corrected and low-luminance VA. The relationship between GA lesion progression and visual function changes will also be evaluated in the Proxima study program; patients will be followed every 6 months, with imaging and functional assessments similar to the ph3 studies. The prognostic nature of the CFI genetic biomarker will also be investigated further.

CONCLUSIONS: The lampalizumab clinical trial program includes 4 studies and will enroll more than 2400 GA patients. Collectively, Chroma, Spectri, and Proxima will provide additional information on the efficacy and safety of lampalizumab in reducing GA lesion progression, comprehensively assess visual function using tools that may better demonstrate the impact of GA on patients as compared with typical BCVA, and collect natural history data on visual function changes in a broad population of GA patients.
**Systemic Treatment of Dry Age-related Macular Degeneration with Sildenafil**

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**PURPOSE:** We have shown that dry age-related macular degeneration (AMD) is significantly related to choroidal ischemia. Additionally, we have shown that sildenafil increases choroidal perfusion and a small off-label series of patients on long-term sildenafil showed positive visual effects and no long-term adverse effects. The purpose of this study is to evaluate the use of systemic sildenafil to treat dry age-related macular degeneration.

**METHODS:** In an IRB (Institutional Review Board) approved study, patients with dry AMD are treated with systemic sildenafil, 20 mg twice daily. Vision, contrast sensitivity testing, and OCT mapping of the macula is performed every 2 months. Choroidal perfusion is measured with high frequency ultrasound before starting sildenafil and at 2 and 12 months after starting sildenafil.

**RESULTS:** Early results with PED (pigment epithelial detachment) elevations show evidence of sub PED-absorption on OCT, improved contrast sensitivity, and maintenance of vision. Perfusion measurements at 2 months showed an increase in choroidal perfusion.

**CONCLUSIONS:** Systemic PDE-5 inhibitors such as sildenafil may have a positive benefit in treating dry age-related macular degeneration. A larger study including other types of AMD appears warranted.
Predictors of Response to Intravitreal Anti-vascular Endothelial Growth Factor Treatment of Age-related Macular Degeneration

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PURPOSE: To identify genetic and environmental factors that influence response to treatment with intravitreal anti-vascular endothelial growth factor (anti-VEGF) medication for neovascular age-related macular degeneration (nAMD).

METHODS: A retrospective chart review of 72 patients previously enrolled in genetic and epidemiologic studies of AMD and treated at a single institution with either bevacizumab or ranibizumab for nAMD was conducted. Best corrected Snellen visual acuity (VA) and central foveal thickness (CFT) on OCT were recorded for each treatment visit and each post-treatment follow up visit, including 6 and 12 month visits. Demographic, lifestyle, and genotype information including all known AMD genes to date were examined, and a CFH risk score including 3 loci was calculated. Primary outcome measures were change in VA and OCT-CFT from baseline to 12 months.

RESULTS: Greater improvement in VA was associated with low-risk CFH genotypes. The CFH Y402H and CFH rs1061147 non-risk genotypes were both associated with improved VA (p-values assessing differences in slope estimates according to genotype =0.026 and 0.028, respectively). A low CFH risk score was associated with improvement in VA after anti-VEGF treatment (p=0.019), while a high risk score was not (p=0.77). The difference in outcome between the low and high risk CFH groups was statistically significant (p=0.037). Improvement in VA for non-risk genotypes was suggested for several other genes: ABCA1, CETP, COL8A1, COL10A1, ARMS2/HTRA1, DDR1, and ADAMTS9/ADAMTS9-AS2, although there were no significant differences in outcome between non-risk and risk genotypes. Younger age groups and males trended toward improved VA, but the p-values were not statistically significant. Also, all categories for each demographic, behavioral, and genetic covariate were significantly associated with improvement in OCT-CFT, and a low CFH risk score was significantly associated with a greater reduction in OCT-CFT (p for comparing low and high CFH risk groups=0.041).

CONCLUSIONS: There is an independent, statistically significant association between fewer high-risk alleles in the CFH gene and better VA and OCT-CFT outcomes after anti-VEGF treatment for nAMD. Further investigation may lead to the development of a clinically relevant prognostic risk score.
Evidence Implicating Role of Circulating MicroRNAs in Resistance to Anti-VEGF Therapy in Exudative Age-related Macular Degeneration

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PURPOSE: To identify microRNA (miRNA) biomarkers that are involved in resistance to antiVEGF therapy for exudative AMD.

METHODS: Serum samples of 47 patients from 5 separate groups were collected from patients seen at UC Davis Department of Ophthalmology. Group 1: 10 age-matched normals with no ocular or systemic disease. Group 2: 10 patients with new onset wet AMD who had not yet received treatment. Group 3: 10 patients with new onset wet AMD who received 4 injections of Ranibizumab and responded to therapy; Group 4: 6 patients who showed acute resistant to Ranibizumab therapy after 4 injections; Group 5: 7 patients with chronic resistance to multiple antiVEGF agents (bevacizumab, ranibizumab, and aflibercept).

RNA was isolated using modified Qiagen microRNAeasy procedure, and quantitated on BioAnalyzer’s with small RNA Analysis kit. Microarray miRNA analysis of serum samples was performed on samples from each group and ran on Affymetrix 3.0 miRNA arrays. Statistical analysis was done by ANOVA. A quantitative real-time PCR (qPCR) was used on the select set of biomarker candidates for the full sample set of each group.

RESULTS: Three miRNAs were identified in the serum for resistance to antiVEGF therapy. miR-1246 was upregulated 2.6 fold; miR-1469 was downregulated 10.9 fold, and miR-let-7b was upregulated 6 fold using microarray and qPCR analysis compared to the untreated new onset wet AMD Group 3 levels (P< 0.05). IPA pathway analysis shows that these miRNAs may be acting to influence MAPK Kinase pathways and TGF Beta signaling pathways to effect resistance to anti-VEGF therapy.

CONCLUSIONS: We have identified a few miRNAs that show differential expression in the serum of wet AMD patients who are resistant to antiVEGF therapy. Each of these miRNAs has shown a role in resistance to chemotherapy in various cancer treatments. The pivotal role of miR-let-7b will be discussed.
Pavingstone Degeneration: Evidence of an Association with the ARMS2 Risk Allele

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PURPOSE: Peripheral retina changes have received limited attention in reference to AMD, in part because they have been difficult to document compared to posterior pole findings. We wished to investigate peripheral retina phenotypes in AMD patients and controls using wide field imaging. We also wanted to determine possible genetic associations with AMD risk alleles.

METHODS: We imaged 150 patients with posterior AMD and 150 age-matched controls with the P200MA wide angle platform. Blood was drawn from each subject for DNA analysis, focusing on AMD risk alleles. Masked readers determined the presence and extent of peripheral retinal findings, including pavingstone degeneration and reticular pigmentation. We compared the anatomic features of the AMD and control cohorts and assessed their genetic differences. We developed odds ratios for the anatomic features when appropriate.

RESULTS: We found that AMD subjects who were homozygous for Y402H had a 4.5X higher likelihood of having drusen in the periphery (OR 1.55-13.02, P=0.006) and 4.49X higher likelihood of having peripheral reticular pigmentation (OR 1.66-12.13, P=0.003). Pavingstone degeneration was present in 18% of patients with AMD and in 3% of controls (P=0.04). We pooled the subjects with pavingstone (n=48) from the AMD and control groups as their numbers were modest. We found that homozygotes for ARMS2 rs10490924 had a 2.5X higher chance of having pavingstone degeneration (OR 1.04-5.76, P=0.041).

CONCLUSIONS: Peripheral retina features are reflective of AMD risk alleles. Pavingstone degeneration, an easily identified but rather mundane retinal finding, appears to be associated with the presence of ARMS2.
Increased Prevalence of Intermediate-stage Age-related Macular Degeneration in Persons with the Acquired Immunodeficiency Syndrome

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PURPOSE: Antiretroviral therapy (ART)-treated, immunorestored, human immunodeficiency virus (HIV)-infected persons have accelerated/accentuated aging, characterized by an increased prevalence of age-related diseases compared to HIV-uninfected persons, and have immunologic changes similar to persons >70 years of age, a phenomenon termed immunosenescence. We evaluated the prevalence of intermediate-stage age-related macular degeneration (AMD) in a cohort of patients with the acquired immunodeficiency syndrome (AIDS).

METHODS: A cross-sectional study of patients with AIDS enrolled in the Longitudinal Study of the Ocular Complications of AIDS (LSOCA) was conducted. Baseline retinal photographs were graded at a centralized Reading Center by graders, who were masked to clinical data, for the features of intermediate-stage AMD, using the Age-Related Eye Disease (AREDS) grading system.

RESULTS: Of 1825 participants with AIDS and no ocular infections, 9.9% had intermediate-stage AMD. The odds ratio for AMD increased 1.9-fold (95% confidence interval 1.6, 2.3) for every decade of age. Compared with the HIV-uninfected cohort in the Beaver Dam Offspring Study, which used a similar grading methodology, there was an ~4-fold increased age- and gender-adjusted prevalence of intermediate-stage AMD among participants in LSOCA. In LSOCA, ART, class of ART, and specific antiretroviral drug use were unassociated with AMD and did not account for the increased prevalence.

CONCLUSIONS: Patients with AIDS have an increased age- and gender-adjusted prevalence of intermediate-stage AMD compared to that found in an HIV-uninfected cohort. This increased prevalence of AMD is consistent with the increased prevalence of other age-related diseases in ART-treated, immunorestored, HIV-infected persons and may relate to the state of chronic immune activation and inflammation seen in these patients.
Encapsulated Cell Therapy for the Long-term Treatment of Neovascular Age-related Macular Degeneration

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PURPOSE: The Encapsulated Cell Therapy (ECT) platform is a surgical implant consisting of a genetically engineered retinal pigment epithelial (RPE) cell line designed to produce therapeutic proteins, a matrix that supports cell survival/function, and a semipermeable membrane that enables the outward passage of therapeutic proteins, while permitting an inward flow of oxygen and nutrients. NT-503 is a soluble VEGF receptor (sVEGFR) fusion protein produced by this platform. In preclinical studies it effectively inhibits choroidal neovascularization (CNV) in a rodent model and has similar binding affinity to VEGF as aflibercept. Herein, we report an open-label, dose escalation trial to evaluate the safety of, and clinical response to two doses of NT-503 ECT, to treat over a 24 month period, neovascular AMD (NVAMD).

METHODS: In the low-dose group, 26 eyes with NVAMD were implanted with a single, ECT implant, releasing 2.0-2.5 µg/d of VEGFR. In the higher dose group, 21 eyes received two ECT implants releasing 4.0-5.0 µg/d of VEGFR. Safety and clinical response measures collected during the study included best-corrected ETDRS visual acuity (BCVA) and retinal thickness measurements from SD-OCT images. The need for rescue therapy with ranibizumab, based upon predefined SD-OCT or visual acuity criteria, was also evaluated.

RESULTS: In the high dose group, median BCVA improved ~20 ETDRS letters and macular thickening decreased by ~170 microns from baseline to month 20. In the lower dose group, median BCVA decreased ~2.5 ETDRS letters and retinal thickness decreased ~140 microns during the same time period. To date, 6 of 26 eyes (23.1%) with a single implant and 4 of 21 eyes (19.0%) with the double implants required rescue therapy after implantation. Most adverse events were related to the surgical procedure, concurrent ocular conditions, or unrelated conditions. There were no cases of treatment-related cataract, infectious endophthalmitis, or treatment discontinuations.

CONCLUSIONS: NT-503 was well tolerated and a clear dose response was observed. A next-generation multi-cassette device, which achieves a 2-3 fold increase in VEGFR is being evaluated in a randomized clinical trial versus Eylea® dosed every 8 weeks.
AVA-101 Gene Therapy Trial for Exudative Age-related Macular Degeneration: Results of a Phase 2a Trial

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PURPOSE: Gene therapy has the potential to provide long duration treatment of exudative AMD and other retinal neovascular diseases following a single administration. We evaluated the safety profile of AVA-101 which results in expression of sFlt-1, a naturally-occurring VEGF inhibitor, in an ongoing, investigator-sponsored, single center, phase 2a trial.

METHODS: Thirty-two individuals with well characterized AMD were randomized to receive either 1E11 vg (n=21) of AVA-101, or a control regimen (n=11). All subjects received ranibizumab at Baseline and Week 4, and rescue treatment if required during follow up. The need for rescue was based on pre-specified criteria including ETDRS BCVA, OCT and FA. Subjects underwent ophthalmic examination at baseline, and clinical laboratory assessments included blood biochemistry, complete blood count, and T-cell response. Anti-AAV antibodies (both total and neutralizing), AAV capsid protein, and sFlt-1 protein levels were also measured. The primary endpoint of this trial was ocular and systemic safety. Secondary endpoints included the number of rescue injections required if any, BCVA and macular center point thickness.

RESULTS: Baseline demographics were consistent with other published studies: 100% Caucasian, 59% female, average age 79±7 years. All subjects were confirmed to have active subfoveal choroidal neovascularization secondary to exudative AMD, with average VA 60±15 EDTRS letters (Snellen equivalent 20/63). Four subjects were treatment-naïve; treatment-experienced subjects received an average of 12 (range 1 to 25) anti-VEGF injections prior to enrollment. Baseline immunology data included: serum neutralizing anti-AAV antibody titers > 1:500 in 1/32 subjects, 1:100-1:500 in 7/32 subjects, 1:20-1/:00 in 7/32 subjects; all fluid samples negative for AAV capsid in all subjects; IgM deficiency in one subject; lymphopenia or T cell deficiency and/or CD8 lymphopenia in 6/32 subjects. No other immune defects potentially hazardous to the use of the rAAV vector were identified. Average sFlt-1 protein levels were within physiologic range: urine 17.0±2.5 pg/ml, serum 113.0±5.7 pg/ml, saliva 220.7±12.3 pg/ml. An interim analysis on short-term safety showed that AVA-101 was well tolerated with no-drug-related SAEs; most adverse events were mild and non vision-threatening.

CONCLUSIONS: 52-week data from this phase 2a trial will first be available mid-2015 and presented. Interim safety data available to date support the continuing evaluation of AVA-101 as a potential long duration treatment option for exudative AMD.
Final Results from a Phase 2 Study of Squalamine Lactate Ophthalmic Solution 0.2% (OHR-102) in Neovascular Age-related Macular Degeneration (AMD)

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PURPOSE: To determine if topical OHR-102 administered BID in combination with Ranibizumab (RBZ) PRN can safely improve visual outcomes and reduce treatment frequency of RBZ compared to RBZ PRN 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 OHR-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 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, mean change in BCVA in the OHR-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% total resolution in the monotherapy group. Visual gains correlated with anatomic improvements in the OHR-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, OHR-102 BID used with RBZ PRN demonstrated marked improvements over RBZ monotherapy in mean gain in visual acuity and percentage of patients gaining ≥ 3 lines, ≥4 lines, and ≥5 lines of vision. Final data will determine the ability of OHR-102 to provide improved vision when used in combination with anti-VEGF treatments.
Safety and Efficacy of RTH258, a Single-chain Anti-VEGF Antibody Fragment, in Patients with Neovascular Age-related Macular Degeneration: Results From Two Phase II Studies

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PURPOSE: Two phase II studies in patients with neovascular AMD have been completed assessing safety and efficacy of RTH258, a novel single-chain antibody fragment (scFv) that inhibits vascular endothelial growth factor (VEGF) and has potential to exhibit better retinal penetration and delivery of VEGF blockade than larger proteins.

METHODS: C-10-083 was a prospective, double-masked, randomized, single-dose ascending, active-controlled, parallel-group study, which assessed change from baseline in central subfield thickness (CSFT) with pre-specified hypothesis testing of noninferiority for the 4.5 and 6.0 mg RTH258 groups vs ranibizumab at Month 1, applying a noninferiority margin of 40 µm.

C-12-006 was a randomized, double-masked, active-controlled study with a duration of 56 weeks, designed to test the hypothesis of noninferiority of RTH258 to aflibercept at weeks 12 and 16. Efficacy assessments included change from baseline in best-corrected visual acuity (BCVA) and in CSFT.

RESULTS: For C-10-083, 194 patients were randomized to one of 5 groups: 11 patients received 0.5 mg, 31 received 3.0 mg, 47 received 4.5 mg, and 44 received 6.0 mg. 61 patients received 0.5 mg ranibizumab. RTH258 4.5 mg and 6.0 mg were found noninferior to ranibizumab in CSFT mean change from baseline at Month 1. Duration of effect was longer for patients receiving RTH258 4.5 mg and 6.0 mg. Adverse events were observed at low and similar rates across treatment arms.

For C-12-006, 44 patients received RTH258 and 45 patients received aflibercept. Noninferiority was met, with patients receiving RTH258 gaining a mean (±SΕ) of 5.8 (1.7) letters and patients receiving aflibercept gaining a mean of 6.9 (1.7) letters at week 12 (P = .63). At week 16, RTH258 patients gained 6.0 (1.7) letters and aflibercept patients gained 6.6 (1.7) letters (P= .81). Fewer rescue treatments were given to RTH258 treated patients, with approximately 50% of patients successfully treated with Q12 dosing. Incidence of systemic adverse events was 68.7% for RTH258 and 80.0% for aflibercept.

CONCLUSIONS: Combining both studies, 177 patients have been exposed to RTH258, and results from both studies support RTH258 as a new treatment option in the management of patients with nAMD. Further studies in larger populations are ongoing.
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

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PURPOSE: Intravitreal anti-VEGF therapy is the treatment of choice for exudative age-related macular degeneration (eAMD), but the therapeutic effect is transient and requires frequent retreatment. Since a synergism between anti-VEGF 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 with subfoveal or juxtafoveal choroidal neovascularization 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 bevicizumab (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 intravitreal anti-VEGF therapies, and change in best-corrected visual acuity (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 21 subjects who completed the one-year follow-up included the following: 24Gy (n=7); 16Gy (n=7); sham (n=7). 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 intravitreal anti-VEGF 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 at 1 year follow-up.

CONCLUSIONS: Interim one-year analysis revealed no safety concerns with combination therapy and a possible synergistic effect combining intravitreal anti-VEGF therapy with 24Gy PBI, resulting in a decreased treatment burden with intravitreal anti-VEGF therapy. The complete one-year follow-up data analysis is on-going to determine whether these initial findings may also be applicable the 16Gy group.
Microvolume Drug Delivery: A Novel Therapeutic Strategy for Patients with Neovascular Age-related Macular Degeneration (nAMD)

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PURPOSE: An important unmet need for patients with neovascular age-related macular degeneration (nAMD) is reducing treatment burden. RTH258, a novel single-chain antibody fragment directed against vascular endothelial growth factor A (VEGF-A), has optimized solubility and can be highly concentrated, allowing reduced injection volumes for intravitreal application. Combined with a novel Posterior MicroPump (PMP) for pulsatile intravitreal drug delivery, RTH258 has the potential to significantly reduce treatment burden.

METHODS: To test performance of the PMP, 7 fully assembled pumps were filled with RTH258 and maintained at 37°C. Each pump was programmed to deliver one pre-determined dose (2.05, 4.15 or 8.3 µL) every month for a total of 6 months, generating a total of 42 doses. The volume delivered by the PMP was quantified to evaluate the accuracy of the device.

RTH258 patients received a microvolume intravitreal injection (cohort 1) or microvolume intravitreal infusion (cohort 2). The primary efficacy endpoint was the percentage of responders, defined as the presence of ≥3 of the following: 1) a ≥4-letter gain in best-corrected visual acuity (BCVA) at day 14; 2) a ≥4-letter gain in BCVA at day 28; 3) a ≥80 µm decrease in central subfield thickness (CSFT) at day 14; and 4) a ≥80 µm decrease in CSFT at day 28. A responder rate of 15% represents no relevant treatment effect (null hypothesis).

RESULTS: For the PMP bench study, 40 of the 42 doses were delivered within the specified volume accuracy of ±20%. In two cases only, the pumps delivered outside the specific range (22% and 30% respectively). In the clinical study, 26 subjects, 13 in each cohort, were randomized. RTH258 produced responder rates of 70% (7/10; 90% confidence interval, 39-91%) when injected and 60% (6/10; 90% CI, 30-85%) when infused, exceeding the 15% responder rate (P≤ 0.0014). No safety issues were reported.

CONCLUSIONS: Microvolumes of RTH258, delivered intravitreally by injection or infusion, are effective in improving BCVA and CSFT in the majority of subjects. The next generation PMP demonstrated the proper function at body temperature for a period of up to 6 months on the bench, demonstrating the essential performance of the device.
Lamp-2 Deficiency Associated with Dysfunctional Autophagosomes and Phagosomes in Age-related Macular Degeneration (AMD)

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PURPOSE: Age-related macular degeneration (AMD) is characterized by accumulation of deposits and dysfunction of the retinal pigment epithelium (RPE) and overlying photoreceptors. Autophagy and phagocytosis are two cellular processes involved in the removal of extracellular and cytosolic components, respectively. Lysosomal-associated membrane protein 2 (Lamp-2) is a major lysosomal membrane protein that has critical roles in the maturation of both phagosomes and autophagosomes. In this study, we investigated the role of Lamp-2 in autophagy and phagocytosis in age-related retinal pathology and degeneration.

METHODS: Autophagy and phagocytosis were studied in histologic specimens from AMD patients using electron microscopy (EM). Mice with impaired maturation of autophagosomes and phagosomes due to LAMP-2 deficiency were studied over time by fundus photography, fundus autofluorescence (FAF), spectral domain optical coherent tomography (SD-OCT), electroretinography, and histology. Mechanistic insights in the basolateral accumulation of extracellular material in the RPE were studied using polarized primary mouse RPE cultures.

RESULTS: Dilated lysosomes, undigested materials, and decreased Lamp-2 expression were detectable in human AMD specimens, suggesting impaired autophagy and phagocytosis. Mice deficient in Lamp-2 showed age-dependent accumulation of indigestible photoreceptor outer segments, lipofuscinosis, and drusenoid deposition under the RPE. We also observed cargo accumulation of canonical autophagy and cellular debris, which was associated with necrotic RPE death in Lamp2-deficient mice. FAF and ERG showed increased autofluorescence and decreased visual function over time respectively. In vitro mechanistic studies using primary polarized RPE indicated that indigestible contents in autophagosomes/autolysosomes were secreted into the extracellular space, particularly from the basolateral RPE, suggesting the involvement of impaired autophagy in dysfunctional exocytic activity of the RPE in drusen formation.

CONCLUSIONS: In Lamp2-deficient mice, alterations in autophagy and phagocytosis were associated with age-dependent pathologies similar to AMD, including RPE dysfunction and necrosis in photoreceptors and RPE. Collectively, our results suggest that an age-related decrease in Lamp-2 function might contribute to drusen formation and dysfunction in photoreceptors and RPE. Modulating these pathways may be a therapeutic approach for AMD and retinal degenerative diseases.
Active Rap1 Inhibits TNFα-induced Choroidal Endothelial Migration via NADPH Oxidase and Nuclear Factor Kappa B Dependent Activation of Rac1

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PURPOSE: When activated choroidal endothelial cells (CECs) migrate into the retina in neovascular age-related macular degeneration (AMD), vision loss invariably occurs. We explored crosstalk between inflammatory and oxidative mechanisms involved in CEC activation and tested the hypothesis that tumor necrosis factor alpha (TNFα)-mediated CEC migration was inhibited by activation of guanosine triphosphatase (GTPase), Rap1.

METHODS: CECs were isolated from de-identified donor human eyes (in accordance with University of Utah Human Studies), expanded and cultured through passage 5 for experimentation. CECs were stimulated with TNFα, vascular endothelial growth factor (VEGF), or phosphate-buffered saline (PBS) control, and cells or lysates analyzed for reactive oxygen species (ROS), active Rac1, or CEC migration. In some experiments, CECs were 1) treated with antioxidant, apocynin, the Rap1 activator, 2′-O-Me-cAMP (8CPT), or PBS; 2) transfected with small interfering RNA (siRNA) to nicotinamide adenine dinucleotide phosphate-(NADPH) oxidase subunit, p22phox, or control siRNA; the nuclear factor-kappa B inhibitor (NF-κB), Bay11-7082 or PBS control; or infected with adenoviral-activated Rap1a (adRap1a) or adenoviral-green fluorescent protein (adGFP) control. Six-week old C57Bl/6 mice underwent laser and were treated with TNFα antibodies, 8CPT, or controls. Lectin-stained choroidal flat mounts were analyzed for volume of choroidal neovascularization (CNV) measured using confocal microscopy. Statistics were analyzed by ANOVA.

RESULTS: Compared to PBS, CECs stimulated with TNFα (or positive control, VEGF) had significantly greater migration (p<0.01). Apocynin or p22phox siRNA reduced TNFα induced ROS, active Rac1, and CEC migration compared to respective controls (all p<0.05). ROS-dependent Rac1 activation and CEC migration were inhibited by nuclear factor-kappa B inhibitor (NF-κB), Bay11-7082.Compared to PBS or adGFP, 8CPT or active Rap1 inhibited ROS, active Rac1, and migrated CECs induced by TNFα. Either TNFα antibody or 8CPT-inhibited laser-induced CNV compared to controls.

CONCLUSIONS: These results support the hypothesis that TNFα mediated ROS-induced NF-κB and Rac1 mediated CEC migration. VEGF can also induce Rac1-mediated CEC migration. Activation of Rap1 with chemical or gene therapies inhibited Rac1-induced CEC migration stimulated by TNFα or VEGF. These results support future studies testing activation of Rap1 as a potential therapy in AMD.
Anti-VEGF Treatment of Macular Edema Secondary to Retinal Vein Occlusion in Clinical Practice: A Retrospective Study of Effectiveness and Patterns of Use

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PURPOSE: To evaluate the efficacy, safety and injection frequency of vascular endothelial growth factor (VEGF) antagonists as used in clinical practice to treat macular edema (ME) secondary to branch or central retinal vein occlusion (BRVO, CRVO).

METHODS: This was a multicenter (10 sites), retrospective study of medical records of 165 patients (95 BRVO, 70 CRVO) who received ≥3 anti-VEGF injections to treat ME due to RVO in the study eye. Data collected for ≥6 months after the first injection included best-corrected visual acuity (BCVA), central retinal thickness (CRT) by time-domain or spectral-domain optical coherence tomography (TD-OCT, SD-OCT), anti-VEGF injections and other treatments/procedures for RVO, intraocular pressure (IOP), and adverse events. The primary endpoint was the percentage of patients with BCVA 20/40 or better and CRT ≤250 µm on TD-OCT or ≤300 µm on SD-OCT at the same visit.

RESULTS: At baseline prior to anti-VEGF treatment, mean BCVA was ~20/80 and mean CRT was 499 µm. Mean number of anti-VEGF injections received by patients was 7.1 during the first year, 5.4 during the second year, and 5.9 during the third year; 51.3% (842/1641) of injections were ranibizumab, 44.1% (724/1641) bevacizumab, and 4.6% (75/1641) aflibercept. One in 5 patients received concomitant focal laser treatment. The percentage of patients achieving both BCVA of 20/40 or better and CRT ≤250 µm on TD-OCT or ≤300 µm on SD-OCT (primary endpoint) was 18.4% (30/163) after the first anti-VEGF injection and ranged from 15.2% (7/46) to 29.0% (45/155) over the first 16 injections. After each anti-VEGF injection from the first to the 16th, 25 mm Hg.

CONCLUSIONS: A mean of 5–7 injections of anti-VEGF were administered yearly to treat RVO-associated ME. After most injections, approximately 1 in 5 patients achieved both 20/40 or better BCVA and normal CRT at the same visit. Anti-VEGF treatment was well tolerated.
Evaluation of Macular Microvasculature and Blood Flow Velocities by Non-invasive, High-resolution Functional Imaging in Central Retina Vein Occlusion

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PURPOSE: To reveal the macular capillary network detail and measure blood flow velocity (BFV) in central retinal vein occlusion (CRVO) using a high-resolution, non-invasive functional imaging device.

METHODS: We enrolled seven eyes of seven subjects with CRVO and eight eyes of seven healthy control subjects. All study participants underwent routine ophthalmic examination followed by scanning with the Retinal Function Imager. The built-in software of the RFI device was used to generate non-invasive capillary perfusion maps (nCPMs) and to segment the retinal vasculature for BFV measurements. Only tertiary vessels were segmented. Vessel segments with a velocity coefficient of variation of >45% were rejected and only analyses with <15% of rejected segments per eye were accepted. The number of accepted vessel segments was recorded and their velocity values were exported. Comparisons were made by two-tailed t-test, the level of significance was set at 5%.

RESULTS: The nCPMs provided high-resolution images of the retinal microvasculature and showed ischemia in all eyes with CRVO. The number of retinal venules was slightly higher in the CRVO group (14±4 segments/eye in CRVO vs 12±4 in healthy, p=0.40), while a comparable number of arterioles was available for analyses in both groups (11±6 segments/eye in CRVO vs 11±3 in healthy, p=0.90). The mean BFV measurements in both venules and arterioles of the CRVO group were significantly reduced (arterioles: 2.82±1.15 vs 4.17±0.81 mm/s and venules: 1.68±0.32 vs 2.81±0.67 mm/s, p=0.026 and p=0.002, CRVO vs healthy, respectively).

CONCLUSIONS: The RFI is a non-invasive tool for the high-resolution functional imaging of retinal microvasculature also enabling the quantitative measurement of retinal blood flow velocities. Our pilot study demonstrated significant decrease in blood flow velocities in both venules and arterioles in the macula of CRVO patients. Taking into account the similar number of vessel segments evaluated in each eye, our results support the highly reduced retinal blood supply in CRVO. This evaluation might corroborate the diagnosis of CRVO in ophthalmoscopically mild cases.
Retinal Metabolic Imaging Using Visible Optical Coherence Tomography in Animal Models of Retinal Ischemia

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PURPOSE: To validate the ability of combination of visible-light OCT and Doppler OCT to quantify the oxygen saturation of hemoglobin and blood flow within inner retinal vessels, enabling us to quantify the inner retinal oxygen consumption and metabolic rate of oxygen (MRO2) in vivo.

METHODS: We compared retinal oxygen delivery, oxygen extraction, retinal blood flow and retinal MRO2 in rats with oxygen induced retinopathy (OIR) to control rat pups at postnatal day 18. These measurements were correlated to retinal morphometric findings on histopathological cross sections and retinal vascular flatmounts revealing retinal vascular density, areas of vaso-obliteration and pathologic neovascularization.

RESULTS: We observed that the retinal oxygen delivery was decreased by 61% in the OIR group compared to controls at postnatal day 18, at the height of proliferative retinopathy in this model. Using confocal microscopy of isolectin-stained retinal vascular flatmounts showed decreased vascular density in the superficial and deep inner retinal networks in OIR rats, suggesting that the abnormal vascular network played an important role in decreased oxygen delivery. Similarly, retinal MRO2 was 59% lower in the OIR group compared to controls. Retinal morphometric measurements on histolopathologic examination showed statistically significant decreased thickness of all retinal sublayers in the OIR group, suggesting that decreased retinal MRO2 was due to decreased retinal neuronal thickness and therefore decreased oxygen consumption.

CONCLUSIONS: Capitalizing on the unique ability of visible OCT to simultaneously measure retinal oxygen saturation of hemoglobin, retinal vessel diameter, and blood flow, we have quantified the retinal MRO2 in healthy rats and OIR at P18. In addition, we combined this new technology with histological and immunostaining analysis to gain an improved understanding of the relevant pathologic changes. The findings in this study add new insights into the pathophysiology of oxygen demand and consumption in rats with OIR, which can be extrapolated to retinal ischemic diseases including proliferative diabetic retinopathy. These results will be discussed in context of their implications for human diabetic retinopathy.
Evaluation of Rescue Treatment with Intravitreal Aflibercept Injection (IAI) in Eyes Randomized to the Laser Control Arm in the VIBRANT Study

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PURPOSE: To evaluate rescue treatment with IAI in eyes randomized to receive laser grid photocoagulation for macular edema following branch retinal vein occlusion (BRVO).

METHODS: VIBRANT was a double-masked, 52-week, phase 3 trial that randomized 183 eyes with macular edema following BRVO to treatment with IAI 2 mg every 4 weeks from baseline through week 24 or grid laser at baseline. From week 24, eyes in the laser group that required rescue per pre-specified criteria received IAI 2 mg every 8 weeks after 3 monthly doses.

RESULTS: During weeks 24-48, 67 eyes in the laser group (67/83 eyes completing week 24 [80.7%]) received a mean of 4.4 IAI; median time (range) from baseline to first rescue IAI was 24.9 weeks (23.1-48.4 weeks). Baseline characteristics for the group requiring IAI rescue were: mean age 65.0 years, mean time from BRVO diagnosis 44.6 days, mean central retinal thickness (CRT) 561.1 µm, and mean baseline BCVA 57.7 letters. At week 24, mean change in BCVA in patients who subsequently received IAI rescue was +5.3 letters. At week 52, mean change in BCVA for this group was +12.0 letters. Mean change in CRT at week 24 for the group rescued with IAI was -114.3 µm. At week 52, the corresponding mean change in CRT was -276.1 µm. The most common ocular adverse event occurring in the laser group (with and without IAI rescue) and the IAI group through week 52 was conjunctival hemorrhage (15.2% vs. 24.2%, respectively).

CONCLUSIONS: Overall, 80.7% of patients originally randomized to laser required IAI rescue starting at week 24. Patients originally randomized to the laser arm who received IAI rescue between weeks 24 and 52 experienced significant improvements in BCVA and CRT.
The Effect of Intravitreal Aflibercept on Capillary Non-Perfusion in Patients with Proliferative Retinopathy and/or Macular Edema Secondary to Proliferative Diabetic Retinopathy and Central Retinal Venous Occlusive Disease (ANDROID Study)

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PURPOSE: To determine the effect of intravitreal aflibercept injections (IAI) on perfusion status in proliferative retinopathy and/or macular edema from proliferative diabetic retinopathy (PDR) and central retinal vein occlusion (CRVO).

METHODS: This single center, open label, prospective study randomized eyes to either monthly IAI for 12 months or to 6 monthly IAI followed by IAI every 2 months. Patients in this latter group could be treated monthly if they met pre-defined re-treatment criteria. Wide-field fluorescein angiography was obtained at baseline, and months 3, 6, and 12. The Digital Angiography Reading Center (DARC) measured peripheral non-perfusion in a masked fashion. Secondary outcomes included change in best-corrected ETDRS vision and change in central subfoveal thickness (CST) as measured on SD-OCT.

RESULTS: Twenty-four patients were enrolled. Fifteen eyes had PDR, 8 had CRVO, and 1 had a hemi RVO. Wide-angle angiography was of sufficient quality to evaluate non-perfusion in 23 patients; 1 patient did not have non-perfusion at baseline and was excluded from analysis. The average total area of peripheral non-perfusion at baseline (155.5mm², n = 22) improved to 92.9mm² at 3 months (p = 0.055, n = 20), 60.7mm² at 6 months (p = 0.004, n = 21), and 44.5mm² at 12 months (p = 0.007, n = 18). Grading was performed by two different readers, and the results were highly correlated and reproducible. At 1 year, 15 eyes (83%) had improved peripheral perfusion, while 3 worsened (17%). Visual acuity improved from 59.8 ETDRS letters (20/63) to 69 letters (20/40, p = 0.0003). The baseline CST of 395µm improved to 295µm (p = 0.006). Results were consistent amongst patients with PDR and CRVO as well as the two different regimens. There were no APTC events, nor were there any serious drug-related adverse events.

CONCLUSIONS: Previous studies have documented prevention of progressive capillary non-perfusion with regular anti-VEGF therapy. This small prospective study provides evidence that peripheral capillary non-perfusion in patients with PDR and CRVO may improve following treatment with IAI. Further large-scale studies are required to explore this finding.
Higher Red Cell Distribution Width Values are Associated with Worse Vision in Retinal Vein Occlusion

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**PURPOSE:** To determine the significance of red cell distribution width (RDW), a parameter that measures variation in red blood cell size or red blood cell volume and is an index of erythrocyte heterogeneity, in patients with retinal vein occlusion (RVO).

**METHODS:** Two groups of patients were included in the study – patients with either branch RVO (70 patients) or central RVO (56 patients) and gender matched controls. Comprehensive ophthalmological examination including fundus fluorescein angiography (FA) and macular optical coherence tomography (OCT) were performed on all subjects. Exclusion criteria included: RVO not confirmed by FA, history of malignancy, anemia ≤ 6 months follow-up duration, and unavailability of RDW value within 3 months of first presentation of RVO. RVO patients were divided into 4 quartiles according to RDW value: quartile 1 (RDW ≤ 13.8%), quartile 2 (13.8%–16.0%), Unpaired samples t-test, Pearson correlation test, chi-square test, ANOVA test and multiple regression analysis were used for statistical evaluation.

**RESULTS:** There was no significant difference in the demographics of study subjects in all 3 groups with respect to age, gender, and associated systemic diseases. RDW value was significantly higher in RVO patients (14.9 ± 1.6) compared to control subjects (12.5 ± 1.4; p<0.0001). There was a statistically significant correlation between RDW value and both initial (r=0.443, p<0.0001) and final best corrected visual acuity (BCVA) (r=0.379, p<0.0001) in RVO patients. Both initial and final BCVA were better in RDW quartiles 1 and 2 compared to RDW quartiles 3 and 4.

**CONCLUSIONS:** RDW value was significantly higher in RVO patients compared to control group. Furthermore, higher RDW value was associated with lower initial and final BCVA. RDW value may be used as a prognostic factor for vision in RVO patients.
Laser Chorioretinal Anastomosis for Central Retinal Vein Occlusion: Success Rates and Technique with a New Photocoagulator System

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PURPOSE: The treatment of central retinal vein occlusion (CRVO) currently focuses on the sequelae of the obstruction to venous outflow rather than addressing causal pathology. Whilst initial results with intra-vitreal therapies are impressive longer term studies do show a continued loss of vision. Combining treatments addressing this such as the laser chorio-retinal anastomosis (L-CRA) may improve outcomes. Current laser systems lack the power densities to reliably create an L-CRA which has been a barrier to the uptake of this treatment technique. The results using a new purpose designed laser system are reported.

METHODS: Patients with a CRVO of less than 9 months duration, perfused macular edema (CRT>250u) and visual acuity (VA) 24-73 letters were treated with an L-CRA as part of an on-going trial into combination treatment for CRVO (ACTRN12612000004864). 2 potential anastomosis sites were created above and below the optic disc using a newly developed laser with power levels capable of up to 5W and a refined beam. Patients were commenced on anti-VEGF treatment at one month and followed monthly.

RESULTS: Thirty-three patients aged between 46-86 years (mean 69) with VA 26-73 letters (mean 56) and a CRVO duration of 2-24 weeks (mean 7.2) were treated with a L-CRA. 29 of the 33 patients developed at least one successful L-CRA (88%). 18 patients developed 2 L-CRAs and the remaining 11 one each. Of the 66 potential sites created in the 33 eyes successful L-CRAs developed at 47 (71%). Time for the development of the L-CRA varied from 1-6 months (mean 1.8). Complications at the 66 sites included closure of the distal segment of the vein at 8 (12%) treated with localised sectorial laser, small new vessel development at 11 (17%), 5 of which regressed spontaneously and the remaining 6 treated with sectorial laser. 2 patients developed minor macular traction from avascular fibrous tissue proliferation treated with a vitrectomy. Follow up varied from 4-36 months (mean 21).

CONCLUSIONS: The success rates for L-CRA development have improved significantly with improvements in laser design and technique. Complications of this procedure are minor and controllable with careful follow-up and combination therapy with intra-vitreal anti-VEGF agents.
Encapsulated Cell Technology Implant to Reverse Retinal Ischemia

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PURPOSE: Ischemic retinal vascular diseases such as diabetic retinopathy and retinal vein occlusion are characterized by a decreased supply of oxygen to retinal photoreceptors. This localized tissue hypoxemia in turn leads to photoreceptor damage and death. We have developed a bioimplant containing oxigenic unicellular organisms using encapsulated cell technology (ECT) to deliver oxygen using in vitro, ex vivo, and in vitro models.

METHODS: Prototype devices consisting of dialysis membranes with a silicone endcap on each end were constructed, with a length of 6 mm and a diameter of 2mm. The devices were designed to allow the passage of light as well as small molecules such as oxygen, carbon dioxide, and sugars, but restrict passage of the cyanobacteria. Three devices were filled with Synechococcus cyanobacteria and three devices filled with saline solution as a control. Each device was then placed in a 50 mL closed container of saline, exposed to room lighting conditions, and continuous recordings taken for nine hours using an oxygen sensor probe. The main outcome measure was the difference in the initial and final oxygen partial pressure (pO2) of the saline, and the two groups were compared using a paired t-test. This testing strategy was repeated ex vivo and in vivo.

RESULTS: At baseline, there was no difference in the pO2 between the active group (108.9 +/- 1.37 mmHg) and the control (110.73 +/- 0.65 mmHg, p = 0.11). After nine hours, the pO2 in the OxyCell group increased 28% from baseline (138.99 +/- 1.71 mmHg, p = 0.0005) and the control group increased by 2% (112.4 +/- 1.10 mmHg, p = 0.07). The difference in the final pO2 concentration between the two groups was statistically significant (p = 0.001). Similar results with statistically significant differences in oxygen content were obtained ex vivo and in vivo as well, including an in vivo model of ophthalmic artery occlusion.

CONCLUSIONS: These results are consistent with the hypothesis that oxygen producing Synechococcus cyanobacteria can be encapsulated in a device and used to produce oxygen. Further in vivo testing is needed, but such a device implanted in the vitreous cavity may prove useful in ischemic retinopathies to reverse local tissue hypoxemia.
PRN Dexametasone Implant for Macular Edema for the Pan-American Collaborative Retina Study Group (PACORES)

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PURPOSE: To evaluate visual acuity, central retinal thickness and number of intravitreal dexametasone implant injections needed to treat macular edema during a 6-month follow-up.

METHODS: We reviewed the charts of 91 patients with macular edema secondary to retinal vein occlusion, diabetic macular edema (DME), uveitis, age-related macular degeneration, Irvine-Gass syndrome and other causes, who received intravitreal dexametasone implant on an “as needed” basis for a period of 6 months. Main outcome measures included number of implants, changes in best-corrected visual acuity and central macular thickness.

RESULTS: A total of 97 eyes of 91 patients (52 men [57.14%], 39 women [42.86%]; mean age 67.8 ± 11.3 years) were included. Retreatment was judged necessary in patients with persistent or recurrent macular edema. Eighty-five eyes (87.62%) needed a single injection for 6 months. Eleven eyes (11.34%) received a second injection for retreatment (median, 5 months). Only one eye (1.81%) needed a third implant 2 months after the second implant for DME. Mean baseline best-corrected visual acuity was 0.89 ± 0.61 logMAR in the overall population; it significantly improved to 0.71 ± 0.63 logMAR 6 months from the first implant (P = 0.001), to 0.61 ± 0.51 logMAR after the 1st month and to 0.63 ± 0.60 logMAR after the 3rd. Mean baseline central macular thickness significantly decreased from 538 ± 198 µm to 370 ± 170 µm after 6 months follow-up (P < 0.0001). No serious adverse events were observed.

CONCLUSIONS: Intravitreal dexametasone implant was an effective treatment for improving visual acuity and reducing central retinal thickness in macular edema due to different causes on an “as needed” basis with a low number of injections, which may lead to long-term clinically significant benefit in the treatment of macular edema from various etiologies.
Correlation Between Optical Coherence Tomographic Hyperreflective Foci and Visual Outcomes After Intravitreal Bevacizumab for Macular Edema in Branch Retinal Vein Occlusion

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PURPOSE: To investigate the correlation between hyperreflective foci (HF) on spectral domain optical coherence tomography (SD-OCT) at baseline and visual outcomes after intravitreal bevacizumab injection (IVB) in branch retinal vein occlusion (BRVO).

METHODS: We retrospectively studied 97 eyes of 97 patients with macular edema secondary to BRVO, who were treated with IVB. The eyes were divided into three groups according to the location of HF on SD-OCT: HF in outer retinal layers, HF in inner retinal layers, and no HF. The baseline and final best corrected visual acuity (BCVA), foveal thickness (FT), external limiting membrane (ELM) status, junction between photoreceptor inner and outer segments (IS/OS) status, and the number of HF were evaluated and compared among three groups.

RESULTS: Baseline BCVA was correlated with baseline FT (R=0.366, p<0.001), but final BCVA was not correlated with final FT (R=-0.008, p=0.942). Baseline BCVA was significantly better in eyes with intact ELM at baseline (p=0.006), and final BCVA was significantly better in eyes with intact ELM and IS/OS at final visit (p<0.001, p=0.003, respectively). At the final visit, 15 of 37 eyes (40.5%) with HF in outer retinal layers had a disrupted ELM (p=0.001); while 28 of 37 eyes (75.7%) with HF in outer retinal layers had a disrupted IS/OS (p<0.001). Final BCVA was poorer in eyes with HF in outer retinal layers groups than those in other two groups (p<0.001), although baseline BCVA was not different between them.

CONCLUSIONS: HF on SD-OCT at baseline might predict the photoreceptor status and final VA after IVB in BRVO.
Sickle Cell Microangiopathy and Biomarkers

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PURPOSE: Correlate presence and severity of ocular microangiopathy with systemic hemolysis, CNS angiopathy and nephropathy.

METHODS: Two hundred patients with sickle cell disease were evaluated for presence of ocular microangiopathy with a complete ocular examination. Fundus photography and fluorescein angiography were performed as needed. The type of sickle cell disease was noted - including SS, SC, S-Thal, SB-, SBO and SO arab. The presence of CNS microangiopathy, leg ulcers and severity of hematologic parameters were also noted.

RESULTS: The patients were divided into two subgroups- Minor (Mild) and Major (Severe) phenotype. Genotypes SC, SB- and SHbF were categorized under the Mild subgroup and SS, SBO, and SOarab were categorized under the severe phenotype. The hemoglobin level, LDH level, renal parameters, presence of ocular microangiopathy and presence of CNS angiopathy by MRI were correlated.

CONCLUSIONS: Those with a higher Hb had more severe retinopathy. The LDH levels correlated with more severe retinopathy, nephropathy and CNS microangiopathy.
The Safety and Feasibility of Office-based Vitreous Aspiration

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PURPOSE: The primary goal was to evaluate the safety and efficacy of office-based vitreous aspiration. The secondary goal was to determine if samples collected in the office setting were amenable to multiplex cytokine analysis.

METHODS: All office- and operating room-based vitreous sampling between November 2011 and November 2014 at the Kellogg Eye Center were reviewed. In-office vitreous aspiration was performed with a 25-gauge needle through the pars plana to acquire a maximum of 0.2 mL of vitreous fluid. The rate of adverse events including endophthalmitis, retinal tear/detachment, posterior vitreous detachment, and cataract from office-based vitreous aspiration was compared to regular vitreous sampling immediately prior to pars plana vitrectomy. The concentrations of vitreous cytokines were analyzed in a subset of samples using a 42-plex cytokine bead array in triplicate using 25μL of vitreous fluid.

RESULTS: Fifty-seven office-based and 179 operating room-based vitreous samples were included. An adequate volume of vitreous fluid was obtained in 88% of office-based sampling attempts. The average length of follow-up was 303 days (range, 42-926 days) and there was only 1 (2%) documented complication, an acute posterior vitreous detachment without retinal tear. There were no intraoperative complications from operating room-based vitreous sampling. Vitreous cytokine and growth factor concentrations were measured in 15 patients: 5 controls, 5 with diabetic macular edema (DME), and 5 with proliferative diabetic retinopathy (PDR). The mean concentration of VEGF was elevated in DME (286.45pg/mL) and PDR (202.24 pg/mL) compared to controls (15.20pg/mL). This comparison did not reach significance given the small sample size. The levels of inflammatory cytokines (IL1R, IL1RA, IL6, IL7, IL8, IL9, IL10, MCP1, MDC, MIP1a), chemotactic agents (Fractalkine, GRO) and growth factors (G-CSF), were elevated in PDR, suggesting a significant inflammatory component.

CONCLUSIONS: Although limited by small sample size, this study suggests that in-office vitreous aspiration is safe as compared to typical vitreous aspiration prior to pars plana vitrectomy. Moreover, in-office biopsies consistently result in sufficient material for multiplex cytokine and growth factor analysis. As such, office-based aspiration may be a safe and effective means to identify novel vitreous factors associated with vitreoretinal disease.
The Effects of Diabetic Retinopathy and Panretinal Photocoagulation on Photoreceptor Cell Function as Assessed by Dark Adaptometry

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PURPOSE: The pathophysiology of visual loss in persons with diabetic retinopathy (DR) is complex and incompletely defined. We hypothesized that rod and cone photoreceptor dysfunction would increase with severity of diabetic retinopathy, and that panretinal photocoagulation would exacerbate this dysfunction.

METHODS: Dark adaptation was measured using the AdaptDx in subjects with diabetes mellitus and healthy volunteers (controls). Dark adaptation was measured at 5 degrees superior to the fovea in response to a 5 \times 10^{-4} \text{ scotopic cd m}^{-2} \text{ s}^{-1} \text{ bleach}. Inclusion criteria were: age \geq 18 years; and best-corrected visual acuity \geq 20/400. Cone sensitivity and rod recovery speed were compared between groups.

RESULTS: The sample consisted of 24 controls and 75 diabetic subjects, of which 12 had Type 2 diabetes mellitus and 63 had Type 1 diabetes mellitus. Beginning at the level of moderate non-proliferative diabetic retinopathy (NPDR), diabetic subjects had significantly impaired rod recovery slopes compared to controls (controls mean: 0.29 log units/min; moderate NPDR mean: 0.20 log units/min; p= 0.042). Subjects who had proliferative diabetic retinopathy (PDR) had significantly impaired cone sensitivity (controls mean: 2.1 log units; T1DM PDR mean: 1.9, p=0.023; T2DM PDR mean: 1.6 p<.001). Neither of the outcomes was significantly different between subjects with untreated PDR compared to those who had PRP.

CONCLUSIONS: The results suggest that photoreceptor cell dysfunction, as assessed by dark adaptometry, begins as early as the moderate NPDR stage, and rod and cone cells are affected to similar degrees. Surprisingly, PRP not further impair dark adaptation. These findings suggest the possibility that diabetes impairs retinal retinoid metabolism, and provides a potential target to improve visual function in persons with DR.
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Pars Plana Vitrectomy After Intravitreal Ocriplasmin for Symptomatic Vitreomacular Adhesion

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PURPOSE: To compare outcomes to relieve vitreomacular adhesion (VMA) with intravitreal ocriplasmin injection vs. ocriplasmin injection and subsequent pars plana vitrectomy (PPV) for surgical VMA release.

METHODS: This is a retrospective case review of 35 patients from 2013-2014 with symptomatic VMA who received intravitreal ocriplasmin injections; 8 patients had subsequent PPV with membrane peeling for persistent VMA. Primary endpoints included release of VMA, macular hole (MH) closure, and need for surgical release. Secondary endpoints included rate cystoid macular edema (CME), posterior vitreous detachment (PVD), and optical coherence tomography (OCT) ellipsoid zone changes, best corrected visual acuity (BCVA), and complications.

RESULTS: The mean age was 69 years with a duration of 7.9 months of VMA prior to injection. 25 (71%) subjects were phakic, and 10 (29%) were pseudophakic. VMA release occurred in 15 (43%) eyes after a mean 10.2 days after injection, with complete PVD in 12 (35%). 27 eyes underwent injection and 8 eyes underwent injection plus surgical release for persistent VMA. The mean age for patients who underwent injection only was 71.1 years vs. 63.8 years for the surgical group (p<.03). The mean pre-injection BCVA was 20/50 (0.37 LogMAR) for the injection only group vs. 20/100 (0.74 LogMAR) for the injection plus surgery group (p<.01). The final BCVA was 20/40 (0.26 LogMAR) for the injection only group vs. 20/100 (0.65 LogMAR) for the injection plus surgery group (p<.01). 4 (50%) eyes in the surgical group had full thickness MH vs. 2 (7.4%) in the injection only group (p<.02). The mean VMA diameter was 825 micrometers for the surgical group vs. 488 micrometers in the injection only group (p<.06). Ellipsoid zone changes occurred in 1 (12.5%) eye in the surgical group vs. 9 (33%) eyes in the injection only group (p<.39). After injection 13 (37.1%) of patients experienced photopsias, 1 (2.9%) had a retinal detachment and 1 (2.9%) patient had an intraocular pressure spike.

CONCLUSIONS: Ocriplasmin may be a treatment option for certain patients with VMA. Younger patients, patients with MH, and worse pre-injection BCVA may require a subsequent surgical release. Patients undergoing ocriplasmin injections require careful follow-up for complications.
Real-life Experience After Intravitreal Ocriplasmin for Vitreomacular Traction and Macular Hole: A Spectral-domain Optical Coherence Tomography Prospective Study

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PURPOSE: To evaluate prospectively the anatomical and functional results after ocriplasmin injection in patients with vitreomacular traction (VMT) or macular hole (MH) combined with VMT, providing the real-life experience of three centers, using spectral domain-optical coherence tomography (SD-OCT).

METHODS: Twenty-four patients with VMT (17 with VMT alone and 7 with MH combined with VMT) were treated with a single ocriplasmin injection and followed-up prospectively at baseline, day 1, 7, 28 and the last examination of the follow-up for each patient (range: 30-127 days). Best-corrected visual acuity (BCVA) and SD-OCT were performed for patients’ assessment, while various adverse events were recorded and analysed. At baseline, univariate analysis was also performed to examine the potential predictive factors for VMT release.

RESULTS: 66.7% of patients presented VMT release at the end of the follow-up, while 28.6% exhibited MH closure. Baseline positive predictive factors for VMT release were young age, female sex, phakic lens status, increased vitreofoveal angle, V-shaped and loose vitreomacular adhesion, thin vitreous strands at the adhesion site and absence of epiretinal membrane. Four new cases of ellipsoid line changes and subretinal fluid development became evident at day 7 compared to baseline. Lamellar macular hole in four cases was first noticed at day 28 post injection. Formation of cystoid macular edema was noticed in three new cases at day 28 compared to baseline.

CONCLUSIONS: Our study demonstrated a VMT release rate of 66.7%. Apart from the known baseline factors that influence the VMT release after ocriplasmin injection, the size of vitreofoveal angle, the V-shaped and loose vitreomacular adhesion, and the thin vitreous strands at the adhesion site could additionally affect the outcome of VMT release. In addition, we studied when the VMT release and concomitant events happen and for how long the induced complications lasted.
Macular Neurosensory Retinal Detachment Associated with MEK Inhibitor Use for Cancer: A Case Series and Review of the Literature

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PURPOSE: Two cases of bilateral macular neurosensory retinal detachment associated with MEK inhibitor use for metastatic cancer will be presented and a review of the literature to describe variable presentations of this condition from a clinical and retinal imaging standpoint will be included.

METHODS: After obtaining approval from the University of Chicago Institutional Review Board, a retrospective chart review was conducted to collect visual acuity, fluorescein angiogram, and OCT data from patients presenting to our clinic who had received treatment with MEK inhibitors. In addition, a comprehensive literature search was performed to summarize previously reported retinal changes with the use of MEK inhibitors.

RESULTS: Case 1. 70-year old with pancreatic CA had blurred vision. Pimasertib was initiated one day prior. BCVA was 20/40 OD and 20/30 OS, reduced from 20/30 OD and 20/25 OS 2 weeks prior. Exam revealed bilateral CME with neurosensory RD. SD-OCT was normal two weeks prior. Four days after starting therapy SD-OCT showed bilateral CME with neurosensory RD. IVFA revealed non leaking CME. Pimasertib was discontinued and vision improved to 20/30 OD and 20/20 OS and SD-OCT normalized.

Case 2. 58-year old with ovarian CA had blurred vision. Pimasertib was initiated one day prior. BCVA was reduced to 20/50 OD and 20/30 OS, from 20/20 OU ten days prior. Exam revealed bilateral multifocal neurosensory RD. Nine days prior to initiating therapy SD-OCT was normal. SD-OCT one day after starting Pimasertib revealed bilateral multiple neurosensory retinal detachments. IVFA revealed non leaking CME. Pimasertib was discontinued and one week later, her vision returned to 20/20 OU and SD-OCT normalized.

CONCLUSIONS: Our case series and review of the literature highlights the need to raise awareness of the retinal side effects of MEK inhibitors. The development of retinopathy will become more prevalent as use of MEK inhibitors for cancer expands. We recommend that patients undergoing treatment with MEK inhibitors undergo routine fundus exam with OCT evaluation prior to and after initiation of these agents.
How do Large Retinal Pigment Epithelial Detachments Respond to Ranibizumab Treatment in HARBOR?

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PURPOSE: Retinal pigment epithelial detachments (PEDs), especially large PEDs, are challenging to manage in patients with wet age-related macular degeneration. An exploratory subanalysis was performed to evaluate the effect of ranibizumab on large PEDs over 2 years.

METHODS: In HARBOR, 1097 patients were randomized to receive 3 consecutive monthly doses of intravitreal ranibizumab 0.5 mg or 2.0 mg. Then, patients either continued with monthly therapy or were re-treated PRN based on VA and strict SD-OCT criteria. Patients’ change in best-corrected visual acuity (BCVA) from baseline, PED resolution, PED thickness reduction, and number of injections in the PRN groups were assessed over 24 months. The development of macular atrophy was assessed at Month 24 (M24) in patients without detectable atrophy at baseline. Vertical heights of PEDs were 35-1400 µm on SD-OCT at baseline and results were evaluated using 4 equal-sized groups based on baseline PED thickness. The current analysis defined large PEDs as those in the largest PED group (≥352 µm).

RESULTS: Of the 598 patients with a PED at baseline, 150 (25.1%) had a large PED. Mean change from baseline in BCVA at M24 was +6.4 and +5.3 letters in patients with large PEDs who received ranibizumab 0.5 mg monthly or PRN, respectively. No additional vision benefit was observed in patients with large PEDs who received ranibizumab 2.0 mg monthly or PRN (mean change at M24 from baseline: -0.8 and +7.7 letters, respectively). There was a slightly larger decrease in PED thickness at M24 in the 2.0 mg arms (0.5 mg: monthly, -257.3 µm, PRN, -277.4 µm; 2.0 mg: monthly, -349.3 µm, PRN, -387.5 µm). Among study eyes with PED at baseline and no detectable atrophy at baseline, more atrophy was seen at M24 in ranibizumab-treated eyes with PED absent (n=101; 44%) than PED present (n=30; 16%).

CONCLUSIONS: These results suggest that ranibizumab 0.5 mg monthly or PRN effectively manages large PEDs and results in clinically significant VA gains over 2 years. While large PEDs had a greater anatomic response to 2.0 mg ranibizumab, no additional vision benefit was seen. More atrophy was seen at M24 in eyes with complete flattening of PED.
Change of Choroidal Structure in Central Serous Chorioretinopathy Analyzed by Binarization Technique on Optical Coherence Tomography

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PURPOSE: To evaluate the choroidal structure in central serous chorioretinopathy (CSC) on optical coherence tomographic (OCT) images.

METHODS: A non-interventional case-control study was done at Kagoshima University. The subfoveal choroidal images (1500 mm width) on enhanced depth imaging (EDI)-OCT were analyzed, and the luminal and interstitial areas were converted to binary images by the Niblack method as we reported earlier (Sonoda et al. AJO, 2015). The low reflective area represents vascular lumen and the high reflective area does interstitial tissue. The inner-choroidal area, choriocapillaris and Sattler’s layer, and the outer choroidal layer, Haller’s layer, were separately quantitated and analyzed. The choroidal structures including the ratio of luminal/interstitial areas were compared in eyes with CSC and control eyes.

RESULTS: Twenty-four eyes with CSC and 24 age-matched control eyes were included in this study. The total cross-sectional choroidal area was significantly larger in eyes with CSC 10.2 x10^5 Qm2 than controls 7.2 x10^5 µm^2 (P<0.01). In eyes with CSC, the inner choroid was 13.5% and the outer choroid was 86.5% of the total choroidal area; while in controls, the inner choroid was 18.1% and the outer choroid 80.8% of total choroidal area, indicating that the outer choroid was significantly increased in eyes with CSC (P<0.01). In terms of the ratio of luminal/interstitial area, in inner choroid, it was 3.31 in controls and 1.91 in CSC eyes (P<0.05), which suggests that the luminal area was smaller in eyes with CSC. In the outer choroid, oppositely, it was 2.42 in controls and 2.78 in eyes with CSC (P<0.05), suggesting that the luminal area was larger in the outer choroid of eyes with CSC.

CONCLUSIONS: The Niblack binarization method can be used to analyze the luminal area of choroid in an OCT image. In CSC eyes, choroidal area is increased mainly due to Haller’s layer. The vascular lumen of the inner choroid (choriocapillaris and Sattler’s layer) was smaller, but that of the outer choroid, Haller’s layer, was larger than those of controls. Vasoconstriction of inner choroid and vasodilatation of outer choroid might play a certain role in pathogenesis of CSC.
Detection of Choroidal Neovascularization (CNV) in Chronic Central Serous Chorioretinopathy (CSCR) with Optical Coherence Tomography Angiography (OCTA)

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PURPOSE: Choroidal neovascularization (CNV) is a potential complication of chronic central serous chorioretinopathy (CSCR). Detection of CNV in CSCR may be challenging due to coexisting anatomical and angiographic changes related to the primary diagnosis. Optical coherence tomography angiography (OCTA) is a novel, non-invasive modality to image the retinal and choroidal vasculature. This study assessed the sensitivity of spectral-domain OCTA to detect CNV associated with chronic CSCR.

METHODS: Observational, cross-sectional study evaluating individuals presenting to New England Eye Center, Boston with suspected CNV secondary to chronic CSCR. All eyes were imaged with a prototype OCTA software on a commercially-available spectral-domain OCT to obtain 3 x 3 mm and 6 x 6 mm OCT angiograms centered on the fovea. Standard imaging with fluorescein angiography (FA) and/or conventional spectral domain OCT was obtained. OCTA images were evaluated in a masked fashion for presence and features of CNV and co-registered OCT b-scans were used to determine CNV location and assess for intraretinal or subretinal fluid. Sensitivity and specificity of OCTA detection of CNV compared to FA was estimated.

RESULTS: Twenty-seven eyes of 23 individuals were included. CNV was diagnosed in 8 eyes (30 %) with FA. OCTA and co-registered OCT B-scans detected 100% (8/8) of CNV and excluded 100% (19/19) of CSCR eyes without CNV. Sensitivity was 100% (95% CI, 0.59 to 1.0) and specificity was 100% (95% CI, 0.79 to 1). From the 8 eyes with confirmed CNV, 4 eyes (50%) had type 1 CNV and 4 eyes (50%) had mixed CNV (type 1 and type 2) detected by both standard OCT and corresponding OCTA b-scans. On OCTA, 5 eyes had well-circumscribed CNV and 3 eyes had poorly-circumscribed vessels. Manual segmentation delineated CNV boundaries in 6 eyes (75%) and feeder vessel in 2 eyes (25%). All 8 eyes with CNV and 9 eyes without CNV presented with domed elevation of the RPE and heterogeneous, hyperreflective material under the RPE line.

CONCLUSIONS: OCTA combined with co-registered OCT b-scans provides flow and structural characteristics respectively, to accurately detect the presence and features of CNV in chronic CSCR.
**En Face Imaging of Pachychoroid Spectrum Disorders with Swept-source Optical Coherence Tomography**

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**PURPOSE:** To correlate clinical manifestations with choroidal morphology in pachychoroid spectrum disorders – central serous chorioretinopathy (CSC), pachychoroid pigment epitheliopathy (PPE), pachychoroid neovasculopathy (PNV) and polypoidal choroidal vasculopathy (PCV) – using en face swept-source OCT (SS-OCT). Long wavelength SS-OCT images the choroid at greater depth and with shorter acquisition times than EDI SD-OCT.

**METHODS:** Patients with pachychoroid diagnoses were recruited non-consecutively for retrospective review of charts and multimodal imaging. Each eye was categorized as uncomplicated pachychoroid, PPE, CSC, PNV or PCV. All patients underwent bilateral SS-OCT prospectively.

**RESULTS:** Sixty-six eyes of 33 patients were included. Numbers assigned to diagnostic categories were: 8 uncomplicated pachychoroid; 13 PPE; 27 CSC; 15 PNV; 3 PCV. One eye was classified normal. SS-OCT choroidal thickness maps confirmed increased thickness under areas of PPE, CSC, type 1 NV (PNV), or polyps (PCV). En face SS-OCT showed dilated outer choroidal vessels in all eyes. In several eyes with chronic disease, focal choriocapillaris atrophy with inward displacement of deep choroidal vessels was also appreciated.

**CONCLUSIONS:** Although clinical manifestations of pachychoroid disorders vary considerably, these entities share morphologic findings in the choroid, including increased thickness and dilated outer choroidal vessels. En face SS-OCT localizes these changes to disease foci and also shows additional findings (e.g. focal choriocapillaris atrophy) that may advance our understanding of pathogenesis.
Increased Inward Deflection (ID) of Cone Photoreceptors is the Earliest Sign of Traction on the Fovea

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PURPOSE: To define physiological limits of foveal ellipsoid zone (EZ) and external limiting membrane (ELM) ID and determine whether increased ID represent an early sign of vitreoretinal traction.

METHODS: Image analyses were performed on high-definition OCT scans of 33 eyes with vitreomacular interface anomalies (14 VMA, 3 VMT and 15 ERM) and 53 age and gender-matched controls. Cartesian coordinate systems were established along a vertical line bisecting the foveola and the angle that subtends between the center s (x0, y0) and the inflection points were measured at inner foveal surface, ELM and EZ. Photoreceptor outer segment integrity was also assessed by computing the optical density in between 2nd and 3rd outer bands.

RESULTS: In normal eye nasal and temporal slopes of the fovea subtends an angle of 17.5º±3.8º and 17.8º±4.5º at the inner retinal surface, 4.0º±3.0º and 4.1º±3.4º at the ELM plane and 3.6º±2.9º and 3.8º±3.0º at EZ. Steepness of the foveal surface correlates negatively with ID of the outer retina. In VMA, inner foveal distortion remains the same, but nasal and temporal ELM (12.4º±5.0º and 10.5º±3.9º) and EZ (10.5º±3.9º and 10.2º±2.6º) distortions increase (p2 SD) ID of ELM and ellipsoid occurs in VMA (53.6%/57.2%), ERM (83.4%/83.4%) and VMT (66.6%/16.7%).

CONCLUSIONS: ELM and ellipsoid lines can physiologically be deflected inwards for up to 10º at the fovea due to longer cone outer segments at fovea. Weaker anteroposterior traction in VMA can only cause ID of the EZ and ELM. It requires a greater tractional force, as in cases of ERM or VMT, to distort the inner retinal architecture. In such cases, inward stretching of the outer retina beyond its elastic limit results in outer segment break down and shedding which becomes evident by increased optical density underneath the fovea.
Pneumatic Vitreolysis for Vitreomacular Traction: A Case Series and Meta-analysis of the Literature

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PURPOSE: To evaluate the efficacy and safety of available treatment options for vitreomacular traction (VMT).

METHODS: This retrospective, consecutive single-center case series and meta-analysis included a total of 1914 eyes diagnosed with VMT from both a single institution consecutive case series (35 eyes) and a meta-analysis of the literature. The main outcome measures were VMT resolution (VMTr) confirmed by OCT at 28 days (primary), and visual acuity at 6 months, macular hole (MH) closure at any point in follow-up, central foveal thickness at 28 days, and complication rate (secondary).

A comprehensive literature search using Boolean search logic for VMT and vitreomacular adhesion on PubMed was performed. Reviews, non-consecutive series, and single case reports were excluded. Patients from studies analyzed, including the presented case series, were placed into five cohorts: (1) observation, (2) intravitreal placebo injection, (3) intravitreal gas injection with face-down positioning (pneumatic vitreolysis, PV [SF6 or C3F8]), (4) intravitreal ocriplasmin (IVO) injection, and (5) pars plana vitrectomy (PPV).

RESULTS: Case Series: Zero of 10 control (0%), 3 of 7 IVO (42.9%; p=0.10), 7 of 8 PV (87.5%; p<0.01), and 10 of 10 PPV (100%; p<0.01) treated eyes experienced VMTr at day 28. A third of IVO and PPV patients and 50% of PV patients had VA improvement. No patients developed retinal tears or detachment. One PV (12.5%) patient developed a macular hole.

META-ANALYSIS: Twenty-three of 241 control (9.5%), 176 of 644 IVO (27.3%; p<0.01), 46 of 63 PV (73.0%; p<0.01), and 252 of 252 PPV (100%; p<0.01) treated eyes experienced VMTr at day 28, and 216 of 660 observation (32.7%) at any follow up period. IVO had a significantly lower rate of VMTr compared to PV (p<0.01). Of the papers reporting complications, 0 of 49 PV (0%), 22 of 674 IVO (3.3%), and 5 of 241 PPV (2.1%) patients experienced a retinal tear or detachment.

Secure Web-based Survey Tool: Based on our results, we developed a secure, HIPAA-compliant, IRB-approved web-based REDCap survey tool accessible by all retina specialists to help further delineate the efficacy and safety of PV for VMT.

CONCLUSIONS: Our case series and meta-analysis of the literature found that PV releases VMT in a majority of patients, and appears to be more effective than other non-surgical methods. The complication rates for PV were similar or better than other treatments for VMT. Further study of PV through secure web-based data collection survey tools and/or randomized controlled trials is certainly warranted.
Formation of an Intraretinal Fluid Barrier in Eyes with Cavitary Optic Disc Maculopathy

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PURPOSE: Cavitary optic disc maculopathy develops when fluctuating pressure gradients along anomalous communications in the optic nerve head induce migration of fluid into the adjacent retinal tissue. We sought to determine whether carefully titrated laser photocoagulation combined with vitrectomy and gas tamponade can safely create an effective intraretinal barrier to fluid egress from the optic disc cavitation.

METHODS: We retrospectively evaluated medical records and imaging studies of consecutive patients with cavitary disc maculopathy evaluated by a single surgeon between 1991 and 2014. Patients requiring surgery underwent carefully titrated juxtapapillary laser photocoagulation (typically at the slit-lamp) combined with vitrectomy and gas tamponade. Where available, OCT was used to guide the extent of laser treatment and assess the intraretinal fluid barrier postoperatively.

RESULTS: Of 22 patients reviewed, 11 patients (11 eyes) had undergone vitreous surgery and were included in the study. Five study patients had undergone at least one previous unsuccessful juxtapapillary laser treatment. No preoperative evidence for vitreous traction on the optic disc or macula was seen in any eye. Nine patients had a single surgery while 2 patients required up to 3 additional procedures to resolve the macular fluid. Mean length of follow-up after the last surgery was 46.4 months. All ten patients (100%) with at least 6 months of postoperative follow-up had complete resolution of macular fluid, with an average time to resolution of 8.9 months (range, 1-20). The remaining patient had resolving macular fluid 5 months postoperatively. Only 1 of 11 patients (9%) had recurrence of macular fluid (14 months postoperatively). The average preoperative visual acuity was 20/125 (logMAR 0.81, SD = 0.36) and improved by nearly 4 lines to an average final visual acuity of 20/57 (logMAR 0.45, SD = 0.37)(p = 0.0072). A possible laser-induced central scotoma was suspected in only one patient who had undergone extensive prior laser treatments.

CONCLUSIONS: An effective intraretinal barrier to fluid migration from cavitary optic disc anomalies can be safely achieved in most patients with carefully titrated juxtapapillary laser photocoagulation combined with vitrectomy and gas tamponade. Once achieved, the barrier results in resolution of macular fluid and long-term avoidance of recurrent maculopathy.
Inner and Outer Retinal Damage in Hydroxychloroquine Toxicity

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PURPOSE: The primary clinical sign of hydroxychloroquine (HCQ) retinopathy is thinning of the photoreceptor layers in the parafovea and eventually beyond. Several papers have suggested that inner retina may be affected to a modest degree during clinical exposure, and the issue has relevance as experimental studies have shown damage across all retinal layers. We have re-examined the question regarding damage during exposure to HCQ by using a larger population of non-toxic users than in previous studies, and by following patients over a number of years.

METHODS: The study population comprised patients followed for HCQ usage without evidence of retinopathy, and was divided into users for 5 yrs or less, and for 15 yrs or more. From these two populations, we compared patients were followed for an average of at least 3 years. And we also compared group data between age-matched patients (49 – 65 yrs). SD-OCT measurements were analyzed both from the instrument itself (ETDRS cube thicknesses and ganglion cell analyses) and by a segmentation program that recognizes inner and outer retinal boundaries pixel-by-pixel across the retina and shows topographic changes.

RESULTS: Neither short- or long-term users showed any change in inner or outer retinal thickness over several years of follow-up. And there was no difference in inner or outer retinal thickness between the two population groups. There were only a couple of outlier values, largely staying within OCT recording error. One patient in the long-term group developed evidence of toxicity (parafoveal outer retinal thinning) at her final visit, although she had shown no abnormalities prior to that visit.

CONCLUSIONS: The results indicate that inner retina is not affected to any significant degree as HCQ exposure increases. We have drawn similar conclusions from patients already showing retinopathy. Some of the prior reports might have reflected population bias, or deformation as the ganglion cell analysis does not always follow outer retinal pathology. We believe that clinical toxicity from HCQ is for practical purposes limited to the photoreceptors and outer retina.
Volume Rendering Optical Coherence Tomography Angiography of Macular Telangiectasia Type 2

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PURPOSE: To evaluate the vascular structure of eyes with macular telangiectasis type 2 (MacTel 2) by using volume rendered optical coherence tomography angiography (OCTA).

METHODS: Fourteen consecutive patients (20 eyes) with MacTel 2 who had a signal strength score of 55 or greater and could maintain fixation during the scan process were evaluated in a retrospective cross-sectional study. The eyes were scanned using optical coherence tomography (OCT) using split spectrum amplitude decorrelation techniques to derive flow information. The flow data was extracted and used to create volume rendered images of the retinal vasculature, an approach inherently better at preserving three dimensional relationships of vessels than en-face imaging techniques. The images could be rotated about 3 different axes for evaluation and a descriptive appraisal of the vascular abnormalities associated with MacTel 2.

RESULTS: Vessels posterior to the outer boundary of the deep retinal plexus were seen to be secondary to retinal thinning, vascular invasion, or a combination of both. These vessels had the same shape and distribution as the late staining seen during conventional fluorescein angiography. Lateral contraction in the temporal macula in 5 eyes created an appearance of vessels radiating from a central locus, which was the site of a right angle vein. Loss of macular tissue as part of the disease process led to a central amalgamation of the inner vascular plexus and the deep vascular plexus, which appeared to be in a state of decline. Subretinal neovascularization originated from the retinal circulation but involved not only the subretinal space, but could also infiltrate the remaining, thinned, retina.

CONCLUSIONS: Volume rendering of OCTA information preserves the three dimensional relationships among retinal vascular layers, and provides opportunities to visualize retinal vascular abnormalities in unprecedented detail. The retinal vascular leakage and invasion in MacTel 2 may arise as a consequence of loss of control with depletion of Müller cells and exposure of the remaining retinal vessels to the more hypoxic environment near the inner segments of the photoreceptors.
Fundus Tessellation: Prevalence and Associated Factors. The Beijing Eye Study 2011

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PURPOSE: To examine the prevalence of fundus tessellation and its associated factors.

METHODS: The population-based Beijing Eye Study 2011 included 3468 individuals with a mean age of 64.6±9.8 years (range: 50-93 years). The participants underwent a comprehensive ophthalmic examination. Using 45° color fundus photographs of the macula and optic disc, fundus tessellation defined as variation in the visibility of the large choroidal vessels was differentiated into three grades.

RESULTS:
Assessment of fundus tessellation was available for 3442 (99.6%) individuals with a mean age of 64.639.8 years (range: 50 to 93 years). In multivariate analysis (correlation coefficient r:0.68), higher degree of fundus tessellation (mean:0.8430.79) was associated with older age (P<0.001; standardized correlation coefficient beta:0.14), male sex (P<0.001; beta:-0.08), lower body mass index (P=0.03; beta:0.03), worse best corrected visual acuity (P<0.001; beta:0.05), thinner subfoveal choroidal thickness (P<0.001; beta:-0.51), longer axial length (P<0.001; beta:0.11), larger parapapillary beta zone (P<0.001; beta:0.08), lower prevalence of intermediate age-related macular degeneration (P=0.02; beta:0.04), and lower prevalence of late age-related macular degeneration (P=0.007; beta:0.04). If parapapillary beta zone was dropped (due to its collinearity with glaucoma), higher glaucoma prevalence was (P=0.003) associated with higher degree of macular fundus tessellation. Prevalence of diabetes mellitus and retinal vein occlusions, mean blood pressure and intraocular pressure were not significantly (all P>0.10) associated with fundus tessellation. In a reverse manner, thinner subfoveal choroidal thickness was associated with higher degree of macular fundus tessellation. Prevalence of diabetes mellitus and retinal vein occlusions, mean blood pressure and intraocular pressure were not significantly (all P>0.10) associated with fundus tessellation. In the multivariate analysis. In univariate analysis, subfoveal choroidal thickness decreased from 322±90µm (95% CI:317,327) in eyes without fundus tessellation to 229±80µm (95% CI:225,233) in eyes with grade 1 of fundus tessellation, to 122±52µm (95% CI:116,128) in eyes with grade 2, and to 81±37µm (95% CI:74,89) in eyes with grade 3 of macular fundus tessellation.

CONCLUSIONS: Fundus tessellation is a surrogate for choroidal thinness and may be a clinical sign for a leptochoroid. After adjusting for ocular and systemic parameters, fundus tessellation is additionally associated with larger parapapillary beta zone and higher glaucoma prevalence, and with lower prevalence of intermediate and late age-related macular degeneration. Its association with lower visual acuity warrants further investigation.
Intravitreal Afibercept for Neovascular Polypoidal Choroidal Vasculopathy (PCV) in a Predominantly Non-Asian Population

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PURPOSE: Evaluation of anti-VEGF therapy for PCV has primarily occurred in Asian patients and little data exist for African-American and Caucasian populations. In fact, African-Americans are hardly represented in neovascular AMD anti-VEGF trials. Ethnic differences in PCV may well affect treatment responses due to genetic makeup, variances in the natural history of disease, and living environments. Given the frequent persistence and recalcitrant nature of PCV-related CNV, as well as infrequent rates of complete polyp regression using ranibizumab or bevacizumab monotherapy, we evaluated the safety and potential efficacy of intravitreal afibercept in the treatment of PCV-related CNV in a predominantly non-asian population.

METHODS: Open-label, unmasked, non-randomized study enrolled 20 eyes (10 treatment-naïve; 10 previously treated) with neovascular PCV from 20 patients. Eyes received monthly afibercept 2.0 mg intravitreally for 3 months followed by mandatory afibercept every 2 months for 12 months. Patients were followed and evaluated monthly with possible additional afibercept or non-anti-VEGF rescue treatment if pre-defined criterial were met.

RESULTS: Twenty of 20 eyes and 17 of 20 eyes have 3 and 6 months follow-up to date, respectively. Average age of participants (10 African Americans, 8 caucasians and 2 asians; 11 males; 9 females) was 69 years (45 – 90 years). At baseline, average visual acuity was 59 letters (21 to 83 letters) with Snellen equivalent of 20/63 (20/320 to 20/20). At baseline, average OCT central subfield thickness (CST) was 280 um (124 to 603 um). At 3 months, average visual acuity was 68 letters indicating an average gain of 9 (range 6 loss to 50 gain) letters (treatment-naïve eyes gained 13.6 letters; previously treated eyes gained 4.2 letters). At 3 months, average OCT central subfield thickness was 214 um indicating an average thinning of 65 um (range 132 um thickening to 325 um thinning). On average treatment-naïve eyes thinned 67 um and previously treated eyes thinned 63um. For eyes completing 6 months follow-up, average visual acuity was 69 letters with an average gain of 10 (range 15 loss to 50 gain) letters (treatment-naïve eyes gained 25 letters; previously treated eyes gained 4 letters). At 6 months, average OCT central subfield thickness was 215 um indicating an average thinning of 77 um (range 73 um thickening to 372 um thinning). On average treatment-naïve eyes thinned 72 um and previously treated eyes thinned 82 um. No endophthalmitis, retinal tears or detachment, vitreous hemorrhage or arterial thrombotic events were observed.

CONCLUSIONS: This data indicates favorable initial and moderate-term visual acuity and anatomic response, as well as safety with afibercept for neovascular PCV in a predominantly non-asian population.
Effects of Intravitreal Aflibercept on Patients with Polypoidal Choroidal Vasculopathy: Results of VAULT Study

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PURPOSE: To investigate efficacy of intravitreal aflibercept injection in patients with treatment-naive polypoidal choroidal vasculopathy (PCV).

METHODS: A prospective, multi-center, single-arm, interventional case series conducted in South Korea. Forty seven patients with PCV confirmed using indocyanine green (ICG) angiography were enrolled for the 1 year study. Aflibercept (2.0 mg) was injected into the vitreous every month three times and then every two months. Visual acuity measurement and optical coherence tomography were performed every visit. Fluorescein and ICG angiography were obtained at baseline and month 3.

RESULTS: After 3 loading doses of aflibercept, visual acuity improved significantly from 53.7 at baseline to 62.8 letters at month 3 (p<0.01). On ICG angiography, complete polyp regression was seen in 25 eyes (55.3%), partial regression in 15 eyes (31.9%), and no change in 6 eyes (12.8%). At 6 months, visual acuity maintained to 63.8 letters, and 95.7% of eyes lost visual acuity less than 15 letters. Central macular thickness changed from 373.7 um at baseline to 256.9 um at month 6 (p<0.01).

CONCLUSIONS: Aflibercept intravitreal injections showed favorable outcomes for PCV at month 6. One-year outcomes will be presented in the meeting.
Effect of Paracentesis on Retinal Nerve Fiber Layer Thickness During Intravitreal Anti-VEGF Therapy

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PURPOSE: To compare change in retinal nerve fiber layer thickness (RNFLT) in eyes treated with intravitreal anti-VEGF injection performed with and without paracentesis.

METHODS: In this prospective cohort study, eyes with newly diagnosed choroidal neovascularization secondary to age-related macular degeneration (AMD) which began intravitreal anti-VEGF therapy (n=179) were treated either with paracentesis (n=75) or without paracentesis (n=104) and followed for at least 8 months. Forty-four untreated fellow eyes served as controls. We obtained ocular coherence tomography (OCT) prior to each injection. Intraocular pressure (IOP) was measured with tonopen prior to, immediately after and 10 minutes after injection. The primary outcome was mean change RNFLT. Secondary endpoints included maximum post injection IOP (max IOP), pre to post injection change in IOP (change IOP), IOP prior to injection at last visit (final IOP), mean number of injections and endophthalmitis.

RESULTS: After mean follow-up of 27.7 and 31.3 months in groups 1 and 2 respectively, mean change in RNFLT was greater in eyes which did not receive paracentesis (-1.3um vs. -5.1um (p <0.0001)). Mean max IOP were 19.1mm hg and 54.1 mm hg and mean change IOP was 4.5mm hg (range -15 to 24) and 39.9 mm hg (range 13 to 60) for groups 1 and 2 respectively (p<0.0001). Similar results were found when using multiple linear regression accounting for age, gender, number of injections, follow-up time, baseline RNFL, and baseline IOP. In these models, maxIOP, change in IOP, and change in RNFL all remained significant (p<0.0001 for each) and final IOP remained not significant (p=0.173). Endophthalmitis requiring vitreous tap and intravitreal antibiotic injection developed in 2 group 2 eyes (2 patients) (0.16% of injections, 2.3% of patients).

CONCLUSIONS: Loss of RNFLT was significantly greater in eyes that received intravitreal anti-vegf injection without paracentesis. Incidence of post injection endophthalmitis was not increased by paracentesis. The clinical significance of the observed RFNLT loss may vary depending on comorbidities including glaucoma, and requires further study.
Genotype- Phenotype Correlation of Mutations Occurring in Wnt-Associated Vitreoretinopathies (WAVR): A Basis for Genetically Tailored Management

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PURPOSE: Mutations in the Wnt Signaling pathway are known to be associated with a spectrum of inherited vitreoretinopathies (WAVR). The severity of retinopathy varies widely within the same family and even between fellow eyes. We sought to determine the phenotypes associated with specific mutations in an effort to understand the functional significance of the genetic loci involved.

METHODS: This is a retrospective chart review of patients with mutations in NDP, Fzd4, TSpan12 and LRP5. Presenting stage and visual acuities were recorded. The locus of each mutation was compared to other mutations at the same residue, within the same exon, and with published mutations. The mutations in NDP and Fzd4 were mapped on available structural data to identify key domains and 3 dimensional analysis was performed.

RESULTS: One hundred thirty eyes from 65 patients were included in the study; 27 mutations in NDP, 33 in Fzd4, 2 in TSpan12, and 2 in LRP5 were identified. 78% of patients with mutations in NDP presented with bilateral stage 5 disease. Structural analysis of these mutations mapped to the pocket responsible for binding to Fzd4. These mutations included residues in all three exons, with greatest severity noted in the cysteine-knot mutations. 43% of patients with mutations in Fzd4 presented with bilateral stage 5 eyes. Nine patients carried mutations in the cysteine-rich domain which has been shown to be required for binding to Norrin. 23% percent of patients with mutations in Fzd4 had stage 1 or stage 2 disease and did not require surgery. Mutations in TSpan12 and LRP5 resulted in mild disease (one eye requiring surgery).

CONCLUSIONS: Patients with the worst disease had mutations in the binding interface between Norrin and the frizzled receptor. Mutations affecting teh coreceptors, LRP5 and TSpan12, resulted in less severe pathology. The tertiary analysis confirms the importance of Norrin:FZD4 binding in the development and maintenance of retinal vasculature. Furthermore, other Wnt ligands capable of binding the FZD4 receptor are not able to rescue development. These data provide insight into the molecular and structural basis of the FEVR phenotype and correlate disease severity and progression to genetic alterations. From this data a more tailored approach to patient management is possible.
Scleral Buckle Surgery for Primary Retinal Detachment without Posterior Vitreous Detachment

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PURPOSE: To present and analyze the anatomical and functional outcomes for scleral buckling (SB) procedure performed in a group of patients with rhegmatogenous retinal detachment (RRD) without posterior vitreous detachment (PVD).

METHODS: An electronic health record search was performed for a single surgeon (awe) for CPT code 67107 (scleral buckle) from 2005 through 2014. From a total of 244 charts, 40 patients (45 eyes) were identified as fulfilling the criteria of presenting with a RRD without PVD. In this case series, we reviewed patient demographics, visual outcomes, preoperative clinical retinal findings in both eyes and applied SB techniques in treated eyes. The main outcome measure was single SB surgery success rate.

RESULTS: The mean age was 29 years (range: 11-51 years). The mean follow up period was 17.7 months. The mean refractive error was -5.15 D (SE). High Myopia (RE>= -6.00D) was present in 18 patients (42.8%) and history of trauma in 10 patients (23.8%). Ten eyes had dialysis and all the other eyes had obvious atrophic holes. 7 cases had bilateral RRD. The fellow eyes of 16 patients underwent prophylactic laser for retinal breaks, lattice degeneration or demarcation of subclinical RRD.

The SB technique most frequently applied was usage of a tire with an encircling band. Subretinal fluid drainage was performed in only 17 eyes (37.8%). The anatomical success rate after single SB surgery was 91.1%. In all of the 4 failed cases, second surgery with vitrectomy was successful. Complications included limited subretinal hemorrhage (4) and diplopia (1).

CONCLUSIONS: In spite of an increasing trend toward vitrectomy as the primary surgical procedure for RRD repair, the SB remains a highly effective and valuable surgical technique, with very few complications. Patients without a pre-existing PVD are ideal candidates for a primary scleral buckling procedure. These detachments are generally inferior in location, the patients are younger with a formed vitreous body, and a stronger vitreo-retinal adhesion, which may increase complications during vitrectomy. Post-operative positioning is often not required, allowing for a faster return to daily activities. In our study, eyes with RRD without PVD, there was a 91.1% primary success rate with SB and 100% with a second surgery.
Fundus Pigmentation as a Risk Factor for Development of Retinopathy of Prematurity

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PURPOSE: Retinopathy of prematurity (ROP) can lead to irreversible vision loss in premature infants. The risk factors for ROP have been described to include younger gestational age, low birth weight, and prolonged unregulated oxygen exposure. Fundus pigmentation has been proposed to be protective in a number of diseases such as AMD due to the ant-oxidant properties of melanin. Here we examined the relationship between fundus pigmentation and ROP development and severity.

METHODS: A multicenter database was prospectively generated from infants screened for ROP at 6 centers in the United States, whose parents consented for participation. 1,336 newborns were screened for the presence of ROP. The database was reviewed to identify all risk factors for the development of ROP in pre-mature infants. Data analysis was performed based on the initial screening exam for infants and included gestational age (GA) at birth, birth weight, ethnicity, fundus pigmentation (light/medium were combined into one group and compared versus dark), ROP stage, and need for treatment.

RESULTS: Patients had a mean GA of 27.8 weeks, mean birth weight of 1035 grams, and 54.8% male gender. Fundus pigmentation (FP) was recorded as 483 (36.2%) light, 729 (54.6%) medium, and 124 (9.3%) as dark. ROP was diagnosed in 536 (40.1%) infants with 122 (22.8%) requiring treatment. The risk of ROP development was not different between dark versus light/medium FP (p>0.05). In infants with ROP, linear regression analysis showed a significant correlation between treatment–requiring ROP and light/medium FP (p<0.05), but not with birth weight or GA. Interestingly darker FP was correlated with younger GA, a known risk factor for ROP (p<0.05). Although ROP patients with light FP had a lower mean stage of ROP at presentation, 1.67 versus 1.88 in medium and 1.90 in dark (t-test p<0.001), patients with dark FP had a lower incidence of requiring treatment (t-test p<0.05) with 24.4% of light/medium versus 6.1% dark FP patients requiring treatment (p<0.005).

CONCLUSIONS: In this study risk of ROP was increased in patients with darker FP, consistent with the finding that increased FP correlates with younger GA, and thus more attenuated vascular development. In contrast, darker FP appeared to be protective in the development of severe ROP requiring treatment. This may be in part related to underlying genetic factors. However, further studies are needed to fully understand the biological basis for this finding.
Development, Implementation, and Evaluation of a Novel Retinopathy of Prematurity (ROP) Tele-Education System

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PURPOSE: To describe the design, implementation, and evaluation of a tele-education system developed to improve diagnostic competency in retinopathy of prematurity (ROP) by ophthalmology residents.

METHODS: A secure web-based tele-education education system was developed utilizing a repository of over 2500 unique image sets of ROP. For each image set used in the system, a reference standard ROP diagnosis was established. Performance by ophthalmology residents (PGY-2 to PGY-4) from the United States and Canada were prospectively evaluated in taking the ROP tele-education program. Residents were presented with image-based clinical cases of ROP during a pretest, posttest, and training chapters. Accuracy and reliability of ROP diagnosis (e.g. plus disease, zone, stage, category) were determined using sensitivity, specificity, and the kappa statistic calculations of the results from the pretest and posttest.

RESULTS: Fifty-five ophthalmology residents were provided access to the ROP tele-education program. Thirty-one ophthalmology residents completed the program. When analyzing all training levels together, a statistically significant increase was observed in sensitivity for the diagnosis of plus disease, zone, stage, category, and aggressive posterior ROP (APROP) \((P<.05)\). Statistically significant changes in specificity for identification of stage 2 or worse \((P=.027)\) and pre-plus \((P=.028)\) were observed. Intra-grader agreement, as determined by the kappa statistic, improved for identification of plus disease, zone, stage, and category of ROP after completion of the ROP tele-education program. In addition, trainees felt that their understanding of the diagnosis of ROP improved after participating in the ROP tele-education program.

CONCLUSIONS: A tele-education system for ROP education is effective in improving diagnostic accuracy of ROP by ophthalmology residents. This system may have utility in the setting of both healthcare and medical education reform by creating a validated method to certify telemedicine providers and educate the next generation of ophthalmologists.
Pediatrician Eye Exam vs Photographics Screening Validation Testing in Newborn Infants

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PURPOSE: The present study aimed to detect the validity of the pediatric ophthalmic exam using digital imaging as a gold standard. We hypothesized that the pediatric newborn ophthalmic exam has poor sensitivity for detecting ophthalmic abnormalities, which may lead to undetected vision disorders.

METHODS: This study included newborns screened in the Newborn Eye Screening Test (NEST) study, a prospective cohort study conducted at Lucile Packard Children’s Hospital at Stanford University. Pathology detected on imaging reviewed by a pediatric vitreoretinal specialist was compared with pathology reported in pediatrician notes prior to newborn discharge.

RESULTS: A total of 202 infants were consecutively screened in Year 1. Compared to 20 subjects with abnormal ophthalmic findings reported in pediatrician notes, 70 subjects demonstrated one or multiple ophthalmic abnormalities on imaging ($\kappa = 0.05$, CI: -0.06-0.16). Only 1/202 subjects demonstrated agreement on the type of abnormality reported by the pediatric ophthalmic exam and the RetCam III. External examination was the most common exam maneuver reported (99.5%) followed by the red reflex exam (96%), the pupillary exam (86.6%) and the extraocular motility and alignment exam (32.2%).

CONCLUSIONS: This study demonstrates low sensitivity (12.9%) and positive agreement (8.5%) of the pediatric ophthalmic exam as compared to digital photographic imaging of newborns. Future studies will monitor the NEST cohort longitudinally to detect changes in vision that may be related to pathology detected with digital ophthalmic imaging.
A Retrospective Comparison of Retinopathy of Prematurity Treated with Bevacizumab versus Laser

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PURPOSE: The BEAT-ROP study demonstrated significantly less recurrence of retinopathy of prematurity (ROP) after bevacizumab injection than after laser ablation at 54 weeks post-menstrual age (PMA). However, we have reported several cases of tractional retinal detachment (TRD) after bevacizumab, occurring up to 80 weeks PMA. Given this risk of recurrence after bevacizumab, we have recommended ablation of persistent avascular retina at 60 weeks PMA. The purpose of our study is to compare 80-week outcomes after initial photocoagulation versus initial bevacizumab and planned subsequent laser.

METHODS: Retrospective chart review was undertaken of patients with ROP at the University of Chicago (UC) from January 2006 to August 2014. Included patients had type 1 pre-threshold ROP and follow-up of 80 weeks PMA. Eyes were treated initially with either intravitreal bevacizumab (0.625 mg) or peripheral laser ablation. Primary outcome was progression to retinal detachment.

RESULTS: Of 561 neonates with ROP during the time period, 66 were treated for ROP, and 58 met inclusion criteria. Patients were excluded for: treatment elsewhere (2), death before treatment (1), missing data (5). There were 32 patients in the bevacizumab group and 26 in the laser group. Mean birth weight was 692 g and 733 g, respectively. Mean PMA at birth and initial treatment was 25 and 37 weeks, respectively, in both groups. No eye in the bevacizumab group progressed to TRD, while 13 in the laser group did (p<0.001). Ten eyes in the bevacizumab group needed early retreatment for recurrent disease, most of which were originally zone 1 eyes, and 19 eyes in the laser group needed subsequent treatment (p=0.001). There were 3 deaths in each group. Home O2 was required in 19 patients (53%) in the bevacizumab group and 16 (59%) in the laser group (p=0.16).

CONCLUSIONS: Eyes treated with bevacizumab as primary treatment for ROP demonstrated significantly less reactivation and less surgical intervention than those treated with laser. Early reactivation was predominantly seen in eyes originally treated for zone 1 disease. Late reactivation of ROP after bevacizumab was not seen using our protocol.
Changes in Retinopathy of Prematurity from 1986 to 2013: Comparison of Three U.S. Studies

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PURPOSE: Compare infant characteristics and ROP status in 3 clinical studies conducted in a 27-year period in the U.S.

METHODS: Common baseline infant characteristics and ROP onset, severity, and time course of ROP were determined using retrospective review of CRYO-ROP and ETROP publications and the primary data from e-ROP. All three studies enrolled infants with birth weight of <1251g.

RESULTS: The CRYO-ROP study enrolled 4099 infants from January 1986 through November 1987 and the ETROP Trial screened 6998 babies for a prospective study to detect prethreshold ROP from October 2000 through September 2002. The e-ROP examined 1257 infants from May 2011 through October 2013. Across the three studies, mean birth weight (BW) and gestational age (GA) decreased from CRYO-ROP (954g) to ETROP (907g) to e-ROP (864g) p<0.0001] with an increase in % infants enrolled <750g (16% CRYO, 25% ETROP, 33% e-ROP, p<0.0001). The percentage of infants who developed ROP varied little (66% CRYO, 68 % ETROP, 64% e-ROP, p=0.003). Moderately severe ROP (defined as prethreshold or referral-warranted) varied somewhat (18% CRYO, 12% ETROP, 19% e-ROP, p<0.0001), while the onset of any ROP varied little (34wks CRYO, 34wks ETROP, 35wks e-ROP) as did onset of stage 3 ROP and plus disease.

CONCLUSIONS: BW and GA of infants enrolled in ROP studies have decreased over the last 27 years in the US, while ROP prevalence and onset of disease are less variable.
Retinal Detachments After Intravitreal Anti-VEGF Injections for Retinopathy of Prematurity Characterize Retinal Detachments that Developed After Intravitreal Anti-VEGF Treatment for Retinopathy of Prematurity (ROP)

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PURPOSE: To characterize retinal detachments that developed after intravitreal anti-VEGF treatment for retinopathy of prematurity (ROP).

METHODS: This is a retrospective, interventional, non-comparative series from two tertiary referral practices for pediatric vitreoretinal diseases. Clinical histories and characterization of the retinal detachment are reported, from patients who developed retinal detachment after intravitreal anti-VEGF treatment for ROP. Excluded were patients who received anti-VEGF injections for preexisting retinal detachment, treated preoperatively as part of staged management, or those with effusive detachments.

RESULTS: Sixteen eyes from 11 infants were included in the study. Median gestational age was 24 weeks (range 22-28), and median birth weight was 730 grams (range 420-1180). All patients had been diagnosed with aggressive posterior ROP at the time of anti-VEGF injection. Nine (82%) infants were treated with half-dose bevacizumab, and 2 with half-dose ranibizumab. The injections occurred at a median post-menstrual age (PMA) of 36 weeks (range 33-40). Photocoagulation was provided before or after the injection in all except one patient. Twelve (75%) eyes demonstrated a progressive tractional retinal detachment, akin to the “crunch” phenomenon of contractile fibrovascular tissue after anti-VEGF treatment. The circumferential tractional vectors were more exaggerated compared to conventional ROP detachments in these eyes. More conventional progression to retinal detachment occurred in the remaining 4 eyes. All but one eye (94%) progressed to stage 4B or 5, and 14 (88%) underwent various vitreoretinal surgeries, after which the posterior pole and/or peripheral retina was attached in 11 (80%) intervened cases. Median follow-up time was 55 weeks after the anti-VEGF injections.

CONCLUSIONS: Intravitreal anti-VEGF treatment for ROP may lead to a progressive atypical tractional retinal detachment caused by a “crunch” phenomenon, or to a severe effusive retinal detachment.
A Natural History Study of Subjects with X-linked Retinoschisis in Anticipation of a Phase I/II Gene Therapy Trial

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PURPOSE: Forty-five subjects with genetically confirmed X-Linked Retinoschisis (XLRS) were enrolled in an 18-month natural history study in preparation for a gene replacement trial using an intravitreally delivered adeno-associated virus vector expressing retinoschisin (RS1) (rAAV2tYF-CB-hRS1). The primary objective was to obtain cross sectional and longitudinal measures of visual acuity, visual field sensitivity, microperimetry, cyst volume by SD-OCT, and electroretinography. The secondary objective was to monitor maculoschisis during treatment with a topical carbonic anhydrase inhibitor (CAI) in a subset of participants.

METHODS: Participants with XLRS were assessed from the retina and ophthalmic practices at Oregon Health & Science University Casey Eye Institute, Retina Foundation of the Southwest and University of Michigan Kellogg Eye Center. Visual function and retinal structure were evaluated.

RESULTS: Forty-five participants with XLRS and confirmed mutations in RS1, ranging in age from 7 to 67 years, were enrolled in the longitudinal study with 17 subjects in the carbonic anhydrase inhibitor (CAI) sub-study. Baseline visual acuity ranged from 0 to 82 ETDRS letters with an average of 58.6 (approximately 20/50). There was a weak relationship between decreased visual acuity and age (r=-0.18). Visual field and microperimetry testing with a Goldmann Size V target was not useful because most patients showed a ceiling effect, but a size III target was better able to reveal defects. Individual responses to CAIs were variable with some patients showing dramatic decreases in cyst volume, some demonstrating little change, and others exhibiting an increase in cyst volume. Changes in visual acuity were minor, and visual acuity was weakly correlated to changes in cyst volume. The majority of patients had the classic negative waveform electroretinogram, although a few demonstrated reduced b-waves that were not negative.

CONCLUSIONS: Patients with XLRS showed a spectrum of visual function but most had reasonably stable visual acuity averaging around 20/50. Visual fields and microperimetry using a size V target were not useful and smaller targets were needed to pick up defects. Perimetry using smaller targets and ERG appear to be sensitive measurement tools, and enrolling patients with worse baseline visual acuity might increase the potential to detect a therapeutic effect.
Phase 3 Trial of AAV2-hRPE65v2 (SPK-RE65) to Treat RPE65 Mutation-associated Inherited Retinal Dystrophies: Mobility Testing and Surgical Experience

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PURPOSE: Multiple early-phase human trials provided preliminary evidence of safety and efficacy for adeno-associated virus-mediated human RPE65 augmentation for RPE65-mutation-associated inherited retinal dystrophies. Herein we report baseline demographics, safety, and surgical experiences of a Phase 3, open-label, randomized, controlled trial that began in November 2012 at Children’s Hospital of Philadelphia and the University of Iowa evaluating the safety and efficacy of AAV2-hRPE65v2 (SPK-RPE65) to treat RPE65-mutation-associated disease (NCT00999609). Additionally, support will be provided that the primary efficacy endpoint of mobility testing is clinically valid.

METHODS: Twenty-eight eligible subjects with disease-causing biallelic RPE65 mutations were randomized 2:1 to intervention or control. Eligibility criteria included age ≥3 years-old; bilateral visual acuity worse than 20/60 and/or visual field less than 20 degrees in any meridian; evidence of sufficient viable retinal cells; ability to be evaluated on mobility testing; and willingness to provide consent or parental permission and assent, where appropriate. Subjects in the intervention group received subretinal injections of AAV2-hRPE65v2 sequentially to each eye within an 18-day window. Subjects in the control group did not receive AAV2-hRPE65v2 for at least 1 year from baseline, but completed the same testing as those in the intervention arm. Using a standardized subretinal delivery procedure and under general anesthesia, 1.5E11 vector genomes/eye were delivered in a total volume of 300 µl. Standardized mobility testing under different luminance conditions was the primary efficacy endpoint.

RESULTS: All subjects completed Year 1 follow-up testing. Phase 3 study results include demographics, safety information, surgical experiences (intervention group), and mobility testing change score (performance at 1 year compared with baseline). A separate study analyzing mobility test data in untreated normal and retinal dystrophy cohorts was used to validate the mobility test’s ability to distinguish low vision from normal-sighted populations, differentiate a range of performance in low vision subjects, and confirm changes in functional vision over time.

CONCLUSIONS: Results of this study, the first Phase 3 gene therapy study completed for a retinal dystrophy, will provide additional evidence regarding the efficacy and safety of gene therapy intervention by surgical subretinal administration of AAV2-hRPE65v2 (SPK-RPE65) as measured by mobility testing, and about aspects of the surgical technique.
Recommendations to Optimize Patient Outcomes from the 2015 Argus II Investigator Meeting

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PURPOSE: To optimize outcomes in patients undergoing implantation of the Argus II retinal prosthesis system from a worldwide investigator collective experience since attaining international regulatory approval.

METHODS: Vitreoretinal surgeons, retinal dystrophy specialists, device programmers, and rehabilitation specialists from the United States, Europe, Canada, and Middle East were convened to the inaugural Argus II Investigator Meeting held in Ann Arbor, MI in March 2015. The recommendations from the collective experiences are reported.

RESULTS: Ideal patient selection, expectation counseling, and preoperative retinal assessment with OCT are critical for successful outcomes. Challenges to surgical implantation include presence of staphyloma. Modified surgical technique may reduce risks of hypotony and conjunctival erosion. Rehabilitation efforts and correlation with validated outcome measures following implantation are critical.

CONCLUSIONS: A collaborative network of Argus II investigators have identified strategies to optimize patient outcomes by refining patient selection criteria, standardizing surgical technique and management of complications, identifying issues with device programming and visual rehabilitation. Future research will be performed in a coordinated manner in areas such as outcome assessment.
Risk of Myocardial Infarction and Stroke with Single or Repeated Doses of Intravitreal Bevacizumab

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PURPOSE: To examine the risk of myocardial infarction and stroke with single and repeated doses of intravitreal bevacizumab.

METHODS: We conducted a case-control and cohort study among 7,452 new users of vascular endothelial growth factor (VEGF) inhibitors between 2009 to 2013 and a cohort of 2,564 subjects with wet age-related macular degeneration (AMD) not receiving any VEGF inhibitors from 2000 to 2007 in British Columbia, Canada.

RESULTS: In the cohort analysis, there were 2,564 AMD subjects not on a VEGF inhibitor and 5,644 subjects receiving intravitreal bevacizumab. The rate of myocardial infarction (MI) among bevacizumab users was 14.9/1000 person-years compared to 11/1000 person-years in non-users. The adjusted RR for MI in the cohort was 0.70 (95% CI: 0.50-1.00). The adjusted RR for MI was 0.70 (95% CI: 0.50-1.00) and 0.71 (95% CI: 0.45-1.13) for the propensity score adjusted analysis. In the nested case-control analysis there were 7,452 new users of VEGF inhibitors within which there were 133 cases of MI with 1,330 matched controls. The adjusted RR for MI among those receiving three or more injections compared to those receiving less than three was 0.71 (95% CI: 0.41-1.22). Also in the case-control analysis, there were 65 cases of stroke in the VEGF inhibitors group with 650 corresponding controls. The adjusted RR for stroke among those receiving four or more injections compared to those receiving less than four was 0.81 (95% CI: 0.39-1.65).

CONCLUSIONS: Single or repeated doses of intravitreal bevacizumab were not shown to increase the risk of myocardial infarction or stroke.
Randomized Trial of Prompt Panretinal Photocoagulation versus Ranibizumab for Proliferative Diabetic Retinopathy: Secondary Outcomes, Safety Assessment, and Clinical Applications

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PURPOSE: The Diabetic Retinopathy Clinical Research Network (DRCR.net) conducted a randomized clinical trial to determine if visual acuity and secondary outcomes at 2 years in eyes with proliferative diabetic retinopathy that receive intravitreous ranibizumab are non-inferior to those in eyes that receive panretinal photocoagulation (PRP). Results related to changes in visual acuity and development or worsening of diabetic macular edema are presented in a separate abstract. The purpose of this abstract is to present an evaluation of secondary outcomes including incidence of retinal detachment and vitreous hemorrhage, changes in visual field sensitivity, changes in diabetic retinopathy, and potential applications to clinical practice.

METHODS: At 56 sites, 394 eyes of 305 adults with proliferative diabetic retinopathy and no prior PRP were assigned randomly to prompt PRP or a standardized treatment protocol of 0.5-mg intravitreous ranibizumab with deferred PRP if needed. Eligible eyes had visual acuity approximately equivalent to Snellen of 20/320 or better. Eyes with or without diabetic macular edema could be eligible, but could not have had intravitreous anti-vascular endothelial growth factor within 2 months or intravitreous or peribulbar steroids within 4 months of enrollment. Follow-up visits occurred every 4 weeks to 16 weeks depending on treatment group and treatment course.

RESULTS: The outcomes evaluated for this presentation include changes in Humphrey visual field, the proportion of eyes requiring vitrectomy for PDR, and frequency of vitreous hemorrhage, retinal detachment, and iris or angle neovascularization. Additional results include changes in the level of diabetic retinopathy on color photographs as graded by a central reading center. Clinical applications of this trial will also be presented; however because of the potential public health impact of these results, the DRCR.net requests that the results be presented only after the 2-year primary manuscript is published, which is expected prior to the 2015 Retina Society Annual Meeting.

CONCLUSIONS: Conclusions will follow from the results presented.
PONT ALEXANDRE III

SUNDAY
Development of an International Standard Set of Patient-Centric Outcome Measures for Macular Degeneration

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PURPOSE: To develop a standardized set of patient-centered outcome measures for tracking, comparing, and improving treatment outcomes of macular degeneration. To define these measures utilizing recommendations from the International Consortium for Health Outcomes Measurement (ICHOM), a working group of international experts in macular degeneration outcomes and registry development, and patient advocates.

METHODS: A modified Delphi technique was used, supported by a series of structured teleconferences for the working group, which were followed by online surveys to reach consensus decisions. Potential outcome metrics were identified by a literature review of outcomes that are collected in existing registries and reported in major clinical trials. These were then refined using the experience of the working group members and prioritized based on degree of patient impact, relationship to good clinical care, and feasibility of their measurement in routine clinical practice. Baseline characteristics that would be required for subsequent risk-adjusted analysis were also determined in a similar fashion.

RESULTS: The ICHOM macular degeneration Standard Set applies to all patients with choroidal neovascular macular degeneration and non-neovascular age-related macular degeneration.

The outcomes that are recommended to be recorded include: Best-corrected distance visual acuity; Mobility and independence; Emotional well-being; Reading and accessing information; Burden of treatment; Complications of treatment; Presence of Fluid, Edema, or Hemorrhage; these can be obtained from clinical visit data and patient-reported sources.

Other characteristics which are recommended to be recorded include: Age; Gender; Ethnicity; Smoking status; Baseline visual acuity; Baseline visual acuity in contralateral eye; Type of macular degeneration; Presence of geographic atrophy, Subretinal fibrosis, and Pigment epithelial detachment; Previous macular degeneration treatment; Ocular co-morbidities.

We also suggest recording of a defined list of interventions that may impact outcomes.

CONCLUSIONS: The development of this Standard Set is a critical step towards enabling meaningful assessment of macular degeneration interventions. We hope that the global adoption of these pragmatic reporting standards will facilitate informed treatment decisions, improve understanding of disease progression and treatment response, and accelerate improvements in outcomes that matter most to patients.
Clinical Utilization of Anti-Vascular Endothelial Growth Factor (VEGF) Therapy for Neovascular Age-related Macular Degeneration—Analysis of Electronic Medical Records from a Large Integrated US Health System Database

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PURPOSE: Clinical trial findings indicate that regular intravitreal vascular endothelial growth factor antagonist (anti-VEGF) injections are required for optimal outcomes in neovascular age-related macular degeneration (nAMD). This study examines treatment patterns and visual outcomes in patients initiating anti-VEGF therapy for nAMD in clinical practice.

METHODS: In this retrospective observational cohort study, the Geisinger Health System (GHS) electronic medical records database was screened to identify patients (i) initiating intravitreal ranibizumab or bevacizumab for nAMD between January 2007 and May 2012, (ii) with corrected visual acuity (CVA) of 20/40 - 20/320 at initial injection (baseline), (iii) with ≥12 months follow-up in GHS, and (iv) with ≥1 CVA assessment ≥60 days post-baseline. Patients with co-existing retinal vein occlusion or diabetic macular edema were excluded. Outcomes of interest were number of ophthalmologist visits and anti-VEGF injections per study eye over 12 months, change from baseline in CVA, and proportion of eyes with ≥10 or ≥15 Early Treatment Diabetic Retinopathy Study (ETDRS) letter gain/loss at 12 months.

RESULTS: Three hundred eleven patients (337 eyes) were eligible for study inclusion. Over 12 months follow-up, mean number of ophthalmologist visits was 9.3 (range 2–20); mean number of anti-VEGF injections was 5.5 (range 1-15), and most eyes (65.3%) received ≤6 injections. Mean CVA change was +5.3 ETDRS letters (mean CVA 53.6 vs 58.9) at 12 months; proportion of eyes gaining ≥10 or ≥15 ETDRS letters was 42.1% and 32.1%, respectively; proportion of eyes losing v10 or ≥15 ETDRS letters was 16.6% and 14.0%, respectively. Eyes receiving ≥7 injections over 12 months had greater mean CVA gain at 12 months (+7.6 ETDRS letters) than eyes receiving 4-6 injections (+5.1 ETDRS letters) or 1-3 injections (+2.5 ETDRS letters). Multivariate linear regression demonstrated a significant association between anti-VEGF injection frequency (continuous or categorical exposure variable) and CVA improvement at 12 months.

CONCLUSIONS: Anti-VEGF injection schedules used for treatment of nAMD in clinical practice are less intensive and produce suboptimal vision outcomes compared to those of the landmark randomized clinical trials in nAMD. The reasons for under-utilization of anti-VEGF therapy in clinical practice are unclear.
Ranibizumab Use, Patterns of Care and Clinical Outcomes in Real-life Settings in Asia-Pacific, the Middle East and North Africa: Results from the UNCOVER Study

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PURPOSE: The UNCOVER study aimed to describe treatment frequency and patterns of care for patients with neovascular AMD (nAMD) from Asia-Pacific, the Middle East and Africa, treated with ranibizumab in a real-life clinical setting within different reimbursement scenarios.

METHODS: This non-interventional study collected retrospective data from patients’ medical charts. Eligible patients diagnosed with nAMD and treated with ranibizumab for at least one-year between April 2010 and April 2013 were entered. Reimbursement scenarios were defined as self-paid, partially-reimbursed, and fully-reimbursed.

RESULTS: The study enrolled 3,445 patients; of which 3,241 were included in the final analysis (3,725 treated eyes). Most patients were in the partially-reimbursed group (n=2,521), followed by fully-reimbursed and self-paid groups (n=532 and 188, respectively). The mean age of the patients was 73.5 years, 50.2% were male, and 46.2% (n=1,496) were Caucasian. Most patients were diagnosed in the year prior to the first treatment reported in the study. Baseline visual acuity (VA) was similar across the three reimbursement groups (58 to 63 letters) whereas baseline mean central retinal thickness (CRT) was higher in the self-paid group (420µm) compared with the other groups (317 and 349µm in the partially-reimbursed and fully-reimbursed groups, respectively). Mean clinic visit frequency was similar across all groups with 6 visits/year. The fully-reimbursed and partially-reimbursed groups received a mean of 4.7 and 4.1 injections/year, respectively. The self-paid group received a mean of 2.6 injections/year. Mean VA change during the observational period was -0.7 letters without a notable difference between the reimbursement scenarios. Modest CRT decrease (mean -44.4 µm) was observed in the overall population, with -36.6, -66.9, and -92.6µm in the partially-reimbursed, fully-reimbursed and self-paid groups, respectively.

CONCLUSIONS: UNCOVER assessed a large, heterogeneous nAMD population observed in real-life clinical practice. Clinic visit frequency was similar across various reimbursement groups but more frequent ranibizumab injections were observed in the fully- and partially-reimbursed groups, compared with the self-paid group. Although ranibizumab reimbursement status can impact the number of injections received, all patients attained vision stabilization and modestly anatomical improvement with CRT reduction.
Long-term Outcomes in Eyes Receiving Fixed-interval Dosing of Anti-vascular Endothelial Growth Factor Agents in Wet Age-related Macular Degeneration

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PURPOSE: To report on long-term visual outcomes in patients receiving continuous fixed-interval dosing of antievascular endothelial growth factor (VEGF) treatment in neovascular age-related macular degeneration (AMD).

METHODS: Single-practice retrospective chart review of eyes with exudative AMD receiving continuous fixed-interval dosing (every 4 to 8 weeks) of anti-VEGF therapy (ranibizumab, bevacizumab, or aflibercept) for at least 5 years. Eyes were excluded if they averaged fewer than 6.5 injections per year. Snellen visual acuity was recorded at baseline and all subsequent injections. Changes from baseline were calculated at yearly intervals. The primary outcome measure was mean change in letter score at 5, 6, and 7 years; secondary outcomes included the percentage of patients with 20/40 vision or better at 7 years and the mean change in letter score at each yearly time point based on baseline visual grouping (20/40 or better, 20/50 to 20/100, and 20/200 or worse).

RESULTS: Forty-four, 75, and 109 patients with 7, 6, and 5 years, respectively, of continuous treatment were identified. Mean change in letter score at year 5 was +14.0 letters (P = 3.9 x 10⁻⁹), +12.2 letters at 6 years (P = 1.5 x 10⁻⁷), and +12.1 letters at 7 years (P = 3.8 x 10⁻⁵). Driving vision (20/40 or better) was achieved in 43.2% of treated eyes. Subanalysis revealed that the greatest visual gains at 5 and 7 years were seen in those patients with baseline visual acuity worse than 20/200 (+24.5 and +25.5 letters), followed by those with 20/50 to 20/100 vision (+6.7 and +6.9 letters), and finally those with 20/20 to 20/40 (+3.7 and +3.4 letters). Patients received an average of 10.5 injections per year.

CONCLUSIONS: Continuous fixed-interval dosing of anti-VEGF therapy in patients with exudative AMD results in favorable long-term preservation out to 7 years, with vision stabilizing or improving in 93.2% of eyes. Additionally, 43.2% of eyes met visual acuity for driving vision in the treatment eye at 7 years compared with 10.1% at baseline. Our data suggest better outcomes with continuous therapy over published results with sporadic, as-needed therapy.
Afiblercept as a Second Line Therapy for Neovascular Age-related Macular Degeneration Following Initial Bevacizumab Therapy

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PURPOSE: Second line therapy in patients with neovascular age-related macular degeneration (nvAMD) was mostly evaluated in chronic cases following prolong usage of first line treatment. This study aims to evaluate second line afiblercept therapy in nvAMD eyes showing partial or lack of response for initial therapy with bevacizumab.

METHODS: The Afiblercept as a Second Line Therapy for nvAMD in Israel (ASLI) study is a prospective, multi-center (n=8), open-label, clinical trial. Forty eight nvAMD eyes that had persistent intra retina or sub retinal fluid, or pigment epithelium detachment following 3-9 initial bevacizumab injections. Three monthly intravitreal afiblercept (2mg) injections were administered followed by two bi-monthly injections (weeks 16 and 24), and a final examination at week 28th. According to the investigator discretion, an additional injection was given at week 20. Best corrected visual acuity (BCVA) was evaluated with an Early Treatment Diabetic Retinopathy Study (ETDRS) chart and spectral-domain optical coherence tomography (SD-OCT) was performed at each visit. Baseline and final fluorescein angiography were also performed. Change in the central sub-field macular thickness (CST) from baseline to week 28 on OCT was defined as the primary end-point. Secondary end-points included the mean change in BCVA, and structural changes in OCT and FA.

RESULTS: Mean±SD patient’s age was 76±8 years. The mean±SD number of bevacizumab injections prior to enrollment to the study was 5.2±2.3 (range 3-9). CST reduced from mean±SD of 465±137 microns at baseline to 358±114 microns at week 8 (n=20, p=0.04; paired T-Test). Mean BCVA for the 13 patients who completed the study improved from 0.43±0.3 LogMAR at baseline to 0.35±0.1 LogMAR at week 28 (approximately 4-letter improvement in the ETDRS chart; p=0.01, paired T-Test). Results for the entire cohort will be available in September 2015.

CONCLUSIONS: Preliminary results from the ASLI study demonstrate decrease in CST after the first 2 afiblercept injections, and improved BCVA at the end of the study. These preliminary results suggest that intravitreal afiblercept may be effective in eyes with nvAMD that show lack or partial response to initial bevacizumab treatment.
A Single Arm, Investigator Initiated Study of the Efficacy, Safety and Tolerability of Intravitreal Aflibercept Injection in Subjects with Exudative Age-related Macular Degeneration Previously Treated with Ranibizumab or Bevacizumab: 24-month Outcome

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PURPOSE: To evaluate the efficacy and safety of IAI in patients previously treated with ranibizumab and/or bevacizumab for active exudative age-related macular degeneration (AMD) over 24 months.

METHODS: This was a 24-month, prospective, interventional, single arm, investigator-initiated study at the Cole Eye Institute among patients (n = 26) with active exudative AMD who were previously treated pro re nata (PRN) and not recalcitrant to ranibizumab and/or bevacizumab. Patients were treated the first 3 months with 2 mg IAI monthly, followed by a fixed dosing schedule every 2 months of 2 mg IAI up to 24 months. The primary outcomes was the mean absolute change from baseline in central subfield thickness (CST) at month 24, as measured by SDOCT. Secondary outcomes included mean change from baseline in best-corrected visual acuity (BCVA) ETDRS letter score, percentage of patients who gained or lost greater than or equal to 15 letters of vision, percentage of patients who are 20/40 or better, percentage of patients who are 20/200 or worse, and the incidence of any adverse events (AEs) and/or serious AEs.

RESULTS: Mean CST at baseline was 304.1 µm and mean BCVA was 56 letters. The 24 month endpoint analysis demonstrated a mean decrease in CST of -45.2 µm (p<0.001) and a mean increase in ETDRS BCVA of +10.6 letters (p<0.001). 45.5% of patients experienced a greater than or equal to 15-letter improvement in visual acuity, 77.3% of patients gained greater than 0 letters of visual acuity, 11.5% of patients were visually stable (VA within the same line on Snellen), and no subject lost ≥3 lines of vision from baseline. 68.2% of patients were 20/40 or better and 9.1% of patients were 20/200 or worse at month 12. Two AEs were encountered and documented; none attributable to IAI.

CONCLUSIONS: In patients with active exudative AMD, treating with a fixed IAI dosing regimen for 24 months demonstrated sustained improvements in anatomic and vision endpoints from baseline in patients transitioned from other anti-VEGF agents.
**Prospective, Multicenter Investigation of Aflibercept Treat and Extend Therapy for Neovascular Age-related Macular Degeneration (ATLAS Study): One-year Results**

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**PURPOSE:** To determine the visual outcomes, anatomic outcomes, and number of injections required with intravitreal aflibercept using a treat and extend regimen for the management of new-onset neovascular age-related macular degeneration (nAMD).

**METHODS:** This was a multicenter, prospective, open label, two year study. Eligible for inclusion were eyes with treatment-naïve nAMD and Early Treatment of Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) of 20/25 to 20/320. Study eyes were treated with intravitreal aflibercept every 4 weeks until no signs of macular exudation by clinical assessment including spectral domain optical coherence tomography (SDOCT). The treatment intervals were then extended by 2 weeks until either an exudative recurrence occurred or a treatment interval of 16 weeks was achieved. Main outcome measures included change from baseline ETDRS BCVA, change in SDOCT central subfield thickness (CST), mean number of annual injections, and adverse events at one and two years of follow-up.

**RESULTS:** Forty eyes of 40 participants met inclusion criteria and were enrolled in the study. The mean ETDRS BCVA improved from 58.5 letters at baseline to 65.9 letters at one year follow-up ($p = 0.0064$), a mean gain of 7.4 letters. The mean SDOCT CST decreased from 395.8 microns at baseline to 255.7 microns at one year ($p = 1.1 \times 10^{-7}$). The mean number of injections over the first year was 7.8, and the mean treatment interval was 6.9 weeks. No related adverse ocular or systemic events were observed.

**CONCLUSIONS:** Aflibercept using a treat and extend regimen led to significant visual and anatomic improvement in eyes with treatment-naïve neovascular AMD. The treat and extend approach may reduce the need for injections and clinical evaluations when compared to phase III studies that mandated fixed intervals of every 4 or 8 weeks of maintenance treatment during the first year.
The EVEN Study: An In-depth Prospective Multimodal Analysis of Aflibercept Therapy for Pigment Epithelial Detachment in Neovascular Age-related Macular Degeneration

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PURPOSE: To study prospectively the visual outcomes and detailed volumetrics of pigment epithelial detachments (PED) treated with aflibercept therapy in eyes with neovascular age related macular degeneration.

METHODS: This multi-center investigator-initiated trial performed complex multimodal assessment of lesion components by a reading center (Doheny Image Reading Center) including visual outcomes and detailed lesion volumetrics. Treatment naïve eyes with vascularized PED (vPED) were enrolled for prospective assessment of visual outcome and lesion components from baseline until 12 months (M). All study eyes received 6 monthly (QM) followed by 3 bimonthly intravitreal injections of aflibercept (2.0 MG). ETDRS visual acuity (VA) and detailed SD-OCT analysis were performed at baseline and QM. FA was performed at baseline, 1-, 6-, 12M and ICG at baseline and 6M. In-depth analyses of PED height, volume and surface area (SA) and choroidal neovascular membrane (CNV) SA were assessed at baseline and follow up. Complex volumetric analysis of subretinal fluid (SRF) and subretinal hyperreflective (SRH) material was also performed.

RESULTS: There were 40 patients (eyes) enrolled in study with mean age of 80.8 years and mean pre- and post-ETDRS VA of 57.4 letters (20/76) and 64.9 letters (20/52) at latest visit, respectively (7.5 letters difference, p=0.0003). Mean pre- vs post-PED volume and SA were 6.3 vs 0.8 µm2 and 1.7 vs, 0.52 mm3 (p<0.001 and < 0.002) respectively. Mean pre- vs post-CNV SA were 9.5 vs 3.7 mm2 (p<0.001). Mean pre- vs post-retinal thickness and volume were 278.8 vs 265.5 µm and 0.21 vs 0.01 mm3 (p=0.01, <0.001) respectively. Mean pre- vs post-SRF Volume were 0.6 vs 0.05mm3 (p=0.009). Mean pre- vs post-SRH thickness and Vol were 101.3 vs 14.0 µm and 0.08 vs 0.01 mm3 (p<0.001, <0.001) respectively. RPE tears formed in 5 eyes (12.5%), and RPE atrophy in 3 eyes (7.5%).

CONCLUSIONS: The EVEN study is unique in providing prospective complex volumetric analysis of vPED and their response to aflibercept therapy. vPED eyes developed progressive and significant reductions in PED volume and surface area with marked improvement in vision at 12M after treatment with aflibercept. Marked reductions in both retinal and subretinal hyperreflective material thickness and volumes (p<0.001) appear to be reliable markers for treatment improvement for vascularized PEDs. There were few ocular complications and no systemic adverse events. This prospective report provides an abundance of high-quality data derived from careful assessment in a reading-center setting on characteristics of vPED following aflibercept treatment.
Pharmacodynamic Profile of Intraocular Afibercept in Patients with Neovascular Age-related Macular Degeneration

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PURPOSE: We investigated the pharmacodynamic profile after intravitreal injections of afibercept in patients receiving intravitreal 2.0 mg afibercept injections for treatment of exudative AMD.

METHODS: A 27-gauge needle connected to a tuberculin syringe was used to retrieve 0.10 to 0.25 mL of aqueous via a limbal paracentesis immediately prior to each intravitreal 2.0mg afibercept injection for treatment of neovascular AMD. All specimen were immediately frozen at -80-degree centigrade. Batches of specimens frozen on dry ice were shipped to University of Bonn for analysis. Each specimen was diluted in phosphate buffered saline (PBS) for enzyme-link immunosorbent assay (ELISA) for analysis of vascular endothelial growth factor (VEGF) levels, after appropriate calibration.

RESULTS: Ninety-three specimens have been retrieved from 45 patients (25 women, 20 men). Ages ranged from 70 to 94 (mean:83.3). The BCVA ranged from 20/25 to 5/400 (mean:20/81). The interval from last injection to specimen retrieval ranged from 25 to 234 days. 6 additional naive eyes had VEGF levels $\geq 10 \mu g/mL$. Marked VEGF suppression was noted for all non-naive eyes with VEGF levels.

CONCLUSIONS: The results are consistent with mathematical model predicting suppression of intraocular VEGF level for 72 days after a single afibercept injection (M Stewart). This is in contrast to 27-38 days for bevacizumab and 30 days for ranibizumab in VEGF-binding after a single injection. Further investigation will detect the upper boundary in duration of suppression.
Anti-VEGF Therapy in Neovascular Age-related Macular Degeneration with Advanced Visual Loss: Prognostic Indicators for Visual Outcome

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PURPOSE: To assess the effect of anti-VEGF intravitreal injections in neovascular AMD with advanced vision loss at the initiation of therapy and to determine factors that predict visual outcome. Most clinical trials on anti-VEGF therapy have excluded subjects with severe degrees of visual loss.

METHODS: A retrospective chart review was performed on a consecutive series of 1410 cases initiated with anti-VEGF therapy for neovascular AMD between January 2006 and December 2012 at the Medical College of Wisconsin. Of these, 134 cases met the study criteria of having 20/200 or worse corrected visual acuity and minimum follow-up of 6 months. Of these, 97 cases were followed for 12 months. Factors for analysis included VA, number of injections received, drug type, ophthalmoscopic findings, FA, and masked evaluation of OCT findings. Visual improvement/worsening was defined as at least ± 0.3 logMAR units change.

RESULTS: Mean patient age was 82.1 years and baseline logMAR was 1.4 (20/500 Snellen equivalent). Mean logMAR at 6 month follow-up was 1.2 (20/320 equivalent, p=0.0001 for change in VA). A discontinuous injection strategy was primarily used. Visual outcomes were similar at 6 and 12 months. At 12 months, VA improved in 44% and worsened in 22% compared to baseline. If baseline VA was worse than 20/400, VA improved in 52% and worsened in 22%. On univariate analysis of baseline factors, retinal hemorrhage was associated with greater improvement (p=0.03), while intraretinal fluid on OCT was associated with less improvement (p=0.02) at 12 months. With multivariate analysis, poorer initial VA was associated with greater visual improvement (p=0.002), as was the larger the number of injections received (p=0.01). Larger macular lesion size (GLD) on FA correlated with worse VA at 6 months (p=0.02), but not at 12 months by multivariate analyses. Injection medication type did not influence outcome.

CONCLUSIONS: Anti-VEGF therapy may be beneficial for many patients with advanced visual loss from neovascular AMD. Number of injections, macular lesion size, and other clinical abnormalities may influence outcome. Future prospective studies are needed to define the role of anti-VEGF therapy in AMD with severe vision loss.
Geographic Atrophy and Visual Acuity Following Anti-VEGF Therapy in the Comparison of Age-related Macular Degeneration Treatments Trial

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PURPOSE: Anti-VEGF therapy provides outstanding vision and anatomical outcomes for exudative AMD. However, there is concern over potential long-term effects of sustained VEGF suppression on atrophy. This analysis evaluates the relationship between geographic atrophy (GA), anti-VEGF exposure and visual acuity (VA) in CATT patients.

METHODS: We analyzed publicly available data from CATT including baseline demographic characteristics, treatment group assignment, treatment frequency (PRN group), VA, presence of GA, and other reading center assessments based on fundus photographs and OCT. In patients without atrophy at baseline, the association of atrophy at week 104 with regimen, anti-VEGF agent and extent of anti-VEGF exposure in PRN or switching regimens, was assessed with descriptive statistics, chi-squared statistics, and multivariable logistic regression modelling.

RESULTS: Development of GA at week 104 was negatively associated with increasing anti-VEGF exposure in PRN patients (P = 0.036) and in patients switched from monthly to PRN after 1 year (P < 0.001), with the highest rates of GA in patients with the fewest number of anti-VEGF injections. In PRN patients that developed new GA, the first observation was most commonly in patients with the lowest anti-VEGF exposure (1-3 or 4-6 injections prior to first GA). For a subset of patients, the presence of GA was confirmed by reading center assessment then graded as absent at a subsequent study visit, an observation, which occurred more commonly in the PRN and switching groups compared to monthly. Multivariable logistic regression models identified several risk factors for GA development including: fewer prior injections (PRN and switching patients), absence of fluid at 2 years, and fellow eye GA. GA was not associated with worse vision compared to patients with no GA. Among GA patients, monthly treated patients did not have poorer VA outcomes compared to other regimens.

CONCLUSIONS: Although previous reports suggest a difference in the incidence of atrophy between continuous and PRN therapy, this analysis of publicly available CATT data suggests GA development within the PRN group may not be related to anti-VEGF exposure and is not likely associated with poor VA outcomes at 104 weeks.
Subretinal Fluid and the Development of Macular Atrophy in Neovascular Age-related Macular Degeneration Treated with Ranibizumab in HARBOR

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PURPOSE: Macular atrophy (MA) development has been reported in several large clinical trials evaluating anti-vascular endothelial growth factor (VEGF) treatment for neovascular age-related macular degeneration (nAMD). This study evaluated the association between the development of macular atrophy and presence of subretinal fluid (SRF) in ranibizumab-treated eyes in HARBOR.

METHODS: This was a retrospective, post hoc analysis of the phase 3 HARBOR study, a multi-center, double-masked, randomized controlled clinical trial that evaluated intravitreal ranibizumab 0.5-mg or 2.0-mg administered monthly or as-needed (PRN) for nAMD. Presence versus absence of SRF and MA development were evaluated in study eyes with no MA detectable at baseline (n = 904 of 1095 eligible study eyes). MA was assessed on fluorescein angiograms (FA) and color fundus photographs at baseline, month (M) 3, M12, and M24, defined as: well-defined areas of depigmentation with increased choroidal vessel visibility, diameter ≥250 µm, corresponding to flat areas of well-demarcated staining on FA; excluding atrophy associated with retinal pigment epithelium tears. Atrophy immediately within, adjacent to and nonadjacent to CNV lesions was included.

RESULTS: Among study eyes with no detectable MA at baseline, 29% developed MA at M24. SRF presence at baseline (76% of all study eyes) was associated with a decreased incidence of MA (hazard ratio [HR], 0.50; 95% confidence interval [CI], 0.33-0.74). Additionally, baseline SRF presence and concurrent SRF presence at M24 were associated with less MA at M24 when compared with eyes that had SRF absent at these time points (M24 MA rates: 23.6% with vs 52.6% without baseline SRF; 8.1% with vs 32.9% without concurrent SRF). Among patients with baseline SRF, risk factors for MA presence at M24 were baseline fellow eye MA (HR, 2.15; 95% CI, 1.38-3.37), baseline intraretinal cysts (HR, 2.72; 95% CI, 1.84-4.04), and monthly treatment (HR, 1.45; 95% CI, 1.04-2.02).

CONCLUSIONS: Lower MA rates at M24 were seen in eyes with SRF present at baseline and in eyes with persistent SRF at M24. At this time, the mechanism by which SRF may impact MA development is unclear.
Intravitreal Bevacizumab for Choroidal Neovascularization in Age-related Macular Degeneration: Five-year Results of the Pan-American Collaborative Retina Study Group

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PURPOSE: To report the long-term anatomical and functional outcomes of patients with choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) treated with intravitreal bevacizumab (IVB).

METHODS: Retrospective case series. A total of 247 consecutive patients (292 eyes) diagnosed with subfoveal CNV secondary to AMD that were treated with at least 1 intravitreal injection of 1.25 mg of IVB and had a minimum follow-up of 60 months participated. Patients underwent best-corrected visual acuity (BCVA) testing, ophthalmoscopic examination, optical coherence tomography (OCT), and fluorescein angiography (FA) at baseline, 1-, 3-, 6-, 12-, 24-, 36-, 48-, and 60-month visits. Main outcome measures included BCVA and central macular thickness (CMT) at 60 months of follow-up.

RESULTS: The mean number of IVB injections per eye was 10.9 ± 6.4 (range: 1-46 injections). At 5 years the BCVA decreased from 20/150 (logMAR 0.9 ± 0.6) at baseline to 20/250 (logMAR 1.1 ± 0.7) (p=0.0001). Fifty five (18.8%) eyes improved ≥2 lines of BCVA, 134 (45.9%) eyes remained within 2 lines of BCVA, and 103 (35.3%) eyes lost ≥2 lines of BCVA. The mean CMT decreased from 343.1 ± 122.3 µm at baseline to 314.7 ± 128.8 µm at 60 months of follow up (p=0.009). Geographic atrophy (GA) was observed at baseline in 47 (16%) of 292 eyes. By 5 years, GA developed or progressed in 124 (42.5%) of 292 eyes (p<0.0001). Ocular complications included uveitis in 6 (2.1%) eyes, endophthalmitis in 2 (0.7%) eyes, and retinal detachment in 1 (0.3%) eye. Systemic adverse events included myocardial infarction in 1 (0.7%) patient, and 1 (0.7%) case of stroke.

CONCLUSIONS: The early visual gains obtained from IVB were not maintained at 5 years of follow-up. In addition, IVB may play a role in the development or progression of GA.
Mineralocorticoid Antagonists as Adjuncts in Neovascular Age-related Macular Degeneration

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PURPOSE: Mineralocorticoid receptor (MR) antagonists have recently been implicated in dehydrating the subretinal space in patients with central serous chorioretinopathy (CSCR). The purpose of this project was to evaluate the role of MR antagonists as an adjunct in patients with neovascular age-related macular degeneration (AMD) who have chronic subretinal fluid.

METHODS: Patients were included in the study if they had a previous diagnosis of neovascular AMD, had completed at least 6 anti-VEGF injections, and had persistent subretinal fluid (SRF) in the absence of intraretinal fluid on optical coherence tomography (OCT) imaging. Patients were then divided into groups with and without moderate-large pigment epithelial detachments (PEDs). Patients were started on oral eplerenone 25 mg PO BID, and were followed every 4-6 weeks with complete exams and OCT. Electrolytes were evaluated if they were maintained on the medication beyond 3 months. Medication dose was increased if SRF persisted, and anti-VEGF interval was extended if SRF resolved.

RESULTS: Twenty-three patients were included in the study. (Mean age = 54.6, 52.2% female, 47.8% male). 10 of 23 patients had moderate-large pigment epithelial detachments associated with chronic subretinal fluid and did not show significant reduction in SRF or extension of injection interval. 13 of 23 patients had predominantly chronic subretinal fluid without PEDs. In this subgroup, mean initial central macular thickness (CMT) prior to starting oral eplerenone was 305.3 microns, and mean injection interval was 40.25 days. Mean final CMT after at least 3 months of adjunctive eplerenone treatment was 240.6 microns and mean injection interval with adjunctive treatment was 54.61 days. Mean extension of injection interval after commencing oral eplerenone was 14.36 days.

CONCLUSIONS: These findings suggest oral MR antagonists may have a role as an adjunctive treatment in neovascular AMD, and may particularly be useful in dehydration of the subretinal space in the setting of chronic subretinal fluid. These findings suggest that neovascular AMD and CSCR may have more overlap than previously recognized. Further research is needed in randomized controlled trials to elucidate the precise role of oral MR antagonists in both CSCR and neovascular AMD.
Translimbal Sutureless Intravitreal Fragmentation

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**PURPOSE:** To describe the efficacy and safety of removing dislocated nuclear fragments by means of intravitreal ultrasonic fragmentation through a limbal/clear cornea self-sealing incision sparing the need for a 20-gauge scleral port.

**METHODS:** Five eyes of five consecutive patients presenting with posteriorly luxated nuclei occurring either after complicated phacoemulsification (3 eyes) or spontaneously (2 eyes with pseudoexfoliation syndrome) were enrolled in a prospective case series. Preoperative examination included evaluation of the corneal endothelium by means of specular microscopy. A 3-port 25+ pars plana vitrectomy (PPV) was initially performed. PPV included posterior vitreous detachment, when not present, core and peripheral vitrectomy. Following vitrectomy, sclerotomies were secured using scleral plugs and a limbal/clear cornea incision was performed for the insertion of the fragmatome. Incision was slightly larger (1mm) than the diameter of the probe (20gauge=0.81mm) to avoid wound overheating. One sclerotomy was kept secured during limbal fragmentation and the other was used for the insertion of the endoillumination probe. At the end of surgery an appropriate intraocular lens either sulcus-fixated or angle-supported was implanted and prior to trocar removal, a partial (50%) fluid/air exchange was performed. Primary outcome measures were mean postoperative visual acuity, intraoperative or postoperative complications and intraoperative challenging features.

**RESULTS:** In all eyes fragmentation was completed successfully with a mean total ultrasound time of 93.4 seconds. Nucleus density was recorded ≥3 in all cases (mean±SD=3.8±0.4). Intraoperative challenges included viewing difficulties due to corneal distortion, being overcome with gaining experience, some degree of nucleus turbulence and fluid from the limbal incision irrigating the non-contact lens temporarily compromising fundus visualization. No corneal wound burn was observed, neither iris/pupil trauma due to the contact of the fragmatome. Mean best corrected visual acuity was assessed 0.28±0.12 LogMAR 4 weeks postoperatively. Endothelial cell density did not demonstrate any statistically significant reduction varying from 1932±187 cells/mm² preoperatively to 1879±213 cells/mm² at the early postoperative period (p=0.79).

**CONCLUSIONS:** The translimbal sutureless intravitreal ultrasonic fragmentation appears to be a safe and efficient method for the removal of hard posteriorly dislocated nuclei, sparing the need for a 20-gauge scleral port.
Chandelier-assisted External Subretinal Drainage in Primary Scleral Buckling for Treatment of Rhegmatogenous Retinal Detachment

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PURPOSE: To describe a new method for external drainage of subretinal fluid in patients undergoing primary scleral buckling for rhegmatogenous retinal detachment.

METHODS: The study is a retrospective review of patients undergoing a primary scleral buckle procedure. At the completion of suturing an encircling buckle, a 25-gauge chandelier light was inserted approximately 3-3.5mm posterior to the limbus. This light provided illumination of the posterior segment, allowing use of a widefield operating microscope. Using the microscope for direct visualization, a 25-gauge 1.5 inch needle on a tuberculin syringe was placed through a transcleral site chosen by surgeon’s preference where the rhegmatogenous detachment was present. The chandelier allowed precise visualization of the tip of the needle in the subretinal space and controlled drainage of the subretinal fluid.

RESULTS: Seven patients with rhegmatogenous retinal detachment underwent primary scleral buckling procedures utilizing this chandelier-assisted external drainage of subretinal fluid. Of these seven patients, six were men and one was a women. Five of the cases were macula-on rhegmatogenous detachments at the time of surgery. The remaining two cases were macula-off detachments. Of these seven patients, one went on to require a vitrectomy procedure for re-detachment. No patients developed iatrogenic cataracts, iatrogenic retinal breaks, or significant sub retinal hemorrhages.

CONCLUSIONS: Chandelier-assisted external drainage in primary scleral buckling surgery allows for more controlled subretinal fluid removal with excellent visualization. The technique has no associated complications with initial primary success. This technique is particularly useful in training residents and fellows.
Long-term Follow-up and Outcomes in Traumatic Macular Holes

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PURPOSE: To review presenting characteristics, clinical course, and both visual and anatomic long-term outcomes of patients with traumatic macular holes at a large tertiary eye center.

METHODS: A retrospective review of consecutive patients with TMH was performed. In addition to visual acuities and treatments throughout the clinical course, specific dimensions of the macular hole, including diameters, height, configuration, shape, and the presence of a cuff of fluid were examined using spectral-domain OCT.

RESULTS: Twenty-eight patients were identified with a mean follow-up of 2.2 years and mean initial VA of logMAR 1.3 (20/400). 11 holes (39.3%) closed spontaneously in median 5.7 wks. Eleven underwent vitrectomy with a median time to intervention of 35.1 wks. Median time to surgery for the 5 eyes with successful hole closure was 11.0 wks vs. 56.3 wks for the 6 eyes that failed to close ($P=.02$). VA improved in closed holes ($P<.01$), whether spontaneously ($P<.01$) or via vitrectomy ($P=.04$), but VA did not improve in holes that did not close ($P=.22$). There was no relation between initial OCT dimensions and final hole closure status, although there was a trend that did not reach statistical significance towards small dimensions for those that closed spontaneously.

CONCLUSIONS: A fairly high spontaneous closure rate was observed, with a trend towards smaller OCT dimensions. We found no relationship between hole closure and the OCT characteristics of the hole. Surgical intervention was less successful at hole closure when elected after 3 months.
Long-term Results of Macular Hole Surgery Using Indocyanine Green to Peel Internal Limiting Membrane

John Thompson, MD
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PURPOSE: To evaluate the long-term results of vitrectomy for macular holes using indocyanine green (ICG) staining of the internal limiting membrane (ILM) to facilitate removal of the ILM. The use of ICG for macular holes has been controversial with some studies reporting toxicity and poor long-term visual results.

METHODS: Macular hole surgery was performed in a retrospective, consecutive case series of 127 eyes using ICG to stain and remove the perimacular ILM.

RESULTS: The mean duration of the macular hole was 5.2 months with a mean preoperative visual acuity of 20/160 +2. The macular hole was closed successfully with one surgery in 126/127 eyes (99.2%). The mean visual acuity was 20/100-2 at 3 months (P=.002), 20/80 at 1 year (P<.001), 20/63+2 at 2 years (P<.001) and 20/63 -1 at a mean of 3.9 years following surgery (P<.001). A total of 42/127 eyes (33%) were followed ≥5 years. The mean visual acuity was 20/50+1 at 2 years and 20/63 at a mean of 7.4 years (P=.353) following vitrectomy in this subgroup. Moderate vision loss (≥ -0.3 and < -0.6 logMAR) developed in 9/127 eyes (7.1%). Severe vision loss (≥ -0.6 logMAR) developed in 3/127 eyes (2.4%) and did not appear related to the macular hole surgery or use of ICG (1 vein occlusion leading to rubeosis, 1 bilateral choroidal neovascularization with prior macular hole in only 1 eye, 1 progressive glaucomatous damage). Visual acuity improved by +0.3 logMAR in 73/127 eyes (57.5%) at the final examination. No eyes had late reopening of the macular hole.

CONCLUSIONS: The results following vitrectomy for macular holes using ICG to assist removal of the ILM are excellent with no late macular hole recurrences and no evidence of ICG toxicity. Visual acuity improved following surgery and was maintained in most eyes for many years.
Brilliant Blue G versus Infracyanine Green in Macular Hole Surgery

Christiane Falkner-Radler, MD
Vienna, Austria

PURPOSE: To compare the staining characteristics and outcomes after macular hole surgery using two different retinal dyes in a randomized clinical trial.

METHODS: Sixty patients with idiopathic full thickness macula hole were randomly assigned to be treated with 23-gauge vitrectomy and internal limiting membrane peeling using Brilliant Blue G (BBG group) or Infracyanine Green (ICG group). Main outcome measure was best corrected visual acuity (BCVA) at 3 months. In addition, the staining quality of the retinal dye, complication rates, and retinal sensitivity were analyzed.

RESULTS: Mean BCVA and retinal sensitivity improved after surgery in both groups, but no significant difference was found between both groups. In the BBG group, the visualization of the stained membrane was graded “poor” in 3 patients, whereas in the ICG group staining quality was graded “good” in all patients. Complication rates were comparable between both groups. Closure of the macular hole was obtained in all patients, although 1 patient in the ICG group needed revision surgery.

CONCLUSIONS: Good and comparable outcomes were achieved in this series, which were not significantly associated with the selection of the retinal dye. Despite the possible side effects of ICG we suggest using BBG assisted macular hole surgery.
Rates of Reoperation and Retinal Detachment Repair Following Macular Hole Surgery

Stephen Schwartz, MD, MBA  
Naples, FL

Kamyar Vaziri, MD, Krishna Kishor, MD, Jorge Fortun, MD, Andrew Moshfeghi, MD, MBA, Harry Flynn Jr, MD

PURPOSE: To evaluate reoperation rates following macular hole surgery and to assess the cumulative incidence of retinal detachment (RD) following macular hole surgery.

METHODS: This is a retrospective study utilizing the nationally pooled, insurance claim-based MarketScan databases from the years 2007 – 2011. Patients with records of macular hole surgery were identified and cases of “definite” (surgeries in which the same eye was coded both times) and “presumed” (surgeries in which the eye laterality was not coded) macular hole reoperations were queried. Subgroup analysis was performed according to whether or not internal limiting membrane (ILM) peeling was coded. In addition, cases of postoperative RD occurring within 2, 3, and 12 months were captured. Kaplan Meier survival analysis was used to evaluate the cumulative incidence rates of postoperative RD and Fisher’s exact test was applied to calculate P values.

RESULTS: There were 23,465 surgeries on 20,764 patients analyzed. Among “presumed” reoperations, 5.5% (5.3% among ILM and 6.2% among non-ILM surgeries; P=0.03) of eyes had a macular hole reoperation within 3 months of the initial surgery, 6.6% (6.5% among ILM and 7.5% among non-ILM surgeries; P=0.1) within 4 months and 7.3% (1,264/16,097; 7.1% among ILM and 8% among non-ILM surgeries; P=0.04) within 5 months. The rates for “definite” reoperations were 1.7% (1.6% among ILM and 2.5% among non-ILM surgeries; P=0.004) at 3 months, 2.5% (2.1% among ILM and 4.3% among non-ILM surgeries; P<0.001) at 4 months, and 3.0% (2.4% among the ILM and 5.6% among non-ILM surgeries; P<0.001) at 5 months. The cumulative incidence rate of postoperative RD ranged from 1.81 ± 0.09% to 2.18 ± 0.5% after 2 months, 2.27 ± 0.10% to 3.18 ± 0.67% after 3 months and 3.65 ± 0.16% to 5.70 ± 1.1% after 12 months.

CONCLUSIONS: In this nationally representative series, reoperations for macular hole were performed at low rates. In general, ILM peeling was associated with significantly lower reoperation rates. Postoperative RD was uncommon.
The Depth of the Epiretinal Traction

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PURPOSE: To describe the correlation between structural and functional retinal changes in antero-posterior vitreomacular traction and epiretinal membrane (ERM) on the base of depth of traction and intraretinal morphology findings using enface OCT.

METHODS: Prospective comparative study on 56 eyes examined using OCT to assess area of traction, depth of traction on enface analysis, macular thickness, presence of intraretinal cysts, and changes of no-flow area at Angio-OCT. The depth of the traction was calculated as the first layer free from traction visible on en-face images going from superficial to deeper retinal layers. Patients were divided into two groups based on the depth of the traction: above 90 microns (group A) or below 90 microns (group B). Correlations were drawn with best-corrected visual acuity (BCVA). For those patients undergoing vitrectomy and ERM peeling, postoperative retinal changes in terms of depth of traction and non-flow area were assessed at 6 months post-operatively.

RESULTS: In group A, no significant correlation between structural and functional retinal changes was seen. In group B, there was a statistically significant correlation between BCVA and area of traction (P < 0.01). In the subgroup of 26 patients treated surgically, a significant increase of no-flow area (0.10 mm² vs 0.19 mm², P=0.02, P=0.02) and a significant reduction in depth of traction (112 μm vs 35 μm, P < 0.01) was seen.

CONCLUSIONS: The area and depth of epiretinal traction are prognostic factors correlated with changes in BCVA. ERM peeling leads to a positive reduction in the depth of traction, but also causes changes in the no-flow area.
Preoperative and Intraoperative Prognostic Factors of Epiretinal Membrane (ERM) Surgery After Internal Limiting Membrane (ILM) Peeling Using Brilliant Blue (BB)

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Sao Paulo, Brazil

L. Machado, MD, B. Furlani, MD, R. Navarro, MD, M. Farah, MD, PhD, O. Magalhaes Jr, MD, PhD, E. Rodrigues, MD, PhD, A. Maia, MD

PURPOSE: To evaluate the preoperative and intraoperative findings as prognostic indicators of functional and anatomic results of idiopathic epiretinal membrane (ERM) surgery.

METHODS: This was a retrospective case series. Inclusion criteria: Idiopathic ERM evaluated by best-corrected visual acuity (BCVA), OCT, fluorescein angiography, and autofluorescence for at least 12 months at baseline and postoperatively. Exclusion criteria: Secondary ERM, diabetic retinopathy and previous vitreoretinal surgery. Vitrectomies included triamcinolone acetonide staining of the ERM and brilliant blue staining of ILM for both ERM and ILM peeling procedures. All phakic eyes were submitted to phacoemulsification and intraocular lens (IOL) implantation. Statistical analysis was performed by Student tailed t-test, ANOVA, Pearson’s, Mann-Whitney and Kruskal-Wallis. P-values of 0.05 or less were considered statistically significant.

RESULTS: Thirty-one eyes were followed for a mean of 16.78 months. After ERM peeling, three intraoperative internal limiting membrane (ILM) patterns were seen: ILM peeled along with the ERM (32.3%), intact ILM (25.8%), and varying sizes of ILM tears (41.9%). BCVA and central foveal thickness (CFT) improved significantly (P<0.001) from baseline at 3 and 12 months. Eyes with lower BCVAs improved more significantly postoperatively. Preoperative hyperautofluorescence was associated with greater CFT reduction (P<0.005). ILM status after ERM peeling did not influence visual recovery, but was associated with anatomical results, as measured by the OCT.

CONCLUSIONS: Preoperatively ooor initial BCVA and RPE defects by FAF were not a contraindication to ERM and ILM peeling. Hyperautofluorescence preoperatively was associated with greater CFT reduction Intraoperative classification of ILM status after ERM and ILM staining/peeling was reported and may be useful for future studies; however, the intraoperative ILM status was not associated neither with preoperative nor postoperative BCVA. Additional studies with larger series are necessary to confirm these findings.
Can Reading Speed Testing (MNREAD) or Video Scanning Laser Ophthalmoscopy Analysis Objectively Account for the Subjective Visual Improvement After Surgery for Vitreous Opacities?

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**PURPOSE:** Patients with visually significant vitreous opacities (VO), which can be imaged by video scanning laser ophthalmoscopy (SLO), often complain of poor reading ability. After surgery, patients report improved vision, despite little change in acuity. Our thesis is that formal reading speed testing and analysis of video SLO footage may provide quantifiable assessments of the VO’s effect on visual function.

**METHODS:** This is a prospective, non-randomized, unmasked study including adult patients who complain of reading difficulty secondary to vitreous opacities (VO). We exclude patients with a best-corrected visual acuity of worse than 20/40 and who have confounding ocular or reading disorders. Dynamic infrared SLO video is used to quantify macular shadowing by a VO after saccade. The VFQ-25 survey gives a subjective score of visual function. The MNREAD test assesses reading speed under a total of six conditions: monocularly for each eye and binocularly, and post-saccade or in standard fashion for each condition. Testing is repeated 4-6 weeks after surgery for comparison.

**RESULTS:** Currently 11 patients have been tested both pre- and post-op. Pre- and post-op BCVAs in the operated eye range from 20/25-20/20, and as predicted show no significant difference after surgery ($p = 0.94$). However, the VFQ-25 composite results show a significant improvement after surgery (average change = 19, $p = 0.002$). The near activities subscale on the VFQ, which encompasses reading ability, also improved significantly (average change = 23, $p=0.014$). The effect of reading speed remains unclear given this limited data set. Reading speed increases for the operated eye, but interestingly in the unoperated eye as well. Currently an approach to define a percentage of time the macula is obscured by a VO using frame-by-frame analysis is being refined. An additional 10 patients have been seen pre-operatively, and we are continuing to enroll more.

**CONCLUSIONS:** In this prospective study, so far the VFQ-25 composite and near activities scores show a significant change after surgery. Reading speed improvements are marginally significant, but do not fully explain the highly significant improvement in VFQ-25 scores. Studies are ongoing to evaluate the effect of reading speed and using video SLO to assess macular obscuration. Vitrectomy for significant VO results in increased patient satisfaction, and as we accrue more data we will look for a method to quantitatively account for this change.
Photopsias: A Key to Diagnosis

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Melissa Brown, MD, MN, MBA

PURPOSE: To assess the cause and character of photopsias in a consecutive cohort of vitreoretinal patients.

METHODS: Two hundred fourteen eyes in 168 consecutive patients who presented with a history of photopsias were evaluated in a cross-sectional fashion. Etiology and photopsia characteristics (duration, frequency, color, location, laterality, shape, diurnal occurrence, relationship to various stimuli, and accompanying symptoms) were recorded.

### Primary Causes of Photopsias in 214 Eyes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Eyes (n)</th>
<th>Eyes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior vitreous detachment, no retinal tear or blood</td>
<td>86</td>
<td>39.7%</td>
</tr>
<tr>
<td>Posterior vitreous detachment with retinal tear</td>
<td>19</td>
<td>8.9%</td>
</tr>
<tr>
<td>Neovascular age-related macular degeneration</td>
<td>17</td>
<td>7.9%</td>
</tr>
<tr>
<td>Posterior vitreous detachment with rheg. retinal detachment</td>
<td>16</td>
<td>7.5%</td>
</tr>
<tr>
<td>Migraine, classic and ophthalmic</td>
<td>14</td>
<td>6.5%</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>6</td>
<td>2.8%</td>
</tr>
<tr>
<td>Vertebrobasilar insufficiency</td>
<td>6</td>
<td>2.8%</td>
</tr>
<tr>
<td>Choroidal neovascularization, not AMD</td>
<td>5</td>
<td>2.3%</td>
</tr>
<tr>
<td>Retinitis pigmentosa</td>
<td>4</td>
<td>1.9%</td>
</tr>
<tr>
<td>Severe cough with acute respiratory infection</td>
<td>4</td>
<td>1.9%</td>
</tr>
<tr>
<td>Posterior vitreous detachment, preretinal blood, no retinal tear</td>
<td>3</td>
<td>1.4%</td>
</tr>
<tr>
<td>Central serous chorioretinopathy</td>
<td>3</td>
<td>1.4%</td>
</tr>
<tr>
<td>Intraocular lens reflections</td>
<td>2</td>
<td>0.9%</td>
</tr>
<tr>
<td>Blue field entoptic phenomenon</td>
<td>2</td>
<td>0.9%</td>
</tr>
<tr>
<td>Charles Bonnet syndrome</td>
<td>2</td>
<td>0.9%</td>
</tr>
<tr>
<td>Traction retinal detachment</td>
<td>2</td>
<td>0.9%</td>
</tr>
<tr>
<td>Proliferative diabetic retinopathy, no retinal detachment</td>
<td>2</td>
<td>0.9%</td>
</tr>
<tr>
<td>Hyperglycemia, glucose &gt; 400mg/dL</td>
<td>2</td>
<td>0.9%</td>
</tr>
<tr>
<td>Digoxin</td>
<td>2</td>
<td>0.9%</td>
</tr>
<tr>
<td>Metastatic adenocarcinoma to the brain</td>
<td>2</td>
<td>0.9%</td>
</tr>
<tr>
<td>Branch retinal vein occlusion</td>
<td>2</td>
<td>0.9%</td>
</tr>
<tr>
<td>Laser photocoagulation</td>
<td>2</td>
<td>0.9%</td>
</tr>
<tr>
<td>Bilateral acute retinal necrosis (BARN)</td>
<td>2</td>
<td>0.9%</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>2</td>
<td>0.9%</td>
</tr>
<tr>
<td>Multifocal choroiditis</td>
<td>1</td>
<td>0.5%</td>
</tr>
<tr>
<td>Combined central retinal artery &amp; central retinal vein occlusion</td>
<td>1</td>
<td>0.5%</td>
</tr>
<tr>
<td>Embolic central retinal artery occlusion</td>
<td>1</td>
<td>0.5%</td>
</tr>
<tr>
<td>Embolic branch retinal artery occlusion</td>
<td>1</td>
<td>0.5%</td>
</tr>
<tr>
<td>Acute idiopathic blind spot enlargement (AIBSE) syndrome/Acute zonal occult outer retinopathy (AZOOR)</td>
<td>1</td>
<td>0.5%</td>
</tr>
<tr>
<td>Toxoplamosis</td>
<td>1</td>
<td>0.5%</td>
</tr>
<tr>
<td>Central retinal vein occlusion</td>
<td>1</td>
<td>0.5%</td>
</tr>
<tr>
<td>Adult onset foveal pigment epithelial dystrophy (AOFPED)</td>
<td>1</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

**TOTAL** 214 100%
The distribution of photopsia etiologies is shown in that Table. Vitreoretinal traction typically produced quick, temporal, white flashes, more pronounced in the dark. Wet AMD characteristically produced more central flashes. Location, laterality and other light symptoms are also important issues. Characteristic patterns for various conditions will be discussed.

**CONCLUSIONS:** Photopsias give important clues as to their etiology and diagnoses. Characteristic patterns associated with different etiologies are described.
PURPOSE: To report the outcomes and describe the surgical technique of a consecutive series of pseudophakic rhegmatogenous retinal detachment (RRDs) with only inferior breaks.

METHODS: Prospective consecutive case series. Inclusion criteria: all primary RRDs with only inferior breaks repaired with PPV alone between January 2006 through January 2014. 20 gauge PPV alone with 160° contact fundus lens was used in all cases as well as 360° intraoperative dynamic scleral depression. Subretinal fluid was completely drained from the retinal breaks during fluid-air exchange. Exclusion criteria: PVR grade C and giant tears. Outcome measures included retinal re-attachment, postoperative volume of tamponade agent, Snellen best corrected visual acuity (BVCA). Air, SF6 and C3F8 were used as tamponade agents. Patients were not instructed on any specific posture during the postoperative period.

RESULTS: One hundred forty-seven eyes of 147 patients, mean age 60 years (range 24 to 89 years), were included in the study. The mean follow-up was 21 months (range 8 to 85 months). A single break was present in 92 cases (62.5%) and 2 or more breaks in 55 cases (37.5%). The macula was detached in 117 cases (79.6%) and attached in 30 cases (20.4%). Mean duration of macular detachment was 11 days (3 to 30 days). The retina was reattached with one procedure in 139 (94.5%) cases. Final reattachment was achieved in 147 (100%) cases. In 3 cases (37.5 %) a new or missed break was responsible for the redetachment while in 5 cases (62.5%) redetachment was due to a treated break. Mean postoperative volume of tamponade agent during the first week was 75% of the vitreous cavity. From the 228 inferior breaks, 152 breaks (66%) were located between 5 and 7 hour and were not isolated by the tamponade agent during the first week postoperatively. Mean final visual acuity was 20/40 (range 20/200 to 20/20).

CONCLUSIONS: Pars plana vitrectomy alone for inferior breaks in pseudophakic retinal detachment achieves a high reattachment rate when a complete drainage of subretinal fluid from the breaks is performed.
The Use of Intraoperative Methotrexate Infusion to Prevent Proliferative Vitreoretinopathy

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PURPOSE: The purpose of this study is to describe our initial experiences with intravitreal methotrexate (IVM) infusion during retinal detachment (RD) repair with pars-plana-vitrectomy (PPV) in high-risk eyes for proliferative retinopathy (PVR) development.

METHODS: A retrospective medical record review was performed on a consecutive series of patients who received IVM during PPV for RD repair between 2008 and 2014 deemed to be at high risk for recurrent RD from PVR. The indications were: Severe recurrent PVR, severe uveitis, or history of severe contralateral PVR. Patients received 40mg of methotrexate into each 500mL BSS infusion bottle during surgery. Preoperative history, surgical details and postoperative course were retrieved from electronic medical records.

RESULTS: Twenty-nine eyes received IVM during PPV: Rhegmatogenous RD with PVR (n=22), primary tractional RD with uveitis (n=2), primary RD with PVR with a complex history of inflammatory complications following surgical repair in contralateral eye (n=3), and epiretinal membrane with uveitis (n=2). Final best-corrected visual acuity (VA) was >20/200 in 18/29 eyes (62.1%). VA improved in 19 eyes (65.6%), remained stable in 3 (10.3%), and worsened in 7 (24.1%). On last follow-up exam, all eyes had excellent anatomical results, 3/29 (10.3%) required intervention for recurrent RD after receiving MTX infusion, 6/29 (20.7%) developed recurrent PVR without recurrent RD. No complications related to IVM occurred.

CONCLUSIONS: In selected eyes at high risk for developing PVR after PPV, our study suggests that IVM infusion may reduce the risk of PVR. A prospective randomized trial is needed.
Unexplained Visual Loss Following Silicone Oil Removal. Results of the Pan American Collaborative Retina Study (PACORES) Group

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PURPOSE: To report the incidence and clinical features of patients that experienced unexplained visual loss following silicone oil (SO) removal.

METHODS: Multicenter retrospective study of patients that underwent SO removal during 2000-2012. Visual loss of ≥2 lines was considered significant.

RESULTS: A total of 324 eyes underwent SO removal during the study period. Forty two (13%) eyes suffered a significant visual loss following SO removal. Twenty three (71%) of these eyes lost vision secondary to known causes. In the remaining 19 (5.9%) eyes, the loss of vision was not explained by another pathology. Eleven of these 19 patients (57.9%) were male. The mean age of this group was 49.2 ± 16.4 years. Eyes that had an unexplained visual loss had a mean IOP while the eye was filled with SO of 19.6 ± 6.9 mm Hg. The length of time that the eye was filled with SO was 14.8 ± 4.4 months. In comparison, eyes that did not experience visual loss had a mean IOP of 14 ± 7.3 mm Hg (p<0.0002) and a mean tamponade duration of 9.3 ± 10.9 months (p<0.0001).

CONCLUSIONS: An unexplained visual loss after SO removal was observed in 5.9% of eyes. Factors associated with this phenomenon included IOP and SO tamponade duration.
Evaluation of a Retinal Patch Biopolymer for the Treatment of Retinal Detachment in Pig Eyes

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Matthew Farajzadeh, Tatsuhiko Sato, MD, Syed Askari, MD

PURPOSE: The purpose of this study is to assess the safety and effectiveness of a novel adhesive biopolymer used as a retinal patch for the treatment of rhegmatogenous retinal detachment in pigs eyes.

METHODS: Six Yorkshire pigs underwent, in both eyes, a 23G pars plana vitrectomy with creation of a retinal detachment with a full thickness retinal hole. After per-operative laser retinopexy, SF6 conventional tamponade agent was used in all right eyes, and the adhesive biopolymer was used as the retinal patch in the fellow eyes (left eyes). Clinical evaluation of the fundus was performed at weeks one, three, and five post operatively using an iPhone fundus imaging technique and a B-scan ultrasonography. For the first, second and third pigs, both eyes were enucleated at weeks 2, 4, and 5 respectively for histological evaluation.

RESULTS: Clinical evaluations have determined that the retina reattached completely following the procedures. The pigs were then euthanized and enucleated at various time points following the surgery for histological examination. Histological examination of the enucleated eyes determined that the biopolymer adhered tightly to the retina and efficiently sealed the retinal tear. Some inflammation was detected, but anatomical success was demonstrated in the eyes repaired with the biopolymer.

CONCLUSIONS: This adhesive biopolymer can be used to adhere and seal retinal tears effectively in pigs eye without causing significant intraocular inflammation or functional/structural retinal abnormalities. The adhesive biopolymer, which demonstrated absence of any functional and anatomical retinal toxicity on previous studies conducted on mice and rabbits. The biopolymer patch could an effective and a safe retinal sealing agent that can be used in the surgical repair of rhegmatogenous retinal detachments in place of conventional tamponade agents.
IOFB Without Endophthalmitis Following Combat Ocular Trauma: A Review of 163 Cases

Marcus Colyer, MD
Bethesda, MD
Denise Ryan, MS, Eric Weichel, MD

PURPOSE: To report the continued absence of post-traumatic endophthalmitis associated with intraocular foreign bodies (IOFB) in combat ocular trauma from Iraq and Afghanistan.

METHODS: Retrospective, non-comparative, consecutive interventional case series analyzing United States service members who were evacuated from combat to Walter Reed Army Medical Center from 2001 through 2011. Primary outcome measure was final visual outcome. Secondary measures included post-injury Ocular Trauma Score, the length of follow up, size of intraocular foreign body, globe survival rate, number of surgical procedures, and incidence of traumatic brain injury.

RESULTS: Of 891 total eye injuries in 654 service members, The majority of injuries were sustained from explosive blasts. All eyes underwent primary globe closure within 24 hours of injury. 119 patients sustained IOFB injuries in one eye while 44 patients suffered bilateral IOFBs. 193 surgical procedures were performed in these patients with 48 eyes having concomitant retinal detachment and intraocular foreign body. Final logMAR acuity was 0.63±0.87 with 34 eyes (21%) developing No Light Perception Vision or undergoing enucleation. No cases of post-traumatic endophthalmitis occurred in this cohort.

CONCLUSIONS: Intraocular foreign bodies were a common and potentially devastating source of ocular morbidity during combat. The previously noted absence of endophthalmitis persisted in this population through the duration of combat.
Autophagy and Control of Photoreceptor Cell Death

David Zacks, MD, PhD
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PURPOSE: Autophagy contributes significantly to the maintenance of homeostasis and cellular response to stress. Within the photoreceptor, the activation of autophagy results, in part from the light-dark dependent translocation of the visual transduction proteins, arrestin and transducin. The purpose of this study was to determine whether modulation of autophagy activity would alter the rate of photoreceptor death in models of hereditary retinal degeneration caused by mutations in phototransduction genes.

METHODS: Autophagy was modulated using both genetic and pharmacologic techniques. Rates of photoreceptor degeneration were examined using optical coherence tomography and histologic analyses. Functional assessment was also performed. Autophagosomes were isolated using immunoprecipitation columns and their contents examined using Western blot and mass-spectroscopy analyses.

RESULTS: Photoreceptor autophagosomes contain phototransduction proteins, confirming their critical role in clearing these proteins from the inner segment after their light-dark translocation from the outer segment. Modulation of autophagy affects the rate of photoreceptor survival.

CONCLUSIONS: Autophagy plays a critical role in maintaining photoreceptor homeostasis. Modulation of autophagy has the potential to serve as a therapeutic intervention in some forms of retinal degeneration.
The Role of the Complement System in Photoreceptor Cell Death During Retinal Detachment

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Boston, MA

Harry Sweigard, PhD, Hidetaka Matsumoto, MD, Kaylee Smith, BS, Leo Kim, MD, PhD, Demetrios Vavvas, MD, PhD, Joan Miller, MD, Kip Connor, PhD

PURPOSE: Photoreceptor loss is irreversible and is the primary cause of vision loss worldwide making the underlying mechanisms surrounding photoreceptor cell death critical to developing new treatment strategies. The complement system is an intricate innate immune surveillance pathway that is able to discriminate between healthy host tissue, diseased host tissue, apoptotic cells and foreign invaders while modulating the elimination and repair of host tissue accordingly. Little is known about the effect of the complement system in retinal detachment (RD), so we designed a study to evaluate the role of complements in RD.

METHODS: We studied the innate immune system regulators in two systems: one is a well-defined mouse model of RD and the other being human vitreous of patients with RD. The mouse RD model allowed us to take advantage of the well-established genetic manipulation platforms in mice (e.g. complement deficient knock out strains). ELISA was used to measure complement levels in both human vitreous and detached mouse retina. RTPCR was used to measure complement activity. TUNEL staining was used to quantify dying cells in ONL of detached mouse retina. Hypoxyprobe TM and electrode oxygen sensors were used to measure hypoxia in mouse retina. Data was analyzed using an unpaired Student t test.

RESULTS: We found that photoreceptors down-regulate Cd55 and Cd59, membrane bound inhibitors of complement during RD, allowing for their selective targeting by the complement system. In RD the retina becomes hypoxic and this causes upregulation of only the alternative complement pathway. This was found to promote early photoreceptor death. Preventing complement production using knockout mice or through pharmacologic inhibition, ameliorates much of the photoreceptor cell death.

CONCLUSIONS: This study identified a new role for the alternative complement pathway in photoreceptor death in RD. Understanding the mechanism by which the innate immune system facilitates photoreceptor cell death will provide new therapeutic targets for this retinal condition and other neurodegenerative conditions.
Macrophage Inflammasomes Exacerbate Photoreceptor Cell Death

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PURPOSE: Separation of photoreceptors from the retinal pigment epithelium is seen in various retinal disorders, including age-related macular degeneration, diabetic retinopathy, and retinal detachment (RD), resulting in photoreceptor death and subsequent vision loss. Cell death results in the release of endogenous molecules, termed inflammasomes, which activate molecular platforms containing caspase-1. Activation of the NOD-like receptor protein 3 (NLRP3) inflammasome in retinal disease has been reported in some cases to be protective and in others to be detrimental, causing neuronal cell death. Moreover, the cellular source of inflammasomes in retinal disorders is not clear.

METHODS: Subretinal fluid and vitreous samples, derived from patients with RD and healthy controls, were analyzed for mature IL1β, the end product of inflammasome activation. To analyze the mechanism of inflammasome activation, we induced RD via subretinal hyaluronate injection in wild type, Rip3-/-, and NLRP3-/- mice, and analyzed the inflammasome pathway by ELISA, immunofluorescence, and Western blot. Laser capture microscopy was used to determine the source of inflammasome activation. Functional effects of inflammasome activation on photoreceptor cell death were analyzed in Nlrp3-/- mice or in WT mice after administration of either caspase1 inhibitor or IL1β-neutralizing antibody.

RESULTS: Patients with photoreceptor injury subsequent to RD displayed increased levels of cleaved IL-1β, an end product of inflammasome activation, in the vitreous and subretinal fluid. In an animal model of RD, photoreceptor cell death led to activation of endogenous inflammasomes, and this activation was diminished in Rip3-/- mice. The major source of IL1β expression was found to be infiltrating macrophages in the subretinal space, rather than dying photoreceptors. Inflammasome inhibition attenuated photoreceptor death after RD.

CONCLUSIONS: Our data implicate the infiltrating macrophages as a source of damaging inflammasomes after photoreceptor detachment. Furthermore, inflammasome activation occurred in a RIP3-dependent manner, which suggests a novel therapeutic target for treatment of retinal diseases.
POSTERS
Retinal Detachment Prevention in Opaque-Cornea Eyes Receiving a Permanent Keratoprosthesis

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PURPOSE: To introduce a new technique of retinal detachment laser prophylaxis, performed after opaque cornea trephination, but before placement of a narrow optical stem, permanent keratoprosthesis (KPro).

METHODS: After removing the opaque central cornea with an 8.75 mm trephine, to accept an 9.00 mm graft with a pre-installed, narrow (<3 mm) optical stem KPro, we place an 8.20 mm, wide-field temporary keratoprosthesis (TKP); perform closed, wide-field (25-gauge) vitrectomy; place encircling laser prophylaxis from the ora serrata to the posterior vitreous base in all quadrants (ora secunda cerclage, OSC); remove the TKP; and finally place the KPro device, installed in an 9.00 mm graft, into the same trephination, all in a single operation.

RESULTS: A 29-year old man with 4/200 visual acuity O.U. lost the right eye to spontaneous retinal detachment with irreparable proliferative vitreoretinopathy and phthisis, 14-months after a standard KPro procedure. Following the above consecutive TKP/OSc/KPro operation in his remaining left eye, having nystagmus, aniridia, aphakia, extreme myopia, congenital glaucoma, glaucoma shunt, failed keratoplasty, and opaque cornea, the left eye remained stable 30-months postoperatively. The retina remained attached, viewed centrally through the narrow optical stem and peripherally with ultrasonography. Visual acuity was 20/100 distant and 20/25 near using low vision spectacles, with an (untreated) ocular pressure of 10 mm Hg.

CONCLUSIONS: Because retinal detachment in KPro eyes often presents at a relatively late stage and is difficult to visualize and repair, this combined TKP/OSc/KPro procedure should be considered for KPro eyes deemed to be high-risk, or in monocular individuals.
Pre- and Post-Vitrectomy Choroidal Thickness in Eyes with Epiretinal Membrane and Macular Hole

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PURPOSE: To evaluate subfoveal choroidal thickness (SFCT) and central macular thickness (CMT) before and after pars plana vitrectomy (PPV) with indocyanine green (ICG)-assisted internal limiting membrane (ILM) peeling for epiretinal membrane (ERM) and full-thickness macular hole (FTMH).

METHODS: A retrospective, consecutive, interventional series of subjects undergoing PPV with ICG-assisted ILM peeling for ERM and FTMH was conducted between 1/1/12 and 1/28/15. SFCT was measured via enhanced depth imaging OCT (EDI-OCT) and CMT was obtained from the center subfield of the macular thickness map before and after vitrectomy in study and fellow eyes using spectral domain OCT.

RESULTS: A total of 131 eyes of 131 subjects (71 ERM, 60 FTMH, mean age 64.6±12.84 years) were included. Mean follow-up was 57 days (ERM) and 51 days (FTMH) (P=0.48). ERM SFCT was 183±84 before and 184±84 microns after vitrectomy (P=0.94). Fellow-eye SFCT 194±89 before and 192±87 microns after vitrectomy (P=0.21, P=0.33 compared to study eye). FTMH SFCT was 182±70 before and 179±73 microns after vitrectomy (P=0.48). Fellow-eye SFCT was 195±87 before and 200±83 microns after vitrectomy (P=0.19, P=0.097 compared to study eye). Pre-vitrectomy ERM SFCT was significantly higher in those with baseline CMT ≥500 microns compared to those <500 microns (206±91 vs. 165±75; P<0.05). Post-vitrectomy ERM SFCT remained higher in those with baseline CMT ≥500 microns compared to those <500 microns (205±85 vs. 166±80; P<0.05). There was a significant difference between the ages of the two surgical groups [ERM 67±11.4 years and FTMH 62±14.0 years (P=0.024)], which had a negative correlation with SFCT; correlation coefficient at baseline=-0.33 (P<0.001) and follow up=-0.29 (P<0.001).

CONCLUSIONS: Microincision PPV with adjunctive ICG for ERM and FTMH does not appear to affect SFCT significantly. Compared to the fellow eye, there was no significant difference in SFCT in these eyes. However, a trend was noted towards thinner SFCT in eyes with FTMH compared to the fellow eye. ERM eyes and fellow eyes with a greater baseline CMT had thicker SFCT at both baseline and post-vitrectomy. SFCT was 182±70 before and 179±73 microns after vitrectomy (P=0.48). Fellow-eye SFCT was 195±87 before and 200±83 microns after vitrectomy (P=0.19, P=0.097 compared to study eye). Pre-vitrectomy ERM SFCT was significantly higher in those with baseline CMT ≥500 microns compared to those <500 microns (206±91 vs. 165±75; P<0.05). Post-vitrectomy ERM SFCT remained higher in those with baseline CMT ≥500 microns compared to those <500 microns (205±85 vs. 166±80; P<0.05). There was a significant difference between the ages of the two surgical groups [ERM 67±11.4 years and FTMH 62±14.0 years (P=0.024)], which had a negative correlation with SFCT; correlation coefficient at baseline=-0.33 (P<0.001) and follow up=-0.29 (P<0.001).
Outcomes of Pars Plana Vitrectomy for Retinal Detachment Complicated by Proliferative Vitreoretinopathy

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PURPOSE: To investigate the anatomic and visual outcomes and complications following pars plana vitrectomy (PPV) for proliferative vitreoretinopathy-related retinal detachments (PVR-RD).

METHODS: Retrospective chart review study of patients who underwent complex retinal detachment repair by a single surgeon (PEC) between September 2007 and January 2015 for PVR-RD with pre-operative data and follow-up of at least 3 months were identified. Patients with a history of trauma, endophthalmitis or proliferative diabetic retinopathy were excluded. The primary outcome was rate of retinal re-attachment with secondary outcomes of change in visual acuity (VA), time to re-operation, average number of surgeries to reach anatomic success, and effect of lens status, scleral buckling, lensectomy, and type of tamponade on success rate.

RESULTS: 24 patients (15 male, 9 female, average age 63 [range 20-90]) were included in the study. Mean vision improved from logMAR 1.8 (Snellen equivalent 3/200, range 0.6-2.5, Snellen equivalent 20/80-LP) pre-operatively to logMAR 1.3 (Snellen equivalent 20/400, range 0.6-2.5, Snellen equivalent 20/60-HM) at 3 months (p=0.0015). Final anatomic success rate was 100% at final follow-up (mean follow-up 19 months, range 3-66 months), with 9/24 (37%) requiring a single surgery, 4/24 (17%) requiring 2 surgeries, 6/24 (25%) requiring 3 surgeries and the remainder (21%) requiring 4 or more surgeries. Of the 9 patients who required a single surgery for repair of their PVR-RD, 5 (56%) had a scleral buckle present preoperatively compared to 1/15 patients requiring more than one surgery (p=0.04). Of the 36 surgical repairs of PVR-RD placed under silicone oil tamponade 21 detached (58%), and of the 20 surgical repairs placed under C3F8 tamponade 9 detached (45%, p=0.6).

CONCLUSIONS: Repair of PVR-RD using current surgical techniques resulted in ultimate reattachment in all patients with significant improvement in vision, although the majority of patients required multiple surgeries. Presence of a scleral buckle was the only factor associated with greater likelihood of single surgery anatomic success. Tamponade agent (silicone oil versus perfluoropropane) choice bore no difference on single surgery failure rate.
HC-HA/PTX₃, a Soluble, Active Matrix Component of Amniotic Membrane, Inhibits Proliferation and Epithelial Mesenchymal Transition of RPE Cells: A Potential Novel Therapy for Proliferative Vitreoretinopathy (PVR)

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PURPOSE: Proliferative vitreoretinopathy (PVR), characterized by retinal surface membranes, is the main cause of failure of rhegmatogenous retinal detachments (RRDs). We and others have reported that PVR is mediated by proliferation and epithelial mesenchymal transition (EMT) of RPE cells under the influence of vitreous growth factors. We have recently purified and characterized heavy chain-hyaluronic acid/pentraxin 3 (HC-HA/PTX₃) complex as a unique matrix component from amniotic membrane that exerts anti-inflammatory and anti-EMT effects. HC-HA/PTX₃ can be solubilized and injected intravitreally. Therefore, we investigated whether HC-HA/PTX₃ may inhibit RPE cell proliferation and EMT in vitro and established rabbit PVR model for future studies.

METHODS: We first tested if 0.1 to 25 µg/ml HC-HA/PTX₃ was toxic to ARPE-19 cells by the Cell Death ELISA in comparison to HA and PBS. We optimized proliferation of ARPE-19 cells measured by BrdU labeling (ELISA and immunofluorescence) regarding the cell density, culturing medium, serum starvation, and addition of different growth factors. EMT was induced by addition of TGFβ1 and measured by nuclear pSMAD2/3 staining. We assessed the inhibitory effect of HC-HA/PTX₃ on proliferation and EMT in vitro. Additionally, four New Zealand white (NZW) rabbits underwent cryotherapy, gas displacement of vitreous with intravitreal perfluoron, gas-fluid exchange, and intravitreal injection of NZW RPE cells to induce PVR.

RESULTS: There was no difference in ARPE-19 cell death by addition of HA-HA/PTX₃ or HA, or PBS. EGF+FGF induced a 7-fold increase (p<0.05) in proliferation and EGF+FGF+TGFβ induced a 3-fold increase in nuclear pSMAD 2/3 staining. Addition of 25 µg/ml HC-HA/PTX₃ inhibited EGF+FGF-induced proliferation 10-fold (p<0.05) and EGF+FGF+TGFβ-induced pSMAD 2/3 staining 2-fold (p<0.05). Addition of 25 µg/ml HA did not inhibit proliferation or nuclear pSMAD 2/3. All four rabbits developed open funnel RDs with PVR membranes.

CONCLUSIONS: HC-HA/PTX₃ is a non-toxic, potent inhibitor of RPE cell proliferation and EMT in vitro. We will further test whether intravitreal injection of HC-HA/PTX₃ can inhibit PVR formation using the established rabbit model of PVR.
Sealing Retina Break with Polyethylene Glycol-Based Synthetic Sealant in Rhegmatogenous Retinal Detachment

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PURPOSE: To investigate the effect of polyethylene glycol-based synthetic sealant (PEG sealant) on patching retinal breaks for rhegmatogenous retinal detachment in rabbit eyes.

METHODS: PEG sealant which has been used to prevent air leaks from pulmonary resections in humans is polymerized under visible xenon light, and forms firmly adherent hydrogel. Experimental retinal detachment with a break was made during a 25-gauge vitrectomy in six rabbit eyes. After performing fluid-air exchange, PEG sealant was applied to cover iatrogenic retinal breaks entirely, and was polymerized with a 60-second application of xenon light in three rabbit eyes (sealant group). Air-fluid exchange was then performed, and operations were finished without intraocular tamponade by air. In other three eyes, the same procedures were performed without PEG sealant application (control group). Funduscopic examination and optical coherence tomography (OCT) was carried out in both groups at 1 and 7 days, and 1 and 3 months postoperatively.

RESULTS: Retina in every eye of the sealant group stayed reattached over 3 months after the surgery meanwhile all three eyes of the control group resulted in proliferative vitreoretinopathy. PEG sealant was observed by OCT on the retinal breaks at 1 and 7 days, but was not observed after 1 month postoperatively.

CONCLUSIONS: We successfully close the retinal breaks with PEG sealant in rabbit eyes with rhegmatogenous retinal detachment, without any intraocular tamponade. PEG sealant was found to be beneficial to seal retinal breaks during and after vitrectomy for rhegmatogenous retinal detachment in rabbits.
The Effects of Diabetic Retinopathy and Panretinal Photocoagulation on Photoreceptor Cell

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PURPOSE: The pathophysiology of visual loss in persons with diabetic retinopathy (DR) is complex and incompletely defined. We hypothesized that rod and cone photoreceptor dysfunction would increase with severity of diabetic retinopathy, and that panretinal photocoagulation would exacerbate this dysfunction.

METHODS: Dark adaptation was measured using the AdaptDx in subjects with diabetes mellitus and healthy volunteers (controls). Dark adaptation was measured at 5 degrees superior to the fovea in response to a 5 X 10^-4 scotopic cd m-2 s-1 bleach. Inclusion criteria were: age ≥ 18 years; and best-corrected visual acuity ≥ 20/400. Cone sensitivity and rod recovery speed were compared between groups.

RESULTS: The sample consisted of 24 controls and 75 diabetic subjects, of which 12 had Type 2 diabetes mellitus and 63 had Type 1 diabetes mellitus. Beginning at the level of moderate non-proliferative diabetic retinopathy (NPDR), diabetic subjects had significantly impaired rod recovery slopes compared to controls (controls mean: 0.29 log units/min; moderate NPDR mean: 0.20 log units/min; p= 0.042). Subjects who had proliferative diabetic retinopathy (PDR) had significantly impaired cone sensitivity (controls mean: 2.1 log units; T1DM PDR mean: 1.9, p=0.023; T2DM PDR mean: 1.6 p<.001). Neither of the outcomes was significantly different between subjects with untreated PDR compared to those who had PRP.

CONCLUSIONS: The results suggest that photoreceptor cell dysfunction, as assessed by dark adaptometry, begins as early as the moderate NPDR stage, and rod and cone cells are affected to similar degrees. Surprisingly, PRP not further impair dark adaptation. These findings suggest the possibility that diabetes impairs retinal retinoid metabolism, and provides a potential target to improve visual function in persons with DR.
Alteration of N-glycan Profiles in Diabetic Retinopathy

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PURPOSE: To investigate the alteration of vitreal N-glycans in patients with proliferative diabetic retinopathy (PDR).

METHODS: Plasma and vitreous samples were collected from 17 patients (10 females and 7 males) with PDR (PDR group), and 17 non-diabetic patients (8 females and 9 males) with epiretinal membrane (ERM) and idiopathic macular hole (MH) (non-DM group). Profiles of N-glycans were analyzed by glycoblotting-based high throughput protocol, which we recently developed. Human retinal microvascular endothelial cells (HRMECs) were cultivated with culture media containing either low glucose (5mM) or high glucose (25mM) and expression levels of sialyltransferases were analyzed by real-time PCR and ELISA.

RESULTS: Amount of N-glycans in the vitreous fluid of PDR was significantly higher than that of non-DM group (495.5±37.4 VS 142.7±30.8pmol/100µg protein, P<0.001). Profile analysis showed that N-glycans with sialic acids increased in the vitreous of PDR group (328.4±25.8pmol/100µg protein) compared to those of non-DM group (92.1±12.2pmol/100µg protein, P<0.0001), whereas there was no significant difference in plasma between PDR and non-DM group. Expression of sialyltransferases ST3GAL1 and ST3GAL4 was up regulated in HRMECs after high glucose stimulation. To accord with the real-time PCR data, high glucose stimulation elevated the protein levels of ST3GAL1 (117.4±14.9pg/mg, P<0.01) and ST3GAL4 (6.1±0.9pg/mg, P<0.05) in HRMECs compared with the cells cultured with low glucose culture media (ST3GAL1, 64.4±5.8pg/mg; ST3GAL4, 3.8±0.3pg/mg).

CONCLUSIONS: Our data demonstrate the distinct changes of N-glycan profile and the increase of sialylated N-glycans in eyes with PDR.
The Role of Carotenoids in Skin and Eye Protection from Ultraviolet and Visible Light Stress

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PURPOSE: The skin and eyes are organ systems exposed to the most light and heat in the human body. Each system has developed intrinsic mechanisms to protect itself from heat and light, but the conserved and different cellular machinery is rarely compared in the literature. The skin uses carotenoids to quench the reactive oxygen species formed from exposure to UV light, which prevents skin aging and cancer. The eyes utilize carotenoids in the membranes of the photoreceptor outer segments to protect against the damaging effects of photon stress. We set out to review the location, structure, and function of carotenoids in the skin and eye, which might elucidate otherwise unknown relationships.

METHODS: We reviewed all relevant literature on carotenoids in the eye and skin, including their function, similarities and differences in accumulation, and evidence of their role in health and disease. We created a detailed comparative table of our findings.

RESULTS: Our results indicate that eye and skin carotenoids possess very similar roles in maintaining eye and skin health. We found a correlation between the concentration of eye and skin carotenoids and certain diseases, such as Age-Related Macular Degeneration (AMD). Concentrations of carotenoids in the eye and skin may serve as a marker of disease or the potential onset of disease.

CONCLUSIONS: Assuming a correlation in concentration between the skin and eye, the known carotenoid status in one organ system may allow for prediction of onset and occurrence of disease in the other organ system. These findings will have significant implications in the development of diagnostic testing modalities, health maintenance strategies, and treatment programs.
Is the Subconjunctival Bleb that Forms at the Injection Site After Intravitreal Injection Drug or Vitreous?

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PURPOSE: To determine whether the subconjunctival bleb that forms following intravitreal injection is drug or vitreous.

METHODS: Bevacizumab, ranibizumab and aflibercept were radiolabeled with iodine-124 and injected intravitreally in the left eye of 29 Dutch-belted rabbits. Immediately following intravitreal injection, each of the subjects was imaged with integrated positron emission and computed tomography (PET/CT).

RESULTS: A bleb extending from the main body of the drug at the injection site was visible in 14/29 subjects.

CONCLUSIONS: The appearance of a subconjunctival bleb on PET/CT following intravitreal injection of a labeled drug would indicate the presence of drug rather than vitreous within the bleb since vitreous cannot be radiolabeled. Refluxed drug rather than vitreous in the subconjunctival space points to the delivery of a smaller than intended intravitreal dosage but also reduces the possibility of complications that may be associated with vitreous loss.
Anatomical Characteristics and Treatment Outcomes of Pediatric Chorioidal Neovascular Membranes

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PURPOSE: To evaluate the anatomical characteristics of pediatric choroidal neovascular membranes (CNV) using SD-OCT and their response to treatment.

METHODS: Retrospective review of patients.

RESULTS: 14 eyes of 10 patients (5 males, 5 females) with a mean age of 68.2 ± 46.2 months (range 6 months to 12.3 years) were reviewed. Four patients had bilateral CNV and 6 were unilateral. CNV was associated with a coloboma (n=4 eyes) Best disease (n=6 eyes), Combined hamartoma of the retina and retinal pigment epithelium (n=1 eye), and others (n= 3 eyes).

Among colobomatous eyes, CNV was associated with PHACES syndrome with morning glory disc anomaly (n=1), iris, optic-disc and retinochoroidal coloboma (n=1), coloboma associated with retinal detachment and CHARGE syndrome (n=1) and microphthalmia with optic-disc, and retinochoroidal coloboma (n=1), CNV was located temporal to the colobomatous disc (n=3) and at temporal edge of the retinochoroidal coloboma closest to macula (n=1).

Vision at presentation ranged from no wince to light to 20/20. Fluorescein angiogram (FA) characteristics included window defects in areas of coloboma or staining but no leakage, suggesting inactivity (n=7), and leakage (n=7). Leakage was subfoveal (n=2), temporal to fovea (n=1), nasal to fovea (n=1) and at temporal edge of optic-disc (n=2) and retinochoroidal (n=1) coloboma. SD-OCT characteristics included subretinal fluid (SRF), intraretinal fluid (IRF), intraretinal cysts (IRC), subretinal hyperreflective material, epiretinal membrane, subfoveal cavitary lesions and a communicating channel from optic disc into the coloboma cavity.

Treatments included intravitreal bevacizumab (n= 7 eyes, mean 3.4±1.9, range 1-6 injections), photodynamic therapy (n=1) and focal peripapillary laser (n=1). Among eyes receiving bevacizumab and with recordable acuity, vision improved from 0.56±0.33 to 0.46±0.3 logMAR, p=0.4. All eyes showed improvement IRF, SRF and IRC to varying extents.

CONCLUSIONS: Pediatric CNV is associated with multiple etiologies, including retinochoroidal and optic disc colobomas, with the predominant location being the temporal edge of coloboma. The lesions exhibit a varied degree of anatomical response to treatment.
Foveal Development After Use of Bevacizumab for Aggressive Posterior Retinopathy of Prematurity (APROP)

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PURPOSE: To report a case of foveal development in aggressive posterior retinopathy of prematurity (APROP) after intravitreal bevacizumab treatment.

METHODS: Retrospective single case review of foveal capillary ring development after treatment with bevacizumab in APROP.

RESULTS: A male twin, born at 31 week post menstrual age (PMA), product of in vitro fertilization, weighing 1310 g, was diagnosed with APROP with absent foveal development at 33 weeks PMA. Intravitreal bevacizumab (0.625 mg) was injected in both eyes. At 37 weeks PMA foveal vascular development was noted to be present clinically, and on fluorescein angiography (FA) peri-foveal capillary ring was nearly complete. Peripheral laser ablation was performed while leaving the avascular temporal macula intact. Also, a second dose of intravitreal bevacizumab (0.625 mg) was injected. At 45 weeks PMA the foveal capillary ring was complete.

CONCLUSIONS: Treating posterior ROP, particularly when fovea is not developed can be challenging. Laser ablation of fovea would halt its development. There is concern of bevacizumab also hindering foveal development, due to its effect of vascular arrest followed by irregular vascular branching seen peripherally when used to treat ROP. We report a case of foveal development after bevacizumab followed by macular sparing laser.
Persistent Vitreofoveal Traction in a Patient with Ocular Toxoplasmosis: A Case Report

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PURPOSE: To describe a case of persistent vitreofoveal traction after a follow-up of 11 years in a patient with toxoplastic macular scar.

METHODS: Case report. We reviewed the medical records of 11 years of a patient with bilateral congenital ocular toxoplasmosis, who has metamorphopsia left eye. We describe clinical and tomographic characteristics and evolution of the case in long follow up.

RESULTS: A 74-year-old man with history of bilateral congenital toxoplasmosis associated to macular scar extrafoveal presented persistent vitreofoveal traction after a follow-up of 11 years. During these years maintained visual acuity of 20/30. Patient has refused invasive vitreous surgery except for one microplasmin intravitreoretinal injection, performed elsewhere on November 2014.

CONCLUSIONS: Vitreofoveal can be stable anatomically and functionally for many years, possibly for a wide adhesion and/or weak traction. Further studies are required to be compared with the evolution of idiopathic vitreomacular traction cases. Multimodal images and measurements of vitreoretinal adhesion will be presented.
Ocular Alterations in Patients with Helicobacter Pylori

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PURPOSE: The Helicobacter pylori (Hp) is a gram negative spiral-shaped bacterium, with great mobility, that colonizes human gastric mucosa. There are several studies discussing Hp’s involvement in ocular diseases such as blepharitis, glaucoma and central serous chorioretinopathy (CSC).

OBJECTIVES: To check if there is an association of gastric Hp infection with ocular diseases such as blepharitis, glaucoma, macular detachment and pigmentary changes suggestive of any prior history of central serous chorioretinopathy.

METHODS: A cross-sectional study was carried out to verify the prevalence of ocular abnormalities associated to Hp’s infection in patients undergoing upper digestive endoscopy from Sector of Upper digestive Endoscopy of Clinic Hospital’s ambulatory from Universidade Estadual de Londrina. The infection by Hp was evaluated by the rapid urease test. Patients were submitted to complete ophthalmologic examination and, later, to color retinography examination and spectral domain optical coherence tomography (OCT). The diagnosis of blepharitis was determined by the presence of eyelid changes characteristic of the disease, viewed by slit lamp examination. Cases of glaucoma were diagnosed by observation of the optic nerve changes associated with the diurnal curve and automated perimetry. The diagnosis of retinal changes was made by biomicroscopy of the macula, under mydriasis, with 78D lens and the help of a slit lamp, digital color fundus and optical coherence tomography.

RESULTS: 158 patients were examined — 52 men (33.0%) and 106 women (67.1%). The minimum age was 25 years and the maximum age was 75 years with average age of 52.34 years. There was the formation of two groups, positive urease with 103 patients and another, negative urease, with 55 patients. Blepharitis was found in 53 patients of the positive urease group and in 18 patients of the negative urease group (p = 0.0242). Glaucoma was found in three patients of the positive urease group and in five patients of the negative urease group (p = 0.1277). There was an alteration on OCT examination of 20 patients, with only three negative urease cases (p > 0.05) and one case of the HP positive group with CSC.

CONCLUSIONS: The prevalence of blepharitis was higher in the urease positive, with statistically significant difference. There was no relationship between Hp infection and glaucoma. This study did not found a significant prevalence of retinal changes suggestive of CSC but one patient with HP presented with CSC, however we still need to take a larger number of patients so that they establish a stronger evidence of causal relationship between the microorganism and the disease.
Funduscopy in Cerebral Malaria Diagnosis: An International Survey of Practice Patterns

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PURPOSE: To assess clinician knowledge, practice patterns, and barriers to the use of funduscopy in the diagnosis of cerebral malaria (CM).

METHODS: Multinational cross-sectional survey study included clinicians who diagnose cerebral malaria, including general medical providers, health workers, pediatricians, neurologists, and intensive care providers in malaria-endemic areas. An online English and French voluntary survey was sent via email through professional contacts in malaria-endemic regions of Africa and Asia. Responses were collected from February-August 2014. Main outcome measure focused on responses on clinical experience, current practice, attitudes, knowledge, and resources relating to cerebral malaria diagnosis and funduscopy.

RESULTS: Seventy-four responses were submitted from sub-Saharan Africa and Asia. Sixty percent (32 out of 53 respondents who answered this question) had diagnosed CM in the last year. Almost half (49%, n=53) never or almost never examine the eyes when diagnosing CM. The most common barriers to funduscopy were lack of a working funduscope (46%), discomfort with retina examination (25%), lack of awareness of the utility of funduscopy in CM (19%), and a belief that funduscopy would not help with CM diagnosis (17%). Eighty-one percent (81%) indicated interest in in-person training on funduscopy.

CONCLUSIONS: Many clinicians who diagnose life-threatening cerebral malaria are not aware that malaria retinopathy is a highly specific finding. Barriers to funduscopic examination include lack of awareness, equipment, and dilating drops.
Endophthalmitis Associated with Glaucoma Drainage Implants

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PURPOSE: To identify the clinical features, organisms, treatment modalities and outcomes of patients with endophthalmitis associated with glaucoma drainage implant (GDIs).

METHODS: A non-comparative case series of patients at the Bascom Palmer Eye Institute diagnosed with culture positive endophthalmitis associated with GDIs between January 1, 1999 and November 1st 2014 was performed.

RESULTS: A total of 13 patients (9 female and 4 male) were identified. Average age was 71 years (range 55-92). Thirteen eyes were included (8 right and 5 left), two of which had two tubes. The average time elapsed from GDI surgery to endophthalmitis was 16 months (range 6 days to 52 months). Eight eyes had conjunctival breakdown with the tube being exposed in 4 eyes, the plate in 1 and scleral patch exposure in 3 eyes. The remaining 4 eyes had a history of either tube placement or revision within four months prior to diagnosis. The most common organism was Staphylococcus epidermidis that grew from 5 eyes (Table 1). Mycobacterium was isolated from two eyes. Multiple organisms were isolated from two eyes. Eleven eyes received intravitreal antibiotics, one eye with no light perception vision was eviscerated as primary treatment and one eye where mycobacterium was cultured from the tube was treated with oral and topical antibiotics. GDIs were not removed in 4 eyes that were successfully treated. Six eyes underwent removal of the GDI and evisceration or enucleation was required in 3 cases. Median pre-infection visual acuity (VA) was 20/80, (range 20/30 to HM). Two patients returned to baseline or better than baseline vision. Six patients had NLP vision, one patient had LP vision and one had HM vision. Of the remaining 5 patients three had vision better than 20/200. Average follow up was 42 months (range 3-96 months).

CONCLUSIONS: A percentage of cases (9/13) are associated with conjunctival breakdown while others associated with a recent surgical procedure. Infections were caused by a broad spectrum of microbes, including mycobacteria with Staphylococcus epidermidis being the most common isolate (5/13). The remaining isolates were predominantly gram-positive organisms.
Aprotinin Reduces Intraocular Inflammation in Endotoxin Induced Uveitis

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PURPOSE: Aprotinin is a broad-spectrum serine protease inhibitor used clinically in the past for the treatment of acute pancreatitis and for decreasing blood transfusion volume in cardiovascular bypass surgery. Recently we have shown that aprotinin reduces retinal vascular permeability in VEGF-induced and early diabetic blood retinal barrier breakdown. Aprotinin also decreases leptin expression in experimental uveitis, however, its effect on ocular inflammation remains unknown. In this report, we investigate the potency of aprotinin for suppressing anterior and posterior segment inflammation in endotoxin-induced uveitis (EIU).

METHODS: EIU was induced by hind footpad injections of LPS (200µg) in male Lewis rats. Animals were treated with 50,000 KIU Aprotinin (5ml of Trasylol) or the equivalent volume of saline, intraperitoneally q8 hrs for 24 hrs. Intraocular inflammation was evaluated 24 hrs after LPS injection. The number of infiltrated cells and protein concentration in the aqueous humor of the anterior chamber (AC) was quantified in normal and EIU animals with or without aprotinin treatment. Retinal leukocyte adhesion was quantified using the Concanavalin A assay. Retinal vascular permeability was measured with the Evans Blue (EB) technique.

RESULTS: Aprotinin treatment of EIU animals significantly reduced the AC cell accumulation by 85% (n=14, p<0.01) and protein concentration by 77% (n=13, p<0.01), compared with vehicle-treated controls (n=12 and n=10 respectively), 24h after disease induction. Aprotinin significantly reduced retinal vascular leakage by 73% (n=14, n=10, p=0.01) and retinal leukocyte adhesion by 80% (n=8 and n=7 respectively, p<0.05).

CONCLUSIONS: Aprotinin significantly suppressed both anterior and posterior segment intraocular inflammation in the LPS-induced panuveitis model. Though the underlying mechanisms are not well understood and may involve multiple pathways, use of aprotinin may become a novel therapeutic approach in treatment of ocular inflammation.
Clinical Presentation, Microbiologic Spectrum, and Visual Outcomes of Acute Infectious Endophthalmitis Undergoing Therapeutic Pars Plana Vitrectomy

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PURPOSE: To report the clinical presentation, microbiologic spectrum, and visual outcomes associated with acute infectious endophthalmitis undergoing therapeutic pars plana vitrectomy (PPV) within 14 days of diagnosis.

METHODS: A non-comparative consecutive case series. Billing records were reviewed to identify all patients undergoing PPV for acute infectious endophthalmitis from January 2011 through December 2014 at 4 large tertiary referral practices. Patients who had PPV after 14 days from presentation were excluded from further analysis. The clinical records were reviewed to evaluate clinical features, microbiologic spectrum, and treatment outcomes.

RESULTS: Sixty-six patients were identified. The most common clinical settings were post-cataract surgery (n=22), post-intravitreal injection (n=14), post-trabeculectomy (n=10), endogenous (n=7), and post-PPV (n=5). Hypopyon was present in 55 of 66 patients (83.3%) and 65 of 66 patients (98.5%) presented with no view of the fundus. Presenting visual acuities were 20/200 (n=1), counting fingers (n=10), hand motions (n=26), light perception (n=27), and no light perception (n=2). Initial treatment strategies were vitreous tap and injection (80.3%, n=53) and PPV with intravitreal antibiotics (19.7%, n=13). All patients eventually underwent PPV an average of 2.5 days after initial presentation (range 0 to 11 days) with 39.4% (26/66) of patients undergoing PPV within 24 hours of presentation. Cannula size used during PPV included 23-gauge (n=44), 25-gauge (n=21), and 20-gauge (n=1). Positive intraocular cultures were obtained in 48 of 66 patients (72.7%). The most common identified organisms were Streptococcus species (n=23) and coagulase-negative staphylococcus (n=9). All organisms were sensitive to the initially administered antibiotics. Visual acuity on final follow-up was 20/400 or better (n=21), counting fingers (n=8), hand motion (n=12), light perception (n=12), and no light perception (n=13). One patient underwent evisceration (1.5%). Final post-operative visual acuity (mean LogMAR 1.936 +/- 0.287) improved from presenting visual acuity (mean LogMAR 2.376 +/- 0.912) (P = 0.002, Wilcoxon signed-rank test).

CONCLUSIONS: PPV for acute infectious endophthalmitis was performed most frequently in post-cataract surgery cases and in cases with proven Streptococcus sp. infection. The overall visual outcomes remained poor. The rate of globe loss was low and about a third of patients achieved 20/400 or better vision.
Oral Fluoroquinolone Use and the Risk of Uveitis

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PURPOSE: Fluoroquinolones (FQ) are the most commonly prescribed class of antibiotic. Recent reports have implicated an association between oral fluoroquinolone use and an increased risk of uveitis. This study aims to determine the hazard of uveitis with oral fluoroquinolone use.

METHODS: This is a retrospective cohort study using medical claims data from a large, national U.S. insurer. Cohorts were created using every person with an oral fluoroquinolone or beta-lactam (BL) antibiotic prescription from 2000-2012. The date of the first prescription each individual received was considered the index date. Exclusion occurred for <24 months of data in the plan prior to index date, antibiotic use prior to index date, history of uveitis, or history of a uveitis-associated systemic illness. The main outcome measure was the hazard of developing uveitis within 30 days of FQ prescription using multivariate Cox regression. Secondary analysis looked at 60-, 90- and 365-day windows. Censoring occurred for end of an observation period, diagnosis of uveitis or uveitis-associated systemic illness, use of the other class of antibiotic, or removal from the insurance plan. Covariates used in multivariate analysis were age, gender, and race.

RESULTS: In total, 4,387,651 patients were included for analysis (843,854 FQ, 3,543,797 BL). In the FQ cohort, there were 226, 404, 609, and 2039 incident cases of uveitis at the 30-, 60-, 90-, and 365-day time points, respectively. In the beta-lactam group, there were 714, 1222, 1726, and 5670 cases at the same time points. Univariate analysis showed a significantly increased hazard of uveitis in the FQ group at each time point (HR range: 1.34-1.63, p<0.001 for all comparisons). Multivariate analysis demonstrated no significant hazard for developing uveitis at the 30-, 60-, or 90-day observation window (HRs 0.97-1.07, p>0.17 for all comparisons). The 365-day observation had a small but significant increase in hazard for the FQ cohort (HR=1.11, 95% CI: 1.06, 1.17; p<0.001).

CONCLUSIONS: When drugs are expelled from the body quickly, adverse events would be expected to occur early after use and decrease with time. As such, these data do not support a strong association between oral fluoroquinolones and uveitis.
Mycobacterium Chelonae Endophthalmitis Management with Dual Antibiotic Therapy and Complete Surgical Debridement

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PURPOSE: To report favorable visual outcomes of two consecutive patients with Mycobacterium chelonae endophthalmitis managed with dual antibiotic therapy and complete surgical debridement.

METHODS: Medical records and histopathologic findings were reviewed for two consecutive patients with M. chelonae endophthalmitis.

RESULTS: A 74-year-old monocular male with exogenous M. Chelonae endophthalmitis following complicated penetrating keratoplasty who had progressive inflammation following vitrectomy and intravitreal amikacin was referred for evaluation. Surgical explantation of intraocular lens and capsule complex was performed followed by dual antibiotic therapy with intravitreal amikacin and 1 year course of oral clarithromycin. Histopathologic analysis revealed acid-fast bacilli (AFB) associated with crystalline lens remnants. Inflammation resolved post-operatively and visual acuity improved to 20/40-20/60 over >4 years follow-up despite repeat penetrating keratoplasty with medial/lateral tarsorrhaphy for severe ocular surface disease.

A 72-year-old aphakic female with exogenous M. Chelonae endophthalmitis following glaucoma drainage explant exposure was referred for progressive inflammation following drainage implant explantation and systemic antibiotic therapy. Significant inflammation persisted despite topical corticosteroids and dual antibiotic treatment with oral clarithromycin and serial intravitreal amikacin injections. Endophthalmitis resolved following surgical explantation of residual peripheral capsule with lens remnants that was identified on ultrasound biomicroscopy. A typical Soemmering ring appearance was noted on histopathology without visualization of AFB. Intraoperative intravitreal amikacin was administered followed by a six-month course of oral clarithromycin. Visual acuity was limited by glaucomatous damage but improved to 20/80-20/100 through 8 months follow-up.

CONCLUSIONS: Mycobacterium chelonae endophthalmitis has been historically associated with poor visual acuity outcomes. Bacterial culture sensitivity-guided combination antibiotic therapy is often preferred for the treatment of rapidly growing non-tuberculous mycobacteria such as Mycobacterium chelonae. Surgical explantation of intraocular implants and lens capsular complexes appears to play an important role in the management of M. chelonae endophthalmitis as both patients had evidence of persistent endophthalmitis prior to complete removal of intraocular implants and lens capsular complexes and one patient had histopathologic evidence of lens remnant-associated AFB.
Spectral-domain Optical Coherence Tomography is Superior in Detecting Epiretinal Membranes in Macular Holes Preoperatively Compared to Time-domain Optical Coherence Tomography: Implications for Pharmacological Vitreolysis

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PURPOSE: To compare the sensitivities of spectral-domain optical coherence tomography (SD-OCT) versus time-domain OCT (TD-OCT) in identifying epiretinal membranes (ERM) preoperatively in patients who underwent surgery for full-thickness macular holes (FTM).

METHODS: This is an interventional retrospective case series of 56 patients who were diagnosed with FTMHs and underwent 25 gauge pars plana vitrectomy with internal limiting membrane (ILM) peeling between 2009 – 2014. Preoperative OCTs were obtained either by SD-OCT or TD-OCT. Images were reviewed to identify the presence of an ERM in addition to the FTMH. Indocyanine green staining was used intraoperatively as the gold standard in all cases to confirm the presence or absence of an ERM based on negative staining, and the findings were correlated with preoperative OCT imaging.

RESULTS: The baseline characteristics (age, gender, ocular comorbidities macular hole size, and follow up duration) between the SD-OCT and TD-OCT groups were comparable. The mean duration of follow up was 43.3 weeks (± 49). Of the 56 patients, 30 (53.5%) exhibited an ERM intraoperatively. Four ERMs found intraoperatively were not imaged preoperatively on SD-OCT, compared to 12 on SD-OCT (P = 0.007). The sensitivity and specificity of SD-OCT in detecting an ERM was 75% and 100%, respectively, while it was 21% and 96% for TD-OCT. Visual acuity improved in both arms (0.46 and 0.38 LogMAR units in TD-OCT and SD-OCT, respectively) (P = 0.003, 0.0005, respectively). All holes were closed at the end of the follow-up period.

CONCLUSIONS: We found that SD-OCT was superior to TD-OCT in identifying the presence of ERMs preoperatively in patients who underwent macular hole surgery. While the presence of ERMs can be effectively addressed during vitrectomy, pharmacologic vitreolysis may fail to do so. With availability of ocriplasmin, the ability to note an ERM is important for management decisions, as the presence of an ERM greatly decreases the chance of success with ocriplasmin. Therefore, we recommend using SD-OCT over TD-OCT in the evaluation of patients with FTMH to more accurately identify ERMs, so that better informed decisions can be made whether to use pharmacologic or surgical approaches.
High-resolution Imaging by Adaptive Optics Scanning Laser Ophthalmoscopy Reveals Two Types of Retinal Hard Exudates

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PURPOSE: Hard exudates are observed in the retinal vascular diseases. Histological studies in autopsy specimen have characterized these exudates to be composed of lipid and proteinaceous material thought to be from leaked serum and/or degenerated products of neuroglia. We studied the characteristics of retinal hard exudates in vivo in patients with retinal vascular diseases using adaptive optics scanning laser ophthalmoscopy (AO-SLO).

METHODS: Twenty-four patients with retinal hard exudates (diabetic retinopathy 18, BRVO 4, hypertensive retinopathy 1, renal retinopathy 1) underwent a full ophthalmologic examination, spectral domain OCT (SD-OCT), and imaging of hard exudates using AO-SLO. The location, size, morphology, reflection pattern and rate of change of hard exudates were examined.

RESULTS: AO-SLO showed two distinct morphological types of hard exudates, which could not be distinguished on fundus examination or by SD-OCT. One type (type 1) consists of accumulation of spherical particles (average of a particle diameter: 28.4±5.1µm, n=235) (round type; major axis: 380.2±199.3µm, area: 55041±51259μm², reflective intensity: 128.2±22.9). Another type (type 2) is an irregularly shaped hyper-reflective deposition (irregular type; major axis: 208.5±108µm, area: 14925±10170μm², reflective intensity:130.8±27.3). The area as well as the major axis in the round type were significantly larger than the irregular type (p<0.001, p=0.0002, respectively). There was no significant difference in the reflective intensity and the vertical location in the retina of the two types of lesion (p=1.0, p=0.3, respectively). The type could change into the other over time. The retinal thickness in area with the round type was significantly thicker than one in area with the irregular type (p=0.008).

CONCLUSIONS: High resolution imaging using AO-SLO enables morphologic classification of hard exudates into two types. The round type (type 1) may represent lipid-laden phagocytes while irregular type (type 2) may consist of lipid or proteinaceous materials, but the clinicopathologic correlation is yet to be made. The ability to differentiate the retinal hard exudates in vivo by AO-SLO may help in understating the pathogenesis and clinical prognosis of retinal vascular diseases.
Swept Source Optical Coherence Tomography (SS OCT) Measurements of Parafoveal Retinal Nerve Fiber Layer/Ganglion Cell Layer (RNFL/GCL) and Inner Plexiform Layer/Inner Nuclear Layer (IPL/INL)

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**PURPOSE:** The retina and the optic nerve originate as outgrowths of the developing brain. Hence, the retina is the only part of the brain that can be imaged directly. Spectral Domain Optical Coherence Tomography (SD OCT) imaging at 50,000 scans/second is limited in measuring the RNFL/GCL and IPL/INL. However the SS OCT has the ability to measure several intraretinal layers utilizing 100,000 scans/second. This study provides a benchmark of normal RNFL/GCL and IPL/INL parafoveal measurements where these layers are the thickest. Establishing a benchmark will provide a valuable comparison to correlate with neurodegenerative disease states, such as Parkinson’s disease—a disease known for depletion of Dopamine in the substantia nigra midportion of the brain. Dopaminergic amacrine cells are located at the interface of the INL/IPL of the retina.

**METHODS:** The SS OCT measured the RNFL/GCL to the INL/IPL in the parafoveal area in 62 normal retina study subjects, a total of 124 eyes. Parafoveal measurements include the superior, inferior, nasal, and temporal quadrants and a total average parafoveal measurement. Parafoveal measurements were done in six age groups and both genders: Groups: A: 10-20, B: 21-30, C: 31-40, D: 41-50, E: 51-60, and F: 61-70.

**RESULTS:**

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<tr>
<th>Group</th>
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**CONCLUSIONS:** Males had higher parafoveal measurements in comparison to females in all six groups. Males peaked in parafoveal measurements in their second decade of life, whereas females peaked in their first decade of life. A steady decline was noted in both genders after their respective peak decades. Males’ average decline was 3.74 µ/decade compared to females’ decline of 2.28 µ/decade. SS OCT benchmark measurements provide a valuable comparison for future studies to correlate neurodegenerative diseases with RNFL/GCL and INL/IPL measurement findings, even identifying noninvasive markers for the diagnosis and the quantification of progression and response to therapy in neurodegenerative diseases.
Quantification of Retinal Vascular Density and Foveal Avascular Zone in Healthy Subjects Using Optical Coherence Tomography Angiography

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PURPOSE: To quantify retinal vascular density and foveal avascular zone (FAZ) area in healthy subjects using optical coherence tomography angiography (OCTA).

METHODS: Healthy eyes of normal subjects were scanned using OCT angiography. Using default auto-segmentation split-spectrum amplitude decorrelation algorithms, images of the superficial and deep retinal capillary plexuses were obtained from a central 3x3 mm area of the macula. Quantitative measurements of vascular density and FAZ were performed using the ImageJ software (National Institutes of Health, Bethesda, MD). Vascular density was defined as percentage of the sample area occupied by vessel lumens following binary reconstruction of images.

RESULTS: A total of 36 eyes from 18 subjects (7 males and 11 females; mean age 38 years, range 26-62) were included. Vascular density in the superficial plexus was 29.8±1.88% for the right and 29.7±2.68% for the left eye. Vascular density in the deep plexus was 39.9±2.17% for the right and 40.5±2.81% for the left eye (P<0.001 compared to corresponding superficial plexus of each eye). FAZ area was larger in the deep compared to superficial plexus in both eyes (0.33±0.098 vs. 0.25±0.099mm² right eye, 0.29±0.126 vs. 0.24±0.112mm² left eye; P<0.001). Superficial and deep vascular plexuses had similar FAZ areas in right and left eyes (P>0.05). Vascular density in the superficial plexus was positively correlated with vascular density in the deep vascular plexus (correlation coefficient=0.47, P<0.05 for right eye and =0.62, P<0.01 for left eye). Vascular density was also correlated between right and left eyes (correlation coefficient=0.53, P<0.05 for superficial plexus and =0.55, P<0.05 for deep plexus). A statistically significant correlation was present between the signal strength of the obtained images and calculated vascular density (correlation coefficient=0.48 right superficial plexus, 0.49 right deep plexus, 0.59 left superficial plexus, 0.50 left deep plexus; P<0.05). There was no significant difference in vascular density between male and female subjects (P>0.05).

CONCLUSIONS: Vascular density and FAZ area is greater in the deep capillary plexus compared to the superficial capillary plexus using OCTA in healthy eyes. Such normative data may serve as a foundation for future comparative studies in non-normal subjects.
Optical Coherence Tomography Angiography of Pigment Epithelial Detachment

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PURPOSE: To noninvasively describe the spectrum of pigment epithelial detachments (PEDs) occurring mainly in age-related macular degeneration (AMD) and central serous chorioretinopathy (CSC) and also in other inflammatory, and traumatic retinal disorders with Optical Coherence Tomography Angiography (OCTA).

METHODS: Observational, cross-sectional study of 30 patients with drusenoid, serous, vascularized or mixed PEDs. OCTA was performed on 3x3 mm area centered on the fovea. The 3D angiography was segmented in 4 layers: superficial and deep (to show retinal vasculature), outer retina (to identify Choroidal neovascularization) and chorio-capillary. En face maximum projection was used to obtain 2-dimensional angiograms from the 4 layers.

RESULTS: En face OCT angiograms of PEDs showed sizes and locations that were confirmed by fluorescein angiography (FA). OCTA of 30 patients detected 30 PED: vascularized in 19 eyes, serous in 5 eyes, 4 drusenoid in 4 eyes, 1 inflammatory PED, 1 traumatic PED of 30 patients.

CONCLUSIONS: OCTA provides depth-resolved information and detailed images of PEDs and may offer noninvasive differentiation between various types of PEDs.
Near-Infrared Reflectance Bull’s Eye Maculopathy may be an Early Indication of Hydroxychloroquine Toxicity

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PURPOSE: To investigate the relationship of near-infrared reflectance (NIR) imaging in detection of hydroxychloroquine (HC) ocular toxicity.

METHODS: Retrospective non-consecutive case series of HC ocular toxicity.

RESULTS: We report three cases suggesting that bull’s eye maculopathy seen on NIR imaging with a confocal scanning laser ophthalmoscope may represent an early, objective manifestation of HC ocular toxicity. This bull’s eye change may disappear with more advanced HC toxicity and does not appear to correlate with ellipsoid zone disruption.

CONCLUSIONS: En-face NIR imaging of HC toxicity provides different diagnostic information as compared to fundus autofluorescence, spectral domain ocular coherence tomography, fluorescein angiography or fundus photography. Knowledge of this difference may allow larger case series to determine sensitivity and specificity of NIR bull’s eye maculopathy in detecting HC toxicity.

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PURPOSE: To determine the impacts of VI and chronic health conditions on HRQoL and whether the impacts vary according to VI presence.

METHODS: Design: Cross-sectional study using a multistage, probability-cluster survey, which can produce nationally representative estimates.

Participants: 29,639 participants aged ≥19 years.

Analysis: We analyzed data from the 2008 – 2012 Korean National Health and Nutrition Examination Survey (KNHANES), which included results for vision assessment and HRQoL, measured using the European Quality of Life-5 Dimensions Questionnaire (EQ-5D). VI was defined as the presenting distance best-corrected visual acuity.

Main Outcome Measures: EQ-5D index score for participants with VI or 14 chronic health conditions and the effect of interactions between VI and each chronic health condition on the EQ-5D index score.

RESULTS: The EQ-5D index score with VI (0.781 ± 0.023) was substantially lower than without VI (0.948 ± 0.001), and the index score with each chronic health condition was also significantly lower than without the chronic health condition. The combination of each chronic health condition and VI resulted in lower EQ-5D index scores than without VI for most health conditions. There were significant interactions between VI and 4 chronic health conditions (stroke, osteoarthritis or rheumatic arthritis [OA/RA], hepatitis B or C, and depression).

CONCLUSIONS: VI has a substantial effect on HRQoL, even in the presence of concurrent chronic health conditions, and the combined effect of VI and stroke, OA/RA, hepatitis B or C, or depression on HRQoL was greater. VI should be screened and properly managed, especially in patients with chronic health conditions; in particular, patients with stroke, OA/RA, hepatitis, or depression should be prioritized for VI-related health care.
In-Vivo Feasibility Study of a Novel Intraocular Drug Delivery System

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PURPOSE: To present a novel system for intravitreal drug delivery. The ex-vivo and in-vivo study sought to examine the feasibility of intraocular implants designed for sustained drug release using specially designed implantation devices in rabbits. The Microsert implant is a miniature inflatable reservoir, design up to 6 months sustained drug release and is refillable, up to two years. The system is inserted using no-incision implantation procedure, is elastic—made of medical grade elastomeric polymers, thus is expected not to cause any inflammatory reaction, and is design for generic vehicle—any protein compound can be released from the reservoir.

METHODS: Custom designed implantation devices pre-loaded with implants were used for insertion, filling (salt solution) and anchoring of each implant. 40 implants were used for ex-vivo cow eyes to evaluate the feasibility and ease of insertion. 6 implantations were conducted on 3 NZW rabbits, 2 attempts on the same eye of each rabbit, of which 3 were properly anchored and left for daily monitoring for any signs of adverse effects. After one month of monitoring the 3 rabbits were sacrificed, the 3 eyes were enucleated and were sent for histopathological examination in a Formalin solution. The tissues of the two parts of each eye were embedded in paraffin; histological sections were performed and stained with H&P and evaluated using light microscope.

RESULTS: In the ex-vivo eyes, we found that insertion, anchoring and filling were easily accomplished after a short learning period. In the in-vivo rabbits, no visual adverse effects were noticed during the follow up. The three eyes were sectioned near the implant and submitted for examination. All 3 examined implants dissolved during the processing of the tissue before sectioning and staining, leaving an empty space in its location. In all of the 3 eyes the sections not including the implant were unremarkable: the anterior segment (cornea, limbal area, anterior chamber angle and iris), and posterior segment (ciliary body, pars plicata, pars plana, retina, choroid, sclera and optic nerve head).

In the sections including the implant, the observations were as following:

In all 3 eyes a fibrous and chronic inflammatory reactions were observed in the implants cross-section. The implants were located at the following positions: in eye R13-86 the implant was seen crossing the peripheral retina; in eye R13-87 it was located between the retina and the pars plana and in eye R13-88 it was seen at the pars plana between the conjunctiva and the sclera.

CONCLUSIONS: In-vivo efficacy and safety principals of a novel intraocular implant were demonstrated in a one month rabbit study, including 3 successful implantations as well as proper anchoring. No significant adverse effects were observed during the experimental follow up. Future in-vivo studies will be performed in order to examine the in-vivo sustained drug release from the intraocular implant.
Effect of Intracameral Carbachol on Macular and Choroidal Thickness Following Phacoemulsification Surgery

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PURPOSE: To investigate the effects of intracameral carbachol in phacoemulsification surgery on macular and choroidal thickness.

METHODS: Prospective interventional study that included patients who received 0.5mL of intracameral 0.01% carbachol at the end of phacoemulsification surgery and a control group which did not receive carbachol. Spectral-domain optical coherence tomography (SD-OCT) choroidal and central macular thickness, and total macular volume parameters were recorded from each visit and subjected to statistical analysis. Enhanced depth imaging (EDI) SD-OCT was performed for choroidal thickness measurement. Subfoveal measurements were taken at 1,000 µm intervals of a horizontal section from 3 mm nasal and temporal to the fovea. Patients who had intraoperative complications or a history of glaucoma, retinal disease or trauma were excluded.

RESULTS: Sixty-eight patients (34 in the study group and 34 in the control group) met the criteria for our analysis. Average age was 72 years, most of the study patients were Caucasian (74%), and there were 40 male and 28 female. At the 2 week follow-up, the average central macular thickness decreased from 237 +/- 101 µm (baseline) to 221 +/- 94 µm (p=0.34, paired t-test), the average total macular volume varied from 7.12 (baseline) to 6.90 (p=0.22, paired t-test), and the choroidal thickness from 264 +/- 119 µm (baseline) to 225 +/- 92 µm (p=0.001, paired t-test). At the 4 week follow-up, the average central macular thickness decreased from 237 +/- 101 µm (baseline) to 229 +/- 96 µm (p=0.38, paired t-test), the average total macular volume varied from 7.12 (baseline) to 6.97 (p=0.27, paired t-test), and the choroidal thickness from 264 +/- 119 µm (baseline) to 248 +/- 108 µm (p=0.01, paired t-test). None of the study patients experienced any serious adverse events over the follow-up period.

CONCLUSIONS: Intracameral carbachol may have some influence on choroidal thickness in the immediate postoperative period. Additional studies are required to determine the significance of our results both statistically and clinically.
Microcystic Macular Degeneration in Late-Stage Optic Neuropathy

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Padova, Italy
Stefania Miotto, MD

PURPOSE: To analyze morphological features of microcystic macular degeneration in patients affected by advanced optic neuropathies by means of spectral domain OCT (SD-OCT).

METHODS: In this retrospective analysis, we evaluated SD-OCT macular scans of patients affected by miscellaneous optic nerve diseases (glaucoma, multiple sclerosis, anterior-ischemic optic neuropathy, optic nerve head drusen, autosomal dominant optic atrophy).

RESULTS: In our study population, seven eyes of five patients with advanced optic nerve damage showed on SD-OCT scans multiple cystic spaces in the inner nuclear layer (INL), associated with a diffuse retinal nerve fiber layer (RNFL) thinning. Two subjects were characterized by large cystic spaces. Blood-retinal barrier breakdown at the posterior pole was excluded by means of fluorescein angiography.

CONCLUSIONS: Optic neuropathies share common features on OCT examination of the macular area, independently of their variable etiology. Though RNFL thinning in the macula is already known, microcystic changes within the macular sensory retina represent a new finding, likely correlated with a retrograde axonal degeneration and associated with poor vision. The identification of these microcysts in the INL and the evaluation of their characteristics (diameter, location) could be useful in monitoring patients affected by optic neuropathies and could also offer fundamental information to explain the pathophysiology of neuronal degeneration.
Nationwide Incidence of Ocular Melanoma and Survival Rate of Ocular Melanoma Patients in Korea, 1999 – 2011: The Korea National Cancer Registry Database Study

Kyu Hyung Park, MD, PhD
Seongnam, Korea

Sang Jun Park, MD, MSc, Hyunsoon Cho, PhD

PURPOSE: To determine the incidence of ocular melanoma and its subtypes as well as the survival rates among patients in Korea from 1999 to 2011.

METHODS: The national cancer registry in Korea was reviewed to ascertain all ocular melanoma incidents between 1999 and 2011. Age-standardized ocular melanoma and subtype incidence rates were calculated. Incidence trends during the study period were estimated via joinpoint regression analysis. The survival probabilities were estimated by tumor site, sex, and study periods.

RESULTS: A total of 464 ocular melanoma cases (227 men, 48.9%) were identified. The incidence rates was 0.60 (95% confidence interval [95%CI], 0.55–0.66). Among ocular melanomas, uveal melanoma had the highest incidence (0.42 [95%CI, 0.38–0.47]), followed by conjunctival melanoma (0.12 [95%CI, 0.09–0.14]). The incidence rate was higher in 2006 – 2011 than in 1999 – 2005, and increasing incidence trends were observed throughout the study period. The overall 5-year relative survival rate was 74.1% (95%CI, 68.7%–78.9%). The 5-year relative survival rate improved significantly from 67.0% for patients diagnosed in 1999 – 2005 to 84.1% for those diagnosed in 2006 – 2011. The Kaplan–Meier analysis revealed that uveal melanoma had the most favorable survival rate among ocular melanomas and that women had a better survival rate relative to men.

CONCLUSIONS: The age-standardized ocular melanoma incidence was quite low in Korea relative to that reported for white populations and exhibited increasing trends throughout the study period. In Korea, survival improved significantly during the study period and women had a better prognosis compared to men.
Tri-Modality Planning Study for Ocular Melanoma

Amanda Deisher, PhD
Rochester, MN

Robert Foote, MD, Jon Kruse, PhD, Erik Tryggestad, PhD, Thomas Whitaker, PhD, Jose Pulido, MD

PURPOSE: For the treatment of ocular melanoma, stereotactic radiosurgery (SRS), proton therapy, and eye plaques have all been demonstrated to provide local control and disease-free survival that is comparable to enucleation. This study investigates whether one of the three radiation modalities allows superior sparing of uninvolved tissues for a given tumor size and position.

METHODS: Retrospective chart review identified five ocular melanoma patients treated with GammaKnife SRS who could have been eligible for treatment with an I-125 eye plaque. Clinical information was used to accurately delineate the extent of disease on patient MR images. The surrounding uninvolved tissues of the affected eye (lens, cornea, retina, optic nerve), the contralateral eye, and the brain were also contoured. Proton treatment plans for a spot-scanning pencil beam machine with patient-specific apertures were calculated with Monte Carlo. The three-dimensional dose distributions for Collaborative Ocular Melanoma Study plaques were taken from published data that included the effect of the gold-alloy backing and silastic insert. The maximum doses to normal structures when a tumoricidal dose was delivered with each of the three modalities were tabulated.

RESULTS: The achievable dose distributions and normal tissue sparing depends greatly on the tumor size and location. Both proton therapy and I-125 plaque therapy plans confine their doses to the ipsilateral orbit. Proton therapy offers a sharp lateral and distal dose fall-off, but entry dose can be 80% of the prescription dose, making the orientation of the eye relative to beam a critical treatment planning consideration. The SRS dose gradient is sharp in all directions, but the low dose region can extend into the brain and contralateral orbit.

CONCLUSIONS: For ocular melanoma patients that would be eligible for proton therapy, I-125 eye plaque application, or stereotactic radiosurgery, there are benefits and draw-backs for all three modalities in terms of normal tissue sparing. The ophthalmologist will weigh each patient’s condition and priorities when determining the optimal treatment plan.
Preclinical Acute Safety Study of Combined Intravitreal Carboplatin and Etoposide Phosphate for Retinoblastoma with Vitreous Seeding

Stephen Smith, MD
Ann Arbor, MI
Victor Elner, MD, PhD, Brian Smith, MD, Brian Mohney, MD, Susan Elner, MD

PURPOSE: To describe the ocular safety of carboplatin and etoposide phosphate (VP16P), cornerstones of systemic retinoblastoma treatment regimens, following intravitreal delivery in Dutch Belted rabbits. Safety was assessed by electroretinogram (ERG) response and clinical toxicity.

METHODS: Twenty-two adult male Dutch Belted rabbits (1.5-2.0 kg) each received a single, bilateral intravitreal injection in a total volume of 0.5ml. The first 5 groups consisted of 2 rabbits (4 eyes) per group and received the following single agent: Group 1: normal saline, Group 2: carboplatin 4mcg, Group 3: carboplatin 8mcg, Group 4: VP16P 75mcg, and Group 5: VP16P 100mcg. Groups 6-9 consisted of three rabbits (six eyes) per group and received the following combination of carboplatin/VP16P respectively: Group 6: 8mcg/75mcg, Group 7: 8mcg/50mcg, Group 8: 4mcg/50mcg, and Group 9: 2mcg/25mcg. Electroretinograms and clinical examinations were performed pre-injection and at 1 week and 4 weeks post-injection in all animals. Histopathologic analysis is pending. Based on pilot ERG variability in control animals, ERG wave amplitude changes >25% from pre-injection values were considered a sign of toxicity. Analysis of variance was used to determine if the difference between pre- and post-injection ERG amplitudes differed between the treatment and control groups. A p ≤ 0.05 was considered significant.

RESULTS: Groups 3-8 demonstrated a statistically significant decrease in waveform amplitudes obtained 4 weeks post-injection (p < 0.05). The most prominent changes were seen in light and dark adapted B-wave amplitudes and the light adapted flicker response. Group 2 (carboplatin 4mcg) showed a non-statistically significant trend toward toxicity. Group 9 (carboplatin 2mcg/ VP16P 25mcg) did not demonstrate ERG changes suggesting toxicity. Fundoscopic toxicity consisted of slight attenuation of vessels in Groups 3-7. There was no definite clinical toxicity in any other group and there was no intra-ocular inflammation noted in any animal.

CONCLUSIONS: Combined carboplatin and VP16P are compatible for intravitreal injection therapy, and a single dose of 2mcg/25mcg appears to be safe in a rabbit model. Dose dependent toxicity of these agents appears to predominantly affect the inner retina. Combined carboplatin and VP16P may be a safer alternative to melphalan for the treatment of vitreous seeds in retinoblastoma.
LE MARCHÉ
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The Retina Society sincerely thanks our corporate supporters at every level for their contributions to our meeting. In addition, we are deeply grateful for their ongoing commitment to provide innovative and sophisticated equipment, pharmaceuticals, and services for the care of patients with vitreoretinal diseases. We acknowledge our debt to their excellence, and are delighted to have such talent in the development of new vitreoretinal treatments.

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