Special thanks to John Focosi for his AV expertise and Barbara Lande for her graphic design savvy.
The Retina Society

49TH ANNUAL SCIENTIFIC MEETING

SEPTEMBER 14 – 17, 2016
SAN DIEGO, CALIFORNIA
THE U.S. GRANT HOTEL
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DEAR COLLEAGUES AND FRIENDS,

WELCOME TO LOVELY SAN DIEGO! The Executive Committee and I are thrilled to gather with you in this vibrant city—a gorgeous setting for our 49th annual meeting. Our venue this year is the beautiful U.S. Grant Hotel, a national icon since 1910 that exudes elegance and historicity befitting The Retina Society. Located in San Diego’s lively downtown Gaslamp Quarter, we will be just steps away from a dazzling and eclectic array of shops, galleries, museums, parks, restaurants and entertainment, and a short drive from the beautiful beaches and wonderful family attractions for which San Diego is justifiably famous. We hope you will have extra time before or after the meeting to enjoy some of what this delightful city and surrounding area have to offer.

THANKS TO A RECORD NUMBER of abstract submissions, our scientific program this year is brimming with a superlative line-up of outstanding podium and poster presentations. We kick off early Wednesday afternoon with our always enjoyable Interesting Cases Conference, followed by our first scientific session. Then please join us just outside the hotel for our Welcome Reception in the fabulous outdoor setting of beautiful Horton Plaza Park, a historic and newly-renovated urban oasis.

AFTER INVIGORATING DAYS of engaging scientific presentations and lively debate, we will spend our evenings enjoying friends, culinary delicacies, and cultural adventures. Please join us for a reception and dinner Thursday evening at the famous Museum of Man in Balboa Park, just blocks from the U.S. Grant Hotel. Reserved exclusively for The Retina Society, this landmark anthropological museum is housed in a beautiful and iconic building with Spanish mission style architecture. Before and after dinner serenaded by Savvy Strings, deepen your understanding of the human experience by exploring the museum’s fascinating exhibits. Then admire the beautiful gardens, natural vegetation zones, walking paths, and lovely architecture of surrounding 1,200-acre Balboa Park, San Diego’s cultural, historical, and artistic hub. Our traditional black-tie optional banquet on Friday evening will be unforgettable, with a delectable dinner and dancing in the ornate Presidential Ballroom of the historic U.S. Grant Hotel.

WE WILL BE SPOTLIGHTING Dr. Thomas Aaberg Sr as our special Guest of Honor at this meeting, honoring him for his leadership, service, and monumental contributions to our field. Drs. Steve Charles and Mark Blumenkranz are our distinguished award recipients. We congratulate them and look forward to their featured presentations as well to those of our Fellow Award recipients, Drs. Elad Moisselev and Xi Chen. Finally, we will be treated this year to a special invited presentation by our friend and colleague Dr. David Parke, Executive Vice-President and CEO of the American Academy of Ophthalmology.

MANY THANKS TO THE PROGRAM Committee for their hard work in putting together a truly exceptional program for this year. And of course, none of this would come together without the herculean efforts of our gracious and savvy Judy Cerone Keenan, the heart of our society! I look forward to greeting you in sunny San Diego and savoring together the many delights of our 49th annual meeting.

Warmest regards,

President, The Retina Society
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<td>Charles L. Schepens*</td>
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<td>1970 – 1971</td>
<td>P. Robb McDonald*</td>
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<td>1972 – 1973</td>
<td>L. Harrell Pierce*</td>
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<td>Charles Regan*</td>
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<td>Alice R. McPherson</td>
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<td>1980 – 1981</td>
<td>Ariah Schwartz*</td>
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<td>1982 – 1983</td>
<td>Robert B. Welch</td>
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<td>1986 – 1987</td>
<td>J. Graham Dobbie*</td>
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<td>C. Pat Wilkinson</td>
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<td>Michael T. Trese</td>
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<td>2008 – 2009</td>
<td>Donald J. D’Amico</td>
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<td>2010 – 2011</td>
<td>Mark S. Blumenkranz</td>
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<td>2012 – 2013</td>
<td>Charles C. Barr</td>
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<td>2014 – 2015</td>
<td>Julia A. Haller</td>
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*deceased

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<td>Michel Michaeides Bsc, Mb, Bs, MD(Res)</td>
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<td>Hendrik Scholl</td>
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<td>Jerry Sebag</td>
<td>MD, FACS, FRCophth, FARVO</td>
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<td>Johanna Seddon</td>
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<td>Chirag Shah</td>
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OF THE RETINA SOCIETY

Albert Vaiser, MD
Wichard van Heuven, MD
James Vander, MD
Brian VanderBeek, MD, MPH
Demetrios Vavvas, MD, PhD
Raul Vianna, MD, PhD
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Tamara Vrabec, MD
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Christopher Walton, MD
Keith Warren, MD
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Leonidas Zografos, MD

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William Tasman, MD
David Telander, MD
Asheesh Tewari, MD
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Cynthia Toth, MD
Giora Treister, MD
Clement Trempe, MD
Michael Trese, MD
Irena Tsui, MD

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NEW MEMBERS 2016

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Charlotte, NC

Steven Bailey, MD
Portland, OR

Cagri Besirli, MD
Ann Arbor, MI

Allen Chiang, MD
Philadelphia, PA

Netan Choudhry, MD
Toronto, ONT, Canada

Dilsher Dhoot, MD
Santa Barbara, CA

Paul Hahn, MD, PhD
Durham, NC

Daniel Kiernan, MD
Rockville Center, NY

Leo Kim, MD, PhD
Boston, MA

Shree Kurup, MD
Winston-Salem, NC
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Anton Orlin, MD
New York, NY

John Payne, MD
W. Columbia, SC

Sandeep Randhawa, MD
Royal Oak, MI

Amy Schefler, MD
Houston, TX

Andre Witkin, MD
Boston, MA

James Bainbridge, MA, PhD, FRCO
London, United Kingdom

Shintaro Nakao, MD, PhD
Fukuoka, Japan

Kyoko Ohno-Matsui, MD, PhD
Tokyo, Japan
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) Apply evidence-based data from randomized, clinical trials to help form treatment plans for patients with medical retinal diseases such as AMD, DR, and RVO. Utilize data from smaller trials and case series to help individualize such treatments for patients with different responses to therapy, such as persistent fluid, elevated intraocular pressure, or inflammation.

2) Apply advanced imaging technologies such as OCT-angiography and ultra-wide field angiography to recognize pathology not previously detected or understood. This includes far peripheral pathology, subtle choroidal neovascularization, and appreciation of retinal vascular abnormalities not noted with conventional imaging modalities.

3) Incorporate new surgical tools, techniques, and intraoperative imaging modalities to improve patient outcomes and minimize complications.

CME ACCREDITATION AND CREDIT DESIGNATION*

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership 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 22.75 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: Wednesday: 4.5; Thursday: 7.5; Friday: 7.5; Saturday: 4.0)

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.
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, SEPTEMBER 14, 2016

<table>
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<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>9:00 am – 12:00 Noon</td>
<td>The Retina Society Executive Committee Meeting — VINTAGE ROOM</td>
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<tr>
<td>11:00 am</td>
<td>Speaker Ready Room Opens — SENATE ROOM</td>
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<tr>
<td>12:00 Noon</td>
<td>Exhibit Set-up — CELESTIAL BALLROOM</td>
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<tr>
<td>12:00 Noon – 5:00 pm</td>
<td>Meeting Registration — PRESIDENTIAL FOYER</td>
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<td>1:00 – 4:25 pm</td>
<td>Interesting Retinal Cases/Video Presentations — PRESIDENTIAL BALLROOM</td>
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<td>5:00 – 6:29 pm</td>
<td>Scientific Session — PRESIDENTIAL BALLROOM</td>
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<tr>
<td>7:00 – 10:00 pm</td>
<td>Welcoming Reception — HORTON PLAZA PARK</td>
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### THURSDAY, SEPTEMBER 15, 2016

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<tr>
<td>7:00 am</td>
<td>Meeting Registration — PRESIDENTIAL FOYER</td>
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<td>Exhibits/Continental Breakfast/Breaks — CELESTIAL BALLROOM</td>
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<tr>
<td>7:30 am – 10:00 pm</td>
<td>Spouses/Guests Hospitality — SYCUAN SUITE, SECOND LEVEL</td>
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<tr>
<td>7:30 am – 12:30 pm</td>
<td>Scientific Session — PRESIDENTIAL BALLROOM</td>
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<tr>
<td>9:30 am – 3:30 pm</td>
<td>Spouses and Guests Explore La Jolla Tour — MEET IN LOBBY AT 9:15 AM FOR BUS</td>
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<tr>
<td>12:30 – 1:00 pm</td>
<td>Scientific Meeting Attendees &amp; Exhibitors Lunch — PALM COURT</td>
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<td>1:00 – 2:00 pm</td>
<td>Dessert and Poster Viewing — GRANT ROOM</td>
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<td>2:03 – 5:15 pm</td>
<td>Scientific Session — PRESIDENTIAL BALLROOM</td>
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<tr>
<td>6:00 – 10:00 pm</td>
<td>Reception and Dinner — MUSEUM OF MAN, MEET IN LOBBY AT 5:45 PM FOR BUS</td>
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### FRIDAY, SEPTEMBER 16, 2016

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<td>Continental Breakfast/Exhibits/Breaks — CELESTIAL BALLROOM</td>
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<td>7:30 am – 10:00 pm</td>
<td>Spouses/Guests Hospitality — SYCUAN SUITE, SECOND LEVEL</td>
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<td>7:30 am – 12:50 pm</td>
<td>Scientific Session — PRESIDENTIAL BALLROOM</td>
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<td>12:50 – 1:45 pm</td>
<td>Scientific Meeting Attendees &amp; Exhibitors Lunch — PALM COURT</td>
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<td>Scientific Session — PRESIDENTIAL BALLROOM</td>
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<tr>
<td>6:00 – 11:00 pm</td>
<td>Reception and Banquet — PRESIDENTIAL BALLROOM</td>
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### SATURDAY, SEPTEMBER 17, 2016

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<td>Continental Breakfast/Exhibits/Breaks (Spouses &amp; Guests Welcome) — CELESTIAL BALLROOM</td>
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<td>7:30 am – 12:05 pm</td>
<td>Scientific Session — PRESIDENTIAL BALLROOM</td>
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WEDNESDAY, SEPTEMBER 14
7:00 - 10:00 PM
WELCOME RECEPTION
HORTON PLAZA

Join us at the newly renovated and reopened Horton Plaza Park just steps from the Grant Hotel. Enjoy a delicious menu of local and classic favorites as you meet and greet old friends while making new ones!

The plaza sports a five-year, $17 million renovation including the restoration of the iconic Irving Gill fountain, originally designed in 1909. The region’s history is evident in many of the architectural details. Sculptura Luminaries enclose the new semi-circular amphitheater with decorative patterns that reflect the native grasses of the region. The plaza’s paving pattern is inspired by traditional basket weave patterns from the Kumeyaay Native-American people. Native shade trees and grasses give this neighborhood a new and fresh appeal, while at the same time honoring San Diego’s beloved Kate Sessions, botanist and landscape architect, also known as the “Mother of Balboa Park.”

THURSDAY & FRIDAY SEPTEMBER 15 AND 16
7:30 - 10:00 AM
HOSPITALITY SUITE
SYCUAN PARLOR, SECOND LEVEL

Spouse and guest hospitality suite will be available for coffee, tea and breakfast, as well as a place to meet friends. On Saturday, spouses and guests are welcome to continental breakfast in the CELESTIAL BALLROOM.

THURSDAY, SEPTEMBER 15
9:30 AM – 3:00 PM
EXPLORE LA JOLLA’S ART AND LUNCH AT GEORGES AT THE COVE
GUEST/SPouse TOuRS

MEET IN THE GRANT HOTEL LOBBY
AT 9:15 AM FOR BUSES

With a dramatic coastline boasting spectacular views, La Jolla is one of the most popular beach destinations in California. Surrounded on three sides by the sea, La Jolla’s coastal atmosphere and quaint village lifestyle continues on next page
ABOUT BALBOA PARK

Named for the Spanish maritime explorer Vasco Núñez de Balboa, Balboa Park is a 1,200-acre urban cultural park filled with open space areas, hiking and biking trails, natural vegetation zones, green belts, gardens, and walking paths, 15 world-class museums and theaters, and the world-famous San Diego Zoo.

Placed in reserve in 1835, the park’s site is one of the oldest in the United States dedicated to public recreation. Many of the museums along Balboa Park’s Prado are housed in magnificent Spanish Colonial Revival buildings, originally constructed for the 1915 – 1916 Panama-California Exposition.

Tremendously varied, among the displays you will find internationally significant art treasures, exotic animal species, unique model railroads, world folk art, sports memorabilia and rare aircraft in the park.

evokes a Mediterranean feel. With a unique microclimate that rarely drops below 50 degrees or exceeds 90 degrees, combined with unmatched natural beauty, an upscale casual vibe and world-class attractions, La Jolla lives up to its nickname as “the jewel” of San Diego. From world-class shopping to shimmering ocean views, there are few other destinations where one can so easily move from beach culture to high couture. In the village, acclaimed galleries showcase classical and modern art including photography, sculptures and paintings. Our tour will introduce you to the best of La Jolla’s art scene. Enjoy the flavor of premium artisan olive oil or chocolate in a local tasting room. You will love the view from the renowned Georges at the Cove where you can enjoy a leisurely lunch of California delicacies served with style.

La Jolla tour continued...
THURSDAY, SEPTEMBER 15
6:30 – 10:00 PM
RECEPTION & DINNER
MUSEUM OF MAN, BALBOA PARK
MEET IN THE GRANT HOTEL LOBBY FOR BUSSES AT 5:45 PM

We will begin the evening with cocktails and hors d’oeuvres before enjoying a delicious dinner and viewing in Balboa Park at the San Diego Museum of Man, located beneath the magnificently decorated 200-foot California Tower. Dedicated to the study of anthropology, the museum’s collections and permanent exhibits focus on the pre-Columbian history of the western Americas, with materials drawn from Native American cultures of the Southern California region, and Mesoamerican civilizations such as the Maya. The museum also holds one of the most important collections of Ancient Egyptian antiquities in the United States, which includes authentic mummies, burial masks, figurines, and seven painted wooden coffins. The landmark building was originally constructed for the Panama-California Exposition in 1915.

Savvy Strings, an all female group will perform classical and contemporary songs throughout what promises to be a delightful evening.

SATURDAY, SEPTEMBER 16
7:00 – 11:00 PM
BANQUET – BLACK TIE
OPTIONAL
U.S. GRANT HOTEL,
PRESIDENTIAL BALLROOM

The Presidential Ballroom, lavishly appointed, pays tribute to the fourteen U.S. Presidents who have stayed at the hotel. Join us for dinner, dancing and conviviality.
GUEST OF HONOR

THOMAS M. AABERG SR, MD
Greensboro, Georgia

It is with great pleasure and fondness that Thomas M. Aaberg Sr, MD—one of retina’s true renaissance men, a leading thinker and innovator in both medical and surgical aspects of our specialty—is very gratefully honored by the Retina Society at our 49th annual meeting in San Diego.

Tom graduated from Dartmouth College and Harvard Medical School, then completed his residency in ophthalmology at the Massachusetts Eye and Ear Infirmary. Tom then worked for two years in the United States Public Health Service. In addition to his medical degree, he pursued a Master of Science in Public Health from the University of Oklahoma. Despite an initial inclination toward subspecialty training in glaucoma, fortunately for us all he aligned himself towards a career in retina and moved his family to Miami where he spent five months studying experimental retinal detachment and giant retinal tears in a primate model with Robert Machemer, MD. He went on to complete a year-long clinical fellowship in medical/surgical retinal disease at Bascom Palmer Eye Institute, University of Miami where he also studied under several of ophthalmology’s most widely recognized leaders—Drs. Ed Norton, Victor Curtin, and J. Donald M. Gass, among others.

Upon completion of his fellowship in 1969, Tom became assistant professor of Ophthalmology and director of the Retina Service at the Marquette Medical School (Milwaukee)—a program which evolved into the Medical College of Wisconsin, where he began MCW’s highly respected vitreoretinal fellowship program.

Tom was recruited by Emory University to rebuild the Department of Ophthalmology. They were looking for a leader with impeccable character and exceptional academic credentials—and they found him. In January 1988 Tom was appointed Chair of Ophthalmology at Emory University School of Medicine and Phinizy Calhoun, Sr. Professor of Ophthalmology and Director of the Emory Eye Center. As with the Medical College of Wisconsin, during Tom’s 20-year tenure the Department of Ophthalmology at Emory grew to be recognized as one of the premier ophthalmology training programs in the country. In 2008 he stepped down as Chair, and now holds the title of M.L. Simpson Professor and Chairman, Emeritus.

Tom has held a variety leadership positions in ophthalmology, serving as senior associate editor of the American Journal of Ophthalmology (AJO) from 1982 – 2002, and has had over 150 manuscripts of his own published in peer-reviewed journals. In addition, he has co-authored a textbook on vitrectomy and published 19 book chapters. He has provided leadership as past president of the Macula Society and the Association of University Professors of Ophthalmology (AUPO). Tom has been a member of the most prestigious societies in our field, including the American Ophthalmological Society, Diplomate of the American Board of Ophthalmology, ARVO, American Academy of Ophthalmology, American Medical Association, American Eye Study Club, Pan-American Ophthalmological Society, the Club Jules Gonin, the Retina Society and The American Society of Retinal Specialists.
He has given nearly 40 named lectureships, including the Edward Jackson Memorial Lecture, AAO, 1988; The Hermann Wacker lecture, Club Jules Gonin, 2000; and Schepens Lecture, AAO, 2009.

Viewed collectively, Tom’s professional accolades and accomplishments place him among the most prolific and decorated retinologists of our time. He is widely regarded as one of vitreoretinal surgery’s founding fathers. As a leader, his quiet charisma and leadership by example engender deep loyalty. He has had a profound impact on subsequent generations of ophthalmologists. Many of the prominent thinkers and leaders in our field proudly lay claim to time under Dr. Aaberg’s aegis.

However, Tom would argue that these numerous accolades and accomplishments are born from relationships. Relationships that he cherishes. If you spend time with Tom, you will quickly learn that his relationships with others hold more value to him than the published paper, the award, or the named lecture. For example, it was his deep friendship with Robert Machemer that lead to his role in performing some of the first pars plana vitrectomies, it was his mentoring and interactions with 100’s of residents and fellows that resulted in mutual enrichment via projects and probing questions, and it was through his children Sarah, Leigh and Tom Jr. that he experienced many of life’s lessons and greatest love. And without question he will tell you that everything just detailed would not have been possible without his most important relationship, his high school sweetheart and life long love, Judy.

Antonio Capone Jr, 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.

We would like to thank all members who have sponsored applicants and ask that all members continue to support this award.

CONGRATULATIONS!

PRIOR RECIPIENTS OF THE AWARD

2015  Yoshihiro Yonekawa, MD, sponsored by Antonio Capone Jr
2014  Francisco Folgar, MD, sponsored by Emily Chew
2013  Glenn Yiu, MD, PhD, sponsored by Glenn Jaffe
2012  Lejla 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 Rocío 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

Sponsor: Susanna Park, MD, PhD
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 15th Margherio Award

Xi Chen, MD, PhD
Durham, NC

Congratulations!

Sponsor: Cynthia Toth, MD

We would like to thank all members who have sponsored applicants and ask that all members continue to support this award.

Prior Recipients of the Award

2015  Devon Ghodasra, MD, sponsored by Thomas Gardner
2014  John B. Miller, MD, sponsored by Evangelos S. Gragoudas
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
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

1978 Charles L. Schepens, MD, Boston, MA
1979 Richard W. Young, PhD, Los Angeles, CA
1980 Robert Machemer, MD, Durham, NC
1981 John E. Dowling, PhD, Boston, MA
1982 Harry G. Sperling, PhD, Houston, TX
1983 Arnall Patz, MD, Baltimore, MD
1984 Werner K. Noell, MD, Kansas City, MO
1985 Oleg Pomeranzoff, Dipl. Eng., Boston, MA
1986 J. Donald M. Gass, MD, Miami, FL
1987 Harris Ripps, PhD, Chicago, IL
1988 Harvey A. Lincoff, MD, New York, NY
1989 Matthew D. Davis, MD, Madison WI
1990 Matthew M. LaVail, PhD, San Francisco, CA
1991 Ronald Michels, MD and Bert Glaser, MD, Baltimore, MD
1992 Ingrid Kreissig, MD, Tubingen, Germany
1993 W. Richard Green, MD, Baltimore, MD
1994 Dr. Kathleen Dorey and Dr. Francois Delori, Boston, MA
1995 D. Jackson Coleman, MD, New York, NY
1996 Gabriel Coscas, MD, Paris, France
1997 Stuart L. Fine, MD, Philadelphia, PA
1998 Joe G. Hollyfield, PhD, Cleveland, OH
1999 Lawrence A. Yannuzzi, MD, New York, NY
2000 Barbara E. K. Klein, MD, MPH, and Robert Klein, MD, MPH, Madison, WI
2002 Bradley R. Straatsma, MD, Los Angeles, CA
2003 Stephen J. Ryan, MD, Los Angeles, CA
2004 Emily Y. Chew, MD, Bethesda, MD and Frederick L. Ferris III, MD, Bethesda, MD
2005 Anthony P. Adamis, MD, Boston, MA
2006 Carol Shields, MD, Philadelphia, PA
2007 Lloyd Paul Aiello, MD, Boston, MA
2008 William S. Tasman, MD, Philadelphia, PA
2009 Mark S. Humayun, MD, PhD, Los Angeles, CA
2010 Eliot L. Berson, MD, Boston, MA
2011 Michael F. Marmor, MD, Stanford, CA
2012 Richard F. Spaide, MD, New York, NY
2013 Cynthia A. Toth, MD, Durham, NC
2014 Peter Campochiaro, MD, Baltimore, MD
2015 Thomas Gardner, MD, Ann Arbor, MI
Steve Charles, MD, Clinical Professor of Ophthalmology at the University of Tennessee and founder of the Charles Retina Institute in Memphis, TN, is one of the giants in the history of vitreoretinal surgery techniques and instrumentation, and one of the busiest retinal surgeons in the world. Born in Raleigh, NC he graduated from the University of Oklahoma in mechanical and electrical engineering. In 1969, he completed his medical training at the University of Miami and his ophthalmology residency at the Bascom Palmer Eye Institute in 1973. He then completed a two year fellowship at the National Eye Institute in Bethesda, MD focusing on vitreoretinal surgery, angiogenesis research, and medical device engineering. He founded the now world famous Charles Retina Institute in 1975.

Steve brought his engineering thought process to the field of retina at a time when vitreous surgery was in its infancy of discovery. He developed numerous landmark surgical instruments such as linear suction, endophotocoagulation, and the first disposable vitreous cutter, as well as surgical techniques such as scissor membrane delamination and internal fluid drainage. His developments led to the issue or pending of over 100 medical patents. He is a consultant for Alcon Laboratories and the principal architect of the Alcon Accurus and Constellation Vision System. Alcon acquired InnoVision, a company started by Dr. Charles, leading to the development of the major features of the Accurus and Constellation systems. His contributions extended to other surgical fields with his founding of MicroDexterity Systems, which developed surgical robots for minimally invasive joint replacement, spine surgery, and skull base neurosurgery. He also cofounded CamPlex Inc which developed advanced visualization technology for neurosurgery and trans-oral approaches to head and neck cancer.

A tireless educator, his prowess in teaching retinal surgery began in the 1970’s with the Ocutome Workshops, teaching retinal specialists around the country this new surgical technique called “vitrectomy” alongside other vitrectomy pioneers such as Robert Machemer, Conner O’Malley, Ronald Michels, and Tom Aaberg Sr. Over the past 40 years, he has lectured in 50 countries and operated in 25, delivered 17 named lectures, and well over 1000 speaking trips. He authored a leading textbook in the field now in the 5th edition and in six languages, and authored over 174 articles and 50 book chapters in the medical literature.

of Ophthalmology, and British Journal of Ophthalmology. He has received the Wacker Medal from the Club Jules Gonin, the first Founders Medal from the Vitreous Society, and was inducted into the University of Miami School of Medicine Alumni Association Hall of Fame. Ocular Surgery News lists Steve as one of the top ten innovators in the past 25 years.

Although retinal surgery is obviously Steve’s passion, there are two others: Flying—he is an airline transport pilot rated for multi-engine jets, flying his own Sabre 65; and family—Steve has three daughters and four grandchildren. His oldest daughter is a gynecological surgeon in Gainesville, FL; his middle daughter is an MD-JD family physician in Denver, CO; and his youngest daughter is owner/operator of Zip Lost Pines in Austin, TX. All share the famous Charles passion for career and life. The Retina Society congratulates Steve as the 2016 Charles Schepens Lecturer.

Kirk Packo, MD
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

2015  Evangelos Gragoudas, MD, Boston, MA
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
RETINA RESEARCH FOUNDATION AND J. DONALD M. GASS

Julia Haller, MD, Chair
Joan Miller, MD
Kirk Packo, MD
George Williams, MD
Marco Zarbin, MD
Mark S. Blumenkranz, MD, MMS

Mark S. Blumenkranz, MD, MMS, is HJ Smead Professor in the Department of Ophthalmology at Stanford University. He received his undergraduate, graduate degree in biochemical pharmacology, and medical education at Brown University between 1968 and 1975. He completed his internship in surgery and ophthalmic residency training at Stanford in 1979, and a fellowship in vitreoretinal diseases at the Bascom Palmer Eye Institute in 1980, where he subsequently served on the faculty for five years. After leaving Bascom Palmer in 1985, he joined Associated Retinal Consultants in Royal Oak, Michigan and became the founding director of the vitreoretinal fellowship program at William Beaumont Hospital, before returning to Stanford in 1992 to lead the retinal service and then the department as Chairman from 1997 until 2015. In 2004 he completed the Executive Program at the Graduate School of Business at Stanford.

Dr. Blumenkranz was an early innovator in vitrectomy techniques and the treatment of macular diseases. He helped to develop methods to treat complex forms of retinal detachment with gases and silicone oil, and usher in the modern era of intravitreal and surgical adjuvant drug therapy with laboratory and clinical studies identifying 5-fluorouracil and low molecular weight heparin as potent agents to inhibit ocular scarring. These studies led to subsequent trials for these agents in glaucoma and proliferative vitreoretinopathy. He was a member of the groups that first reported the herpetic etiology and successful acyclovir treatment of acute retinal necrosis, the use of bio-erodable polymers to deliver intraocular steroids for macular edema (Ozurdex) and was an investigator and co-author on the first human safety study of ranibizumab (Lucentis), gene therapy for macular degeneration, and emerging applications of photodynamic therapy. He has also published extensively in the area of new lasers and laser tissue interactions including the PASCAL and Catalys lasers for retinal and cataract applications respectively. He has published more than one hundred and fifty manuscripts in peer-reviewed journals, 18 patents, and multiple book chapters, abstracts and patents in the field.

Dr. Blumenkranz has served on the Editorial Boards of The American Journal of Ophthalmology, Retina, Ophthalmology, and Graefe’s Archives for Ophthalmology. He is a past recipient of the Heed Award, the Rosenthal Award in Visual Sciences, the American Academy of Ophthalmology Lifetime Achievement Award, the Alcon Research Institute Award, ARVO Fellows and the Gertrude Pyron Award from the ASRS for lifetime contributions in vitreoretinal surgery. He delivered the Kreissig Lecture in Hamburg 2013 at Euretina, and the Jackson Memorial Lecture at the American Academy of Ophthalmology in New Orleans in 2013. He delivered the Schepens Award Lecture at the American Academy of Ophthalmology in November 2015 and the Wacker Prize Lecture at the Club Jules Gonin in 2016.
He is a past President of the American University Professors of Ophthalmology (AUPO), the Retina Society, and the Macula Society. He is a member of the Steering Committee of the Audacious Goals Initiative of the NEI, and is a Fellow of the Corporation of Brown University, where he is the long serving Chair of the Medical School Committee. He played a leading role in the planning, fundraising and construction of the Byers Eye Institute at Stanford and served as inaugural Director between 2010 through June 2015. Dr. Blumenkranz has a longstanding interest and expertise in university corporate technology transfer and early stage biomedical company development having either founded or served on the Boards of Directors of a number of successful medical drug and device companies. He has been a Director of OIS, Midlabs and Oculex Pharmaceuticals. At Oculex he was also Chairman of the SAB and the principal designer of the successful phase 2 Ozurdex trial, leading to its acquisition by Allergan in 2003. He was a founder and director of Peak Surgical, an innovator in pulsed plasma mediated electrosurgery that was acquired by Medtronics in 2011. In 2004 he co-founded Optimedica Corporation for which he co-wrote the foundation IP for the PASCAL and Catalys lasers, and which was acquired by AMO in 2013. He was a co-founder and director of Oculeve, a dry eye company employing a neuro-stimulatory approach to therapy, which was acquired by Allergan in August of 2015. He is currently a co-founder and director of Digisight Corporation, an early stage venture financed digital health company, and Lagunita Biosciences LLC an early stage medtech and biotech investment company. He is also a co-founder and Chairman of the Board of Adverum Biotechnologies a publicly traded ocular gene therapy company.

In his spare time Mark enjoys sailing, tennis, golf, playing and listening to all forms of music, viticulture and reading. He and his wife, Recia Kott Blumenkranz, MD have lived and raised their three children Carla, Scott and Erik, now grown, in Portola Valley, California, adjacent to the nearby Stanford Campus for the past twenty-five years. The Retina Society is pleased to present the 2016 J. Donald M. Gass, MD Award to Mark Blumenkranz.

George Williams, MD
MAP OF EXHIBITOR AND POSTER LOCATIONS

CESTIAL FOYER AND BALLROOM

CESTIAL FOYER

ENTRANCE

1. Allena Sciences
2. Spark Therapeutics
3. Aveilla Specialty Pharmacy
4. OD-OS GmbH
5. Pine Pharmaceuticals
6. Carl Zeiss

CESTIAL BALLROOM

12. Alcon Laboratories
13. Alcon Laboratories
14. Janssen Pharmaceuticals
15. Genentech
16. Regeneron Pharmaceuticals
10. Regeneron Pharmaceuticals
11. Heidelberg Engineering

Food & Beverage
STAGE

POSTERS GRANT ROOM

19. Bausch & Lomb
20. Notal Vision
21. Mallinckrodt Pharmaceuticals
22. Optovue, Inc
23. Genentech
24. Allergan
25. Genentech
26. Mallinckrodt Pharmaceuticals

34. Optos
35. Regeneron Pharmaceuticals
36. Regeneron Pharmaceuticals
37. Alcon Laboratories
38. Alcon Laboratories
39. Alcon Laboratories
40. Alcon Laboratories

17. Dutch Ophthalmic USA
18. LKC Technologies
19. Bausch & Lomb
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34. Optos

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<td>Avella Specialty Pharmacy</td>
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<td>Retinal Physician</td>
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<td>Retina Today</td>
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<td>Retina Specialist</td>
<td>TABLE 4</td>
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**WEDNESDAY, SEPTEMBER 14, 2016**

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<tr>
<th>Time</th>
<th>Session</th>
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<tr>
<td>12:00 Noon</td>
<td><strong>REGISTRATION — PRESIDENTIAL BALLROOM FOYER</strong></td>
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**PRESIDENTIAL BALLROOM**

**INTERESTING CASES I**

**MODERATORS:** Michael Jumper, MD and Fernando Arevalo, MD, FACS

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<tr>
<th>Time</th>
<th>Speaker(s)</th>
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<tr>
<td>1:00 pm</td>
<td><strong>Doctor My Eyes</strong>&lt;br&gt;<strong>Jose Pulido, MD</strong></td>
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<tr>
<td>1:05</td>
<td><strong>Severe Vision Loss in a Surgeon (Tree Surgeon, That Is)</strong>&lt;br&gt;<strong>Michael Jumper, MD</strong></td>
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<td>1:10</td>
<td><strong>Laser Tag</strong>&lt;br&gt;<strong>Shlomit Schaal, MD, PhD</strong></td>
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<td>1:15</td>
<td><strong>Purtscher-like Retinopathy Secondary to Gemcitabine Therapy</strong>&lt;br&gt;<strong>Jaclyn Kovach, MD</strong></td>
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<td>1:20</td>
<td><strong>Macular Enigma</strong>&lt;br&gt;<strong>Mark Johnson, MD</strong></td>
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<td>1:25</td>
<td><strong>Release of Vitreomacular Traction in Diabetic Macular Edema with Aflibercept</strong>&lt;br&gt;<strong>Robert Wiznia, MD</strong></td>
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<td>1:30</td>
<td><strong>Intravitreal Triamcinolone in Susac’s Syndrome</strong>&lt;br&gt;<strong>Fernando Arevalo, MD, FACS</strong></td>
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<td>1:35</td>
<td><strong>Subretinal Suture Misdirection during Trabeculotomy</strong>&lt;br&gt;<strong>Robert Sisk, MD</strong></td>
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<tr>
<td>1:40</td>
<td><strong>Intraocular Lens Surprise after Pars Plana Vitrectomy</strong>&lt;br&gt;<strong>Rahul Khurana, MD</strong></td>
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<td>1:45</td>
<td><strong>Mystery Case</strong>&lt;br&gt;<strong>Jerry Shields, MD</strong></td>
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<td>1:50</td>
<td><strong>Infection, Inflammation, Both or Neither? The Not-So-Binary Case of Patient 0-1-0</strong>&lt;br&gt;<strong>Scott McClintic, MD</strong></td>
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<tr>
<td>1:55</td>
<td><strong>Retinal Vasculopathy in Cutis Marmorata Telangiectatica Congenita</strong>&lt;br&gt;<strong>Cagri Besirli, MD, PhD</strong></td>
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<tr>
<td>2:00</td>
<td><strong>Vision Loss in a Patient with Primary Pulmonary Hypertension and Long-term Use of Sildenafil</strong>&lt;br&gt;<strong>Christina Weng, MD, MBA</strong></td>
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<tr>
<td>2:05</td>
<td><strong>Bilateral Pigmentation of the Posterior Segment</strong>&lt;br&gt;<strong>John Mason III, MD</strong></td>
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<tr>
<td>2:10</td>
<td><strong>Total Exudative Retinal Detachment</strong>&lt;br&gt;<strong>Arun Singh, MD</strong></td>
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</tbody>
</table>
INTERESTING CASES II
MODERATORS: Carol Shields, MD and Prithvi Mruthyunjaya, MD

2:20 pm  Bilateral Vision Loss Associated with Progressive Outer Retinal Abnormality
          Gregg Kokame, MD, MMM
2:25    Serous Retinal Detachment in Treated Retinoblastoma
          Anita Agarwal, MD
2:30    Cancer Associated Retinopathy
          Charles Barr, MD
2:35    An Unusual Presentation of Spontaneous Epiretinal Membrane Resolution
          James Lin, MD
2:40    Unknown Reflective Foreign Body Following Vitrectomy for Retinal Detachment Repair
          Jonathan Chang, MD
2:45    Coats’ Disease-associated Vasoproliferative Tumor of the Retina with Epiretinal Membrane, Uveitis, and Uncontrolled Glaucoma
          John Allen, MD
2:50    Retinal Lesion after Returning from Haiti
          Wilkin Parke, MD
2:55    Late Onset Retinal Degeneration and Progressive Visual Loss
          Thiran Jayasundera, MD
3:00    A Curious Case of Perivasculaer Infiltrates
          Sandeep Randhawa, MD
3:05    A Soupy Mess in a Patient with Scleritis Treated with Systemic TNF-Alpha Inhibition
          Prithvi Mruthyunjaya, MD
3:10    Bilateral Central Retinal Vein Occlusion due to Polyclonal Gammopathy
          Kirk Packo, MD
3:15    Not One, but Two
          Carol Shields, MD
3:20    A Tale of Two Brothers: An Interesting Phenotype-Genotype Correlation
          Seema Garg, MD, PhD
3:25    Orange Tumor?
          Tara McCannel, MD, PhD
3:30    White Dots Gone Wild
          Monica Michelotti, MD

continued on next page
VIDEO PRESENTATIONS

MODERATORS: Kirk Packo, MD and Raymond Iezzi, MD, MS

3:40 pm  It’s a Terson’s Again....
Audina Berrocal, MD

3:45 Toward More Precise Subretinal Therapeutic Delivery: New Techniques and Instrumentation
Allen Ho, MD, FACS

3:50 Diabetic Tractional Detachment. Mixed Gauges, miOCT, and Preop Planning
Tamer Mahmoud, MD, PhD

3:55 “Stretch” Technique for Management of Retinal Detachment Associated with Severe Peripheral Vitreoretinopathy
Homayoun Tabandeh, MD, MS

4:00 Microscope Scleral Buckling with Chandelier and Illuminated Laser Probe
Maria Berrocal, MD

4:05 Broad Internal Limiting Membrane Peeling for No Face Down Macular Hole Repair
Raymond Iezzi, MD, MS

4:10 Adjunctive Use of Platelet-rich Plasma in Repair of a Myopic Macular Hole/Schisis-associated Retinal Detachment: Intraoperative Optical Coherence Tomography Findings
Scott Walter, MD, MSc

4:15 Analysis of an Epiretinal Membrane that Developed after Subretinal Delivery of a Cell Therapy Product in a Subject with Retinitis Pigmentosa
Rand Spencer, MD

4:30 REFRESHMENT BREAK — PRESIDENTIAL FOYER
MISSION SAN DIEGO DE ALCALÁ
**WEDNESDAY, SEPTEMBER 14, 2016**

12:00 noon  **REGISTRATION — PRESIDENTIAL BALLROOM FOYER**

**PRESIDENTIAL BALLROOM**

5:00 pm  **WELCOME**
Mark Johnson, MD, *President*

**OTHER MACULAR DISEASE**
*PRESIDING OFFICER: Mark Johnson, MD*
*MODERATOR: Jason Hsu, MD*

5:05  The LIBERTY Study: Assessing the Impact of Self-monitoring on Visual Outcomes in Previously Treated Patients with Neovascular Age-related Macular Degeneration
Pravin Dugel, MD

5:11  Discussion

5:14  Spontaneous Avulsions of the Internal Limiting Membrane—A Possible Cause of Epiretinal Membrane Formation
Kirk Packo, MD

5:20  Discussion

5:23  Increased Vitreopapillary Traction in Eyes with Small Optic Nerves May Contribute to the Development of Non-arteritic Ischemic Optic Neuropathy
Tongalp Tezel, MD

5:29  Discussion

5:32  Early Spectral Domain Optical Coherence Tomography Findings after Acute Spontaneous Vitreomacular Traction Release
Jason Hsu, MD

5:38  Discussion

5:41  *Efficacy and Safety Outcomes for Ocriplasmin Intravitreal Injection from Multiple Prospective Clinical Trials (MIVI-TRUST, OASIS, and ORBIT)*
Kapil Kapoor, MD

5:47  *Macula Society Collaborative Retrospective Study of Ocriplasmin for Vitreomacular Traction*
Jennifer Lim, MD

5:53  *Combined Discussion*

5:56  *Pharmacologic Closure Rate of Full Thickness Macular Hole with Ocriplasmin*
Priya Sharma, MD

6:02  *Macular Hole Enlargement after Ocriplasmin Injection for Full-thickness Macular Hole*
Daniel Roth, MD
6:08 pm *Combined Discussion
6:11 Lamellar Macular Hole: Two Distinct Clinical Entities? Jean-Pierre Hubschman, MD
6:17 Discussion
6:20 Yellow Micropulse Laser vs. Photodynamic Therapy in Eyes with Chronic Central Serous Chorioretinopathy. Results of the Pan American Collaborative Retina Study (PACORES) Group Lihteh Wu, MD
6:26 Discussion
6:29 ADJOURN

THURSDAY, SEPTEMBER 15, 2016

7:00 am REGISTRATION — PRESIDENTIAL BALLROOM FOYER

CONTINENTAL BREAKFAST/EXHIBITS — CELESTIAL BALLROOM

PRESIDENTIAL BALLROOM

DIABETIC RETINOPATHY
PRESIDING OFFICER: Jeffrey Heier, MD
MODERATOR: Victor Gonzalez, MD

7:30 Analysis of Intravitreal Levels of Neurotrophins in Diabetic Retinopathy Joseph Boss, MD
7:35 *Association between Baseline Characteristics and Changes in Diabetic Retinopathy Severity Scale (DRSS) Score: Analyses from the VISTA and VIVID Studies Rishi Singh, MD
7:41 *Visual and Anatomic Outcomes before and after Cataract Surgery in Patients Treated for Diabetic Macular Edema (DME) in the VISTA and VIVID Studies Andrew Moshfeghi, MD
7:47 *Change in Retinal Perfusion Status in Patients Treated for Diabetic Macular Edema (DME) in the VISTA Study Charles Wykoff, MD
7:53 *Combined Discussion
7:57 Randomized Trial comparing Ranibizumab Monthly to Treat and extend with and without Angiography-guided Laser for Diabetic Macular Edema (DME): TReX-DME 1 Year Outcomes John Payne, MD
8:03 Discussion
8:06 am  Predicting Visual Acuity Response to Anti-VEGF DME Therapy in Protocol I: A Post-hoc Analysis of Outcomes in Patient with Limited (<5 letter) and Intermediate (5-9 letter) Response at 12 Weeks  
Victor Gonzalez, MD

8:12  Discussion

8:15  Quantifying Microvascular Density and Morphology in Diabetic Retinopathy Using Spectral Domain Optical Coherence Tomography Angiography (SD-OCTA)  
Amir Kashani, MD

8:21  Discussion

8:24  Distribution of Hemorrhages and/or Microaneurysms (H/Ma) Identified on Ultra-wide Field (UWF) Retinal Images and the Risk of Progression Over Four Years  
Paolo Antonio Silva, MD

8:30  Discussion

8:33  *Safety and Efficacy of Intravitreal Ranibizumab for Diabetic Macular Edema in Eyes Previously Treated with Intravitreal Bevacizumab: A Randomized Dual-arm Comparative Dosing Trial. The REACT Study  
Justis Ehlers, MD

8:39  *Ranibizumab (0.3mg) for Persistent Diabetic Macular Edema after Recent, Frequent and Chronic Bevacizumab: 1 Year Trial Results  
Dennis Marcus, MD

8:45  *Conversion of Aflibercept after Prior Anti-VEGF Therapy for Persistent Diabetic Macular Edema  
Mohammad Khan, MD

8:51  *Combined Discussion

8:55  Short-term Results of Fluocinolone Acetonide Intravitreal Implant for Diabetic Macular Edema in Highly Treated Eyes  
Sumit Shah, MD

9:01  Discussion

9:04  *Ranibizumab Induces Regression of Diabetic Retinopathy (DR) in Over Seventy-five Percent of Patients with Highest Risk Non-proliferative Diabetic Retinopathy (NPDR), Independent of Examined Baseline Characteristics  
Geeta Lalwani, MD

9:10  *The Clinical Importance of Changes in Diabetic Retinopathy Severity Score  
Michael Ip, MD

9:16  *Efficacy of Ranibizumab in Eyes with Diabetic Macular Edema and Macular Nonperfusion  
Dante Pieramici, MD

9:22  *Combined Discussion
9:26 am Potential Beneficial Effect of Low Dose Danazol in Combination with Renin Angiotensin Inhibitors in Diabetic Macular Edema: Results of the Optimeyes Trial
Michael Singer, MD

9:32 Discussion

9:35 North Carolina Diabetic Retinopathy Telemedicine Network
Seema Garg, MD

9:41 Discussion

9:44 REFRESHMENT BREAK/EXHIBITS — CELESTIAL BALLROOM

SURGERY I
PRESIDING OFFICER: Harry Flynn Jr, MD
MODERATOR: Judy Kim, MD

10:14 Outcomes after Failed Pneumatic Retinopexy for Retinal Detachment
Joseph Anaya, MD

10:19 Macular Hole after Pars Plana Vitrectomy for Rhegmatogenous Retinal Detachment
Harry Flynn Jr, MD

Homayoun Tabandeh, MD

10:29 Effect of Scleral Buckling on Eyes that had Previously Undergone LASIK Surgery
Thomas Friberg, MD

10:34 Persistent Indocyanine Green Fluorescence Following Macular Hole Repair
Judy Kim, MD

10:39 Peeling or Not Peeling the Internal Limiting Membrane in Macular Pucker Surgery: A Microperimetric Response
Guido Ripandelli, MD

10:45 Discussion

10:48 *Should Epiretinal Membranes be Peeled before Vision Drops Below 20/40?
John Pollack, MD

10:54 *Macular Pucker Surgery Outcomes in Good Vision Eyes
Colin McCannel, MD

11:00 *Combined Discussion

11:03 Internal Limiting Membrane Peeling (ILMP) Reabsorbs Macular Edema (ME) and Improves Visual Acuity Precisely because it is a Retinal Trauma of Mechanical Nature
Claude Boscher, MD
<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>11:09</td>
<td>Discussion</td>
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<tr>
<td>11:12</td>
<td>Management of Focal Vitreomacular Traction with Pneumatic Vitreolysis</td>
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<td><strong>Clement Chan, MD</strong></td>
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<td>11:18</td>
<td>Discussion</td>
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<td>11:21</td>
<td>Optical Coherence Tomography-guided Short-duration Face-down Positioning after Vitrectomy for Macular Hole</td>
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<td><strong>Theodore Leng, MD</strong></td>
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<td>11:27</td>
<td>Discussion</td>
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<td>11:30</td>
<td>Autologous Neurosensory Retinal and Choroidal Free Flap for Closure of Refractory Large Macular Holes</td>
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<td><strong>Dilraj Grewal, MD</strong></td>
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<td>11:36</td>
<td>Discussion</td>
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<td>11:39</td>
<td>Displacement of Submacular Hemorrhage with Subretinal Air. Initial U.S. Experience</td>
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<td><strong>Tamer Mahmoud, MD</strong></td>
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<td>11:45</td>
<td>Discussion</td>
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<td>11:48</td>
<td><strong>FELLOWSHIP RESEARCH AWARD PRESENTATION</strong></td>
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<tr>
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<td><strong>INTRODUCTION: David Zacks, MD</strong></td>
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<td>Protective Effect of Mesenchymal Stem Cell Derived Exosomes in a Model of Retinal Ischemia</td>
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<td><strong>Elad Moisselev, MD</strong></td>
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<td>12:03</td>
<td><strong>RETINA RESEARCH FOUNDATION AWARD OF MERIT — CHARLES L. SCHEPENS LECTURE</strong></td>
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<tr>
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<td><strong>INTRODUCTION: Kirk Packo, MD</strong></td>
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<td>Evolution of Vitreoretinal Techniques and Technologies</td>
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<td><strong>Steve Charles, MD</strong></td>
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<td>12:33</td>
<td><strong>LUNCHEON FOR MEETING ATTENDEES AND EXHIBITORS — PALM COURT</strong></td>
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<td>1:03</td>
<td><strong>POSTER VIEWING SESSION AND DESSERT — GRANT HALL</strong></td>
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<tr>
<td>2:03</td>
<td><strong>Ultra-wide Field Retinal Imaging in the Staging and Management of Sickle Cell Retinopathy</strong></td>
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<td><strong>Adrienne Scott, MD</strong></td>
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<td>2:08</td>
<td><strong>Late-phase Fluorescein Angiographic Findings which Predict Capillary Dropout and Subsequent Drug Treatment which can Lead to Capillary Preservation</strong></td>
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<td><strong>Michael Trese, MD</strong></td>
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<td>Presentation</td>
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<tr>
<td>2:13 pm</td>
<td>Norrin Regulates Vascular Development and Capillary Regeneration</td>
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<td>2:19</td>
<td>Discussion</td>
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<tr>
<td>2:22</td>
<td>*Late-stage Management of Macular Edema Secondary to Retinal Vein Occlusion: Collective Analysis of the BRAVO, CRUISE, HORIZON, and SHORE Studies</td>
</tr>
<tr>
<td>2:28</td>
<td>*Long-term Outcomes of Eyes with Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO) Treated with Intravitreal Bevacizumab. Results of the Pan American Collaborative Retina Study (PACORES) Group</td>
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<tr>
<td>2:34</td>
<td>*Combined Discussion</td>
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<tr>
<td>2:37</td>
<td>Combination Therapy of Ranibizumab Plus Laser-induced Chorioretinal Anastomosis for Central Retinal Vein Occlusion</td>
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<td>2:43</td>
<td>Discussion</td>
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<td>2:46</td>
<td>Oral Niacin as a Modulator for Central Retinal Vein Occlusion</td>
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<td>2:52</td>
<td>Discussion</td>
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<td>2:55</td>
<td>REFRESHMENT BREAK/EXHIBITS — CELESTIAL BALLROOM</td>
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**TUMORS**

**PRESIDING OFFICER:** Timothy Murray, MD  
**MODERATOR:** Amy Schefler, MD

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<thead>
<tr>
<th>Time</th>
<th>Presentation</th>
<th>Speaker</th>
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<tr>
<td>3:25</td>
<td>Genetic Risk Factors for Radiation Vasculopathy</td>
<td>Thanos Papakostas, MD</td>
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<tr>
<td>3:30</td>
<td>Novel Classification System for Combined Hamartoma of the Retina and Retinal Pigment Epithelium</td>
<td>Vaidehi Dedania, MD</td>
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<tr>
<td>3:35</td>
<td>Germline BAP1 Mutation in Familial Uveal Melanoma: Report of Twenty-six New Families</td>
<td>Colleen Cebulla, MD</td>
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<td>3:40</td>
<td>Intra-arterial Chemotherapy in Very Small Infants (&lt; 10kg) with Retinoblastoma</td>
<td>Amy Schefler, MD</td>
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<td>3:45</td>
<td>Association Between Choroidal Nevus Risk Factors and Gene Expression Profile Prognostic Class</td>
<td>William Harbour, MD</td>
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<td>3:51</td>
<td>Discussion</td>
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<td>3:54</td>
<td>Mushroom Shaped Choroidal Lesions other than Melanoma</td>
<td>Jerry Shields, MD</td>
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<td>4:00</td>
<td>Discussion</td>
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<tr>
<td>Time</td>
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<td>Presenter</td>
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<tr>
<td>4:03 pm</td>
<td>Tumor Regression Patterns Based on Gene Expression Profile Testing Radiotherapy for Uveal Melanoma: A Multicenter Study</td>
<td>Prithvi Mruthyunjaya, MD</td>
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<td>4:09</td>
<td>Discussion</td>
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<td>4:12</td>
<td>Optical Coherence Tomography Angiography of the Macula after Plaque Radiotherapy of Choroidal Melanoma: Comparison of Irradiated versus Non-irradiated Eyes in Sixty-five Patients</td>
<td>Carol Shields, MD</td>
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<td>4:18</td>
<td>Discussion</td>
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<td>4:21</td>
<td>Prognostic Value of Vascular Congestion in Mushroom-shaped Uveal Melanomas Treated with Proton Beam Irradiation</td>
<td>Leonidas Zografos, MD</td>
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<td>4:27</td>
<td>Discussion</td>
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<td>4:30</td>
<td>Survival in a Large Cohort of Patients with Metastasis from Uveal Melanoma</td>
<td>Evangelos Gragoudas, MD</td>
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<td>4:36</td>
<td>Discussion</td>
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<tr>
<td>4:39</td>
<td>Vision Loss Following Episceral Brachytherapy: A Risk Calculator</td>
<td>Arun Singh, MD</td>
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<td>4:45</td>
<td>Discussion</td>
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<td>4:48</td>
<td>Vitreoretinal Surgical Management of Uveal Melanoma: Unique Intraoperative Findings and Outcomes</td>
<td>Timothy Murray, MD</td>
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<tr>
<td>4:54</td>
<td>Discussion</td>
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<tr>
<td>4:57</td>
<td>Visual Benefit of Iodine-125 Brachytherapy with Vitrectomy and Silicone Oil for Large Choroidal Melanoma: 1-to-1 Matched Case-control Series</td>
<td>Tara McCannel, MD</td>
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<td>5:03</td>
<td>Discussion</td>
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<tr>
<td>5:06</td>
<td>Safety and Efficacy of 25g Vitrectomy with Needle Biopsy of Choroidal Melanoma for Gene Expression Profiling (GEP) during Brachytherapy</td>
<td>John Mason III, MD</td>
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<td>5:12</td>
<td>Discussion</td>
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FRIDAY, SEPTEMBER 16, 2016

7:00 am  REGISTRATION — PRESIDENTIAL BALLROOM FOYER

CONTINENTAL BREAKFAST/EXHIBITS — CELESTIAL BALLROOM

PRESIDENTIAL BALLROOM

AGE-RELATED MACULAR DEGENERATION I
PRESIDING OFFICER: Allen Ho, MD
MODERATOR: Deeba Husain, MD

7:30  Prevalence of Drusen and Conversion to Neovascular Age-related Macular Degeneration in Fellow Eyes in the HARBOR Study
Caroline Baumal, MD

7:35  Type 1 versus Type 3 Neovascularization in Pigment Epithelial Detachments (PEDs) Associated with Age-related Macular Degeneration after Anti-VEGF Therapy in the EVEN Study: Post-hoc Analysis of a Prospective Study
Xuejing Chen, MD

7:40  Correlation of Optical Coherence Tomographic Hyperreflective Foci with Visual Outcomes after Treatment in Age-related Macular Degeneration and Polypoidal Choroidal Vasculopathy
Hyung Chan Kim, MD

7:45  En-face Spectral Domain Optical Coherence Tomography in Polypoidal Choroidal Vasculopathy
Gregg Kokame, MD

7:51  Discussion

7:54  Changes in Dark Adaptation and Structure by Optical Coherence Tomography in Age-related Macular Degeneration
Deeba Husain, MD

8:00  Discussion

8:03  Adjunctive Indocyanine Green Angiography-directed Verteporfin Photodynamic Therapy for the Treatment of Persistent Disease Activity in Neovascular Age-related Macular Degeneration
Priyatham Mettu, MD

8:09  Discussion

8:12  Impact of Anti-VEGF Therapy on Photoreceptors in Patients with Exudative Age-related Macular Degeneration
Shintaro Nakao, MD

8:18  Discussion

8:21  Evaluation of Choroidal Perfusion with Rapid-scan Plane Wave Ultrasonography
Jackson Coleman, MD
<table>
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<tr>
<th>Time</th>
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<tbody>
<tr>
<td>8:27 am</td>
<td>Discussion</td>
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</table>
| 8:30  | Maculopathy in Patients with Monoclonal Gammopathy of Undetermined Significance  
Stephen Smith, MD |
| 8:36  | Discussion                                                              |
| 8:39  | NEI VQF-25 Responsiveness to Changes in Area of Geographic Atrophy in Patients with Age-related Macular Degeneration  
Neil Bressler, MD |
| 8:45  | Discussion                                                              |
| 8:48  | A Simple Optical Coherence Tomography-based System for Scoring the Risk of Progression in Eyes with Intermediate Age-related Macular Degeneration  
SriniVas Sadda, MD |
| 9:03  | Discussion                                                              |
| 9:06  | Evaluating Intravitreal Brimonidine Tartrate Drug Delivery System (Brimonidine DDS) in Patients with Geographic Atrophy in a Phase 2 Study  
William Freeman, MD |
| 9:12  | Discussion                                                              |
| 9:15  | INTRODUCTION OF GUEST OF HONOR — THOMAS AABERG SR, MD  
Antonio Capone Jr, MD |
| 9:25  | REFRESHMENT BREAK/EXHIBITS — CELESTIAL BALLROOM                          |
| 9:54  | Discussion                                                              |
| 9:57  | Prevalence and Natural History of Asymptomatic Macular Neovascularization in Non-exudative Age-related Macular Degeneration Diagnosed using Optical Coherence Tomography Angiography  
Philip Rosenfeld, MD |
| 10:00 | Ultra-wide Field Autofluorescence in ABCA4 Stargardt Disease  
Steven Schwartz, MD |
| 10:05 | Features of Posterior Staphylomas Analyzed by Ultra-wide Field Optical Coherence Tomography and 3D MRI  
Kyoko Ohno-Matsui, MD |
<table>
<thead>
<tr>
<th>Time</th>
<th>Title</th>
<th>Presenter</th>
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<tbody>
<tr>
<td>10:10 am</td>
<td>Choroidal Changes Associated with Serous Macular Detachment in Eyes with Staphyloma or Dome-shaped Macula</td>
<td>Anna Tan, MD</td>
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<tr>
<td>10:16</td>
<td>Discussion</td>
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<tr>
<td>10:19</td>
<td>Optical Coherence Tomography-Angiographic Vascular Perfusion Density Mapping Findings in Optic Disc Pit</td>
<td>Netan Choudhry, MD</td>
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<tr>
<td>10:25</td>
<td>Discussion</td>
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<tr>
<td>10:28</td>
<td>Dueling Imagers: Adaptive Optics Scanning Laser Ophthalmoscope Fluorescein Angiography Challenges Optical Coherence Tomography Angiography</td>
<td>Richard Rosen, MD</td>
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<tr>
<td>10:34</td>
<td>Discussion</td>
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<td>10:37</td>
<td>Power Law Flow Patterns in the Choriocapillaris as Imaged by Optical Coherence Tomography Angiography</td>
<td>Richard Spaide, MD</td>
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<tr>
<td>10:43</td>
<td>Discussion</td>
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<tr>
<td>10:46</td>
<td>Sensitivity and Specificity of Choroidal Neovascularization Detection with Optical Coherence Tomography Angiography in Age-related Macular Degeneration</td>
<td>Steven Bailey, MD</td>
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<tr>
<td>10:52</td>
<td>Discussion</td>
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<tr>
<td>10:55</td>
<td>Comparison of Optical Coherence Tomography Angiography Biomarkers for Distinguishing Diabetic Subjects with Varying Levels of Retinopathy from Non-diabetic Healthy Controls</td>
<td>Abtin Shahlaee, MD</td>
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<td>11:04</td>
<td>Intraoperative Ultra-high Speed Swept Source Optical Coherence Tomography (OCT) for Wide-field Imaging, OCT Angiography, and 4D Imaging</td>
<td>Andre Witkin, MD</td>
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<td>Physician-industry Interactions and Anti-VEGF Utilization among U.S. Ophthalmologists</td>
<td>Stanford Taylor, MD</td>
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<td><strong>INVITED PRESENTATION</strong> Certification in Retina and Its Related Issues</td>
<td>David Parke II, MD</td>
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<td>Executive Vice-President and CEO, American Academy of Ophthalmology</td>
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<td>11:32</td>
<td>Discussion</td>
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SCIENTIFIC PROGRAM

11:37 am RAYMOND R. MARGHERIO AWARD PRESENTATION

**INTRODUCTION:** David Zacks, MD, PhD
Spectral-domain Optical Coherence Tomography Imaging of the Retinal Vascular-avascular Junction in Infants with Retinopathy of Prematurity

Xi Chen, MD

11:52 J. DONALD M. GASS AWARD

**INTRODUCTION:** George Williams, MD
Surveying the Past and Charting a Path Forward for the Successful Treatment of Macular Degeneration with Gene Therapy Techniques

Mark Blumenkranz, MD

12:22 pm ANNUAL BUSINESS MEETING, THE RETINA SOCIETY — PRESIDENTIAL BALLROOM

12:50 – 1:45 LUNCHEON FOR MEETING ATTENDEES AND EXHIBITORS — PALM COURT

RETINAL DYSTROPHIES AND DEGENERATIONS

**PRESIDING OFFICER:** Jenny Lim, MD
**MODERATOR:** Thiran Jayasundera, MD

1:45 The Impact of Exercise on the Quality of Life and Progression of Disease in Retinitis Pigmentosa

Jiong Yan, MD

1:50 Glucose Re-establishes Cone Outer Segment Synthesis and Function in Retinitis Pigmentosa

Henry Kaplan, MD

1:56 Discussion

1:59 The Role of Autophagy in Photoreceptor Degeneration in the P23h Mouse Model of Autosomal Dominant Retinitis Pigmentosa (ADRP)

David Zacks, MD

2:05 Discussion

2:08 Distinguishing Retinitis Pigmentosa from Severe Hydroxychloroquine Toxicity

Michael Marmor, MD

2:14 Discussion

2:17 Long-term Outcomes of Human Embryonic Stem Cell Derived Retinal Pigment Epithelial Cell Transplantation for Retina Degeneration

Ninel Gregori, MD

2:23 Discussion

2:26 Comparing iPSC Derived Retinal Pigment Epithelial (RPE) Cell Cultures and Commonly Used RPE Cell Lines: What a Clinician Should Know

Jose Pulido, MD

2:32 Discussion
2:35 pm  Phenotypic Matching for Genetic Confirmation of Retinal Dystrophies  
Thiran Jayasundera, MD

2:41      Discussion

2:44      Orally Delivered, Synthetic Chromophore Therapy for Inherited Retinal Disease Due to Genetic Defects in the Visual Cycle  
David Saperstein, MD

2:50      Discussion

2:53      Pathogenesis in Autoimmune Retinopathy  
John Heckenlively, MD

2:59      Discussion

3:02      North Carolina Macular Dystrophy (NCDR1): Mutations Found Affecting PRDM13  
Kent Small, MD

3:08      Discussion

3:11      REFRESHMENT BREAK/EXHIBITS — CELESTIAL BALLROOM

INFLAMMATION AND LATE BREAKERS
PRESIDING OFFICER: Bernard Doft, MD  
MODERATOR: James Folk, MD

3:41      Endophthalmitis after Open Globe Injuries with and without Retained Intraocular Foreign Bodies  
Tanuj Banker, MD

3:47      Discussion

3:50      Post-injection Endophthalmitis Rates and Characteristics Following Intravitreal Bevacizumab, Ranibizumab and Aflibercept  
Nadim Rayess, MD

3:56      Discussion

3:59      Do Vancomycin and Amikacin have Synergistic or Additive Effects against MRSA Organisms at the Intravitreal Drug Concentrations used for Endophthalmitis  
Bernard Doft, MD

4:05      Discussion

4:08      Twenty-four Months’ Follow-up of Intravitreal Bevacizumab Injection versus Intravitreal Triamcinolone Acetonide Injection for the Management of Refractory Non-infectious Uveitic Cystoid Macular Edema  
Fernando Arevalo, MD

4:14      Discussion

4:17      Sarilumab for Non-infectious Uveitis (SARIL-NIU): Results at Sixteen Weeks from the Phase 2 SATURN Study  
Quan Dong Nguyen, MD
4:23 pm Discussion

4:26 Corticosteroid Tapering Success with Every-other-month Injections of Intravitreal Sirolimus in Subjects with Active Non-infectious Uveitis of the Posterior Segment (NIU-PS): SAKURA Study 1 Results
Thomas Albini, MD

4:32 Discussion

4:35 Optical Coherence Tomography Angiography of Placoid Related Disorders
David Sarraf, MD

4:41 Discussion

4:44 Late Onset Severe Visual Field Loss in Patients with Retinal Vasculitis
James Folk, MD

4:50 Discussion

4:53 Variables Related to the Ophthalmoscopic Findings Identified in Infants with Presumed Zika Virus Congenital Infection
Mauricio Maia, MD

4:59 Discussion

5:02 LATE BREAKING PRESENTATION
Panretinal Photocoagulation versus Intravitreous Ranibizumab for Proliferative Diabetic Retinopathy (PDR): Worsening of PDR
Susan Bressler, MD

5:08 Discussion

5:11 LATE BREAKING PRESENTATION
Continued Ranibizumab Therapy for Diabetic Macular Edema in Patients with Limited Early Response: A Retrospective Analysis of RIDE/RISE Trial Data
Rishi Singh, MD

5:17 Discussion

5:20 LATE BREAKING PRESENTATION
Intraocular Pressure Changes: Three-year findings of the Prospective Retinal and Optic Nerve Vitrectomy Evaluation (PROVE) Study
Stephen Kim, MD

5:26 Discussion

5:29 ADJOURN
SATURDAY, SEPTEMBER 17, 2016

7:00 am  REGISTRATION — PRESIDENTIAL BALLROOM FOYER

CONTINENTAL BREAKFAST/EXHIBITS — CELESTIAL BALLROOM

PRESIDENTIAL BALLROOM

PEDIATRICS

PRESIDING OFFICER: Antonio Capone Jr, MD
MODERATOR: Baker Hubbard III, MD

7:30  Spectral-domain Optical Coherence Tomography in Older Patients with History of Retinopathy of Prematurity
Aristomenis Thanos, MD

7:35  Abnormal vessels in the Foveal Center in Premature Eyes: An Optical Coherence Tomography Angiography Study
Irena Tsui, MD

7:40  Familial Exudative Vitreoretinopathy: Outcomes of 332 Eyes with Retinal Detachment
Yoshihiro Yonekawa, MD

7:46  Discussion

7:49  Immediate Sequential Bilateral Pediatric Vitreoretinal Surgery: An International Multicenter Study
Antonio Capone Jr, MD

7:55  Discussion

7:58  Near-term Safety of Intravitreal Bevacizumab and Diode Laser Photocoagulation Treatments for Type 1 Retinopathy of Prematurity
Darius Moshfeghi, MD

8:04  Discussion

8:07  National Trends in Retinopathy of Prematurity over Sixteen Years in the United States
Ron Adelman, MD

8:13  Discussion

8:16  577-nm Yellow Laser Photocoagulation for Coats’ Disease
Baker Hubbard III, MD

8:22  Discussion

SURGERY II

PRESIDING OFFICER: Dean Eliott, MD
MODERATOR: Cynthia Toth, MD

8:25  Novel Approach to Surgical Trochar Insertion: Advantages of the Autoinseter
Brandon Busbee, MD
8:30 am  27-Gauge Vitrectomy for Vitreoretinal Disorders
  Christiane Falkner-Radler, MD

8:35  Modulation of Vitrectomy Console Parameters to Minimize Retinal
  Motion in Small-gauge Vitrectomy for Retinal Detachment
  Yannek Leiderman, MD

8:40  Vitreous and Contrast Sensitivity
  Jerry Sebag, MD

8:45  *Multiple Intravitreal Methotrexate Injections for the Prevention
  of Proliferative Vitreoretinopathy
  Dean Eliott, MD

8:51  *OM-101 Attenuates the Formation of Fibrotic Response Associated
  with Proliferative Vitreoretinopathy
  Ayala Pollack, MD

8:57  *Combined Discussion

9:00  Four-dimensional Optical Coherence Tomography-guided
  Vitreoretinal Surgery with Surgeon-controlled Heads Up Display
  Cynthia Toth, MD

9:06  Discussion

9:09  Fluid-air Exchange during Silicone Oil Removal is Not Effective,
  but Harmful for Reducing the Residual Silicone Oil
  Taiji Sakamoto, MD

9:15  Discussion

9:18  A Porcine Model for Venous Air Embolism from Fluid Air Exchange
  Andrew McClellan, MD

9:24  Discussion

9:27  Analysis for Pars Plana Vitrectomy Incisions Using Live Bacteria
  Omesh Gupta, MD

9:33  Discussion

9:36  A Single-center, Randomized, Prospective Study Evaluating the
  Safety and Efficacy of YAG Vitreolysis versus Sham for Symptomatic
  Weiss Ring Due to Posterior Vitreous Detachment
  Chirag Shah, MD

9:42  Discussion

9:45  REFRESHMENT BREAK/EXHIBITS — CELESTIAL BALLROOM
AGE-RELATED MACULAR DEGENERATION II
PRESIDING OFFICER: Daniel Martin, MD
MODERATOR: Mary Elizabeth Hartnett, MD

10:15 am Simultaneous Dexamethasone Intravitreal Implant and Anti-VEGF Therapy for Neovascular Age-related Macular Degeneration Resistant to Anti-VEGF Monotherapy
Bozho Todorich, MD

10:20 Phase III Studies Comparing the Efficacy and Safety of Brolucizumab vs. Aflibercept in Subjects with Neovascular Age-related Macular Degeneration: Testing an Alternative Treatment Regimen
Baruch Kuppermann, MD

10:25 Phase I Study of Combination Therapy with Nesvacumab, an Anti-angiopoietin 2 Antibody, and Aflibercept, an Anti-Vascular Endothelial Growth Factor Agent, for Neovascular Age-related Macular Degeneration and Diabetic Macular Edema
David Boyer, MD

10:30 Choroidal Neovascular Lesion Characteristics as a Predictor of Visual Outcome in Wet Age-related Macular Degeneration Patients Receiving Combination Therapy of Intravitreal Ranibizumab and Squalamine Lactate Ophthalmic Solution
Nauman Chaudhry, MD

10:35 Is there a Role for Fluorescein Angiography in the Monitoring of Eyes with Neovascular Age-related Macular Degeneration Receiving Anti-VEGF Therapy?
Rahul Khurana, MD

10:41 Discussion

10:44 Are Dilated Fundus Exams Needed for the Management of Neovascular Age-related Macular Degeneration (nAMD)?
Daniel Miller, MD

10:50 Discussion

10:53 Response of Eyes with Pigment Epithelial Detachments Treated with Ranibizumb, Including those that developed Retinal Pigment Epithelial Tears: Data from the HARBOR Study
Nadia Waheed, MD

10:59 Discussion

11:02 Prospective, Multicenter Study of Aflibercept Treat-and-Extend for Neovascular Age-related Macular Degeneration (ATLAS): One and Two Year Results
Murtaza Adam, MD

11:08 Discussion

11:11 A Meta-analysis of Anti-VEGF Treatment Regimens for Neovascular Age-related Macular Degeneration: One Year Results are Driven in Part by the Injection Frequency
Thomas Ciulla, MD
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<td>Five-year Outcomes with Anti-VEGF Treatment of Neovascular Age-related Macular Degeneration in the Comparison of Age-related Macular Degeneration Treatment Trials (CATT)</td>
<td>Daniel Martin, MD</td>
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<td>11:20</td>
<td>Macular Morphology and Visual Acuity at Year 5 of the Comparison of Age-related Macular Degeneration Treatment Trials (CATT)</td>
<td>Glenn Jaffe, MD</td>
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<td>Thy-1 Induces Activation and Migration of Choroidal Endothelial Cells: Relevance to Neovascular Age-related Macular Degeneration</td>
<td>Mary Elizabeth Hartnett, MD</td>
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<td>Semaphorins Inhibit Choroidal Neovascularization</td>
<td>Shlomit Schaal, MD</td>
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<td>11:53</td>
<td>A Novel Subretinal Access Procedure Using a Suprachoroidal Approach</td>
<td>Jeffrey Heier, MD</td>
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GUARDIAN OF WATER BY DONAL HORD
**PEDIATRICS**

**POSTER 1**  Macular Hole in the Pediatric Population: A Retrospective Review  
Audina Berrocal, MD

**AGE-RELATED MACULAR DEGENERATION**

**POSTER 2**  High-dose Ranibizumab for Exudation and Hemorrhage in Polypoidal Choroidal Vasculopathy: PEARL 2 Trial  
James Lai, MD

**POSTER 3**  Submacular Hemorrhage in Patients on Novel Oral Anticoagulants (NOACs)  
Jonathan Hu, MD

**POSTER 4**  Management of Choroidal Neovascularization (CNV) through the Implantable Miniature Telescope (IMT)  
Melanie Fortin, MD

**POSTER 5**  Reticular Pseudodrusen and Systemic Disease  
Jaclyn Kovach, MD

**POSTER 6**  Systemic Beta-blockers in Neovascular Age-related Macular Degeneration  
Anastasia Traband, MD

**POSTER 7**  The Relationship between Non-steroidal Anti-inflammatory Drug Use and Age-related Macular Degeneration  
Bobek Modjtahedi, MD

**POSTER 8**  Investigation of Risk Alleles for Macular Degeneration among Severe Drusen Phenotypes and Retinal Pigment Epithelial Alterations  
Matthew Guess, MD

**POSTER 9**  RETeval and Age-related Macular Degeneration Patients with Good Visual Acuity  
Gloria Wu, MD

**POSTER 10**  Wet Age-related Macular Degeneration in Asian-Americans and Non-Asians: An Analysis of Comparative Outcomes  
Samuel Kim, MD

**POSTER 11**  Intravitreal ICON-1 in Patients with Choroidal Neovascularization (CNV) Secondary to Age-related Macular Degeneration (AMD): A Phase 2 Study EMERGE  
Brian Berger, MD

**OTHER MACULAR DISEASE**

**POSTER 12**  The Prevalence of Myopic Choroidal Neovascularization in the United States: Analysis of the IRIS Registry and National Health and Nutrition Examination Survey  
Jeffrey Willis, MD

**POSTER 13**  Frequency of Alternative Use among Intravitreal Anti-vascular Endothelial Growth Factor Drugs  
Ravi Parikh, MD
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<td>A Mouse Model of Chloroquine Retinal Toxicity</td>
<td>Leo Kim, MD</td>
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<td>Long-term Follow-up of Persistent Outer Retinal Defects (Micro Holes) Following Macular Hole Surgery</td>
<td>Mehrdad Malihi, MD</td>
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<td>Central Serous Chorioretinopathy Secondary to Cushing’s Disease</td>
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<td>Scleral Fixation of an Akreos AO60 Intraocular Lens Using Gore-Tex® Suture: One Year Outcomes and Comparison to Anterior Chamber Intraocular Lens Placement</td>
<td>Mohammad Khan, MD</td>
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<td>How does Internal Limiting Membrane Peeling with Chromovitrectomy Augment Closure of Macular Holes and Resolution of Retinal Schisis?</td>
<td>Ahmet Hondur, MD</td>
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<td>Open Angle Glaucoma Following Surgery for Primary Rhegmatogenous Retinal Detachment</td>
<td>Jonathan Greenberg, MBBCH</td>
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<td>Silicone Oil Tamponade as a Pharmacological Modulator</td>
<td>Jesse McCann, MD</td>
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<td>23 and 25 Gauge Pars Plana Vitrectomy have Similar Rates of Clinically Significant Complications</td>
<td>Brock Alonzo, MD</td>
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<td>In-office Vitrectomy for the Removal of Retained Lens Cortex</td>
<td>Saad Shaikh, MD</td>
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<td>Is it Worth Operating Lamellar Macular Holes?</td>
<td>Gibran Khurshid, MD</td>
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<td>Vitreoretinal Disorders in Patients with High Myopia and Pars Plana Vitrectomy</td>
<td>Prarthana Dalal, BA</td>
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<td>Investigating the Posterior Pole: A Tool and Technique for Post Mortem Tissue Recovery in Enucleated Human Eyes</td>
<td>Jerome Giovinazzo, MD</td>
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<td>Surgical Management and Outcomes of Pars Plana Vitrectomy for Late Sequelae of Infectious Endophthalmitis</td>
<td>Jeremy Wolfe, MD</td>
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<td>Optical Coherence Tomography Findings in Eyes with Unexpected Visual Loss after Vitrectomy</td>
<td>Sara Haug, MD</td>
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<td>The Comparison of Regional versus General Anesthesia for Surgical Repair of Open Globe Injuries: A 20-Year Experience</td>
<td>Kimberly Tran, MD</td>
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<td>Visual and Anatomical Outcomes of Diabetic Tractional Retinal Detachment Repair</td>
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<td>Visual and Anatomic Outcomes of Pars Plana Vitrectomy with Membrane Peel in the Elderly</td>
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<td>Diurnal Variations in Luminal and Stromal Areas of Choroid in Normal Eyes</td>
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<td>Optical Coherence Tomography Angiography Findings in Acute Macular Neuroretinopathy</td>
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<td>Dexamethasone Implant with Rescue Ranibizumab for Treating Macular Edema Secondary to Retinal Vein Occlusion: DRIVEN Study</td>
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<td>Sequential Optical Coherence Tomography Changes of Macular Star in Cat Scratch Disease</td>
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<td>POSTER 36</td>
<td>Analysis of Predisposing Factors and Management Course of Endogenous Fungal Endophthalmitis: A Five-year Experience in a Tertiary Referral Center</td>
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<td>POSTER 37</td>
<td>A Literature Review and Update on the Incidence and Microbiology Spectrum of Post-cataract Surgery Endophthalmitis Over Past Two Decades in India</td>
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<td>Surgical Outcomes of Epiretinal Membranes in Patients with Uveitis</td>
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<td>Accumulation of Acrolein-Lys Adduct in the Vitreous Fluid of Proliferative Diabetic Retinopathy</td>
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<td>POSTER 40</td>
<td>Systemic Risks Associated with Treatments for Diabetic Macular Edema: A Cohort Study of 27,664 Patients</td>
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THE LIBERTY STUDY: ASSESSING THE IMPACT OF SELF-MONITORING ON VISUAL OUTCOMES IN PREVIOUSLY TREATED PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

Pravin Dugel, MD
Phoenix, AZ

PURPOSE: Frequent monitoring of vision is important to provide appropriate and timely treatment in patients with neovascular age-related macular degeneration (nAMD). The aim of this study was to determine whether patient self-monitoring can help to maintain and/or improve visual and anatomical outcomes through the rapid identification of changes indicative of disease activity, without increasing—and potentially even decreasing—treatment and office visit burden.

METHODS: LIBERTY was a 12-month, randomized, open-label study. Previously treated patients with nAMD aged ≥50 years were randomized into three treatment arms: A, ranibizumab injections every 4 weeks; B, ranibizumab given according to a capped PRN regimen with monthly office visits; C, ranibizumab given at the physician’s discretion according to a watch-and-extend regimen. Participants in each group self-monitored their vision at least once every two days using a vision assessment system, and the study site received a vision alert via email if a patient experienced significant change in vision, prompting a clinic visit and evaluation.

RESULTS: A total of 60 patients were enrolled; of these, 51 completed the study. At 12 months, all three groups demonstrated improvements in best-corrected visual acuity from baseline which were statistically non-inferior across groups (gains of 2.88, 2.06 and 2.29 letters in Groups A, B and C, respectively). Though not statistically significant, we noted a trend towards less frequent office visits and fewer injections among patients in Group C. Examination of patient-level data revealed that self-monitoring often detected disease progression earlier than would have occurred with office visits alone. Five unscheduled office visits were prompted by vision alerts over the course of the study; three of these visits resulted in treatment.

CONCLUSIONS: In this single-center pilot study, self-monitoring using a vision assessment system enabled early detection of vision changes and more timely treatment among patients given ranibizumab. A trend towards fewer office visits and injections among patients on a watch-and-extend regimen supplemented with home self-monitoring suggests that additional study is warranted to investigate the benefits of self-monitoring, particularly in patients managed using regimens with variable monitoring intervals.
**SPONTANEOUS AVULSIONS OF THE INTERNAL LIMITING MEMBRANE—A POSSIBLE CAUSE OF EPIRETINAL MEMBRANE FORMATION**

**Kirk Packo, MD**  
**Chicago, IL**

**PURPOSE:** To describe a new clinical entity of spontaneous avulsion of the internal limiting membrane (ILM). This finding is seen clinically during vitreous surgery as strips of absent staining along vessels in eyes with concurrent posterior vitreous detachment (PVD) and epiretinal membrane (ERM). It is hypothesized that during the natural development of a PVD, some patients will have an avulsion of strips of ILM from the perivascular retina. This incites an injury that upregulates factors leading subsequently to the development of the ERM. This paper will present the varying clinical & surgical findings of ILM avulsions. Additionally, ILM rips (tectonic plate movement of ILM due to overlying ERM contraction) are also described. The findings are correlated with preop and postop imaging. Histologic evidence of this hypothesis from the literature will be presented.

**METHODS:** Forty consecutive cases of idiopathic epiretinal membrane and 6 cases of stage IV macular holes undergoing vitreous surgery by the author were reviewed. All patients underwent preoperative color photography and SD-OCT imaging of the central macula and along the superotemporal and inferotemporal arcades. Intraoperative photographs were obtained to document the appearance of the ILM staining pattern with either indocyanine green (16 eyes) or brilliant blue dye (30 eyes). The staining patterns were examined for strips of absent staining along either retinal arteries or veins. Findings of missing perivascular strips of ILM and ILM rips are correlated with their appearance on SD-OCT en face and line scan images.

**RESULTS:** 36/40 eyes had ILM avulsions noted (78% of ERM cases). All 36 cases had PVDs, while 4 cases had still attached posterior hyaloid membranes with the ERM. The ILM avulsions were graded as subtle (4 eyes), moderate (4 eyes), or prominent (28 eyes). The avulsions were noted along veins only (20 eyes), arteries only (4 eyes), or both (12 eyes). In addition to ILM avulsions, ILM rips were seen in 29 eyes (80%) defined as thickened scrolls of ILM on the ERM side of the avulsion. The 6 stage IV macular holes all had ILM avulsions, most of which were very subtle and none were associated with ILM rips. ILM rips were easy to identify on preoperative OCT imaging, however the ILM avulsion was difficult to see preoperatively due to the thin nature of the absent tissue. The development of an ILM rip may correlate with progressive loss of vision preoperatively.

**CONCLUSIONS:** ILM avulsions in eyes with visually significant ERMs are common. It is unknown how often ILM avulsions occur with posterior vitreous detachments since the reliable identification is not possible with SD-OCT imaging, and is only seen when the ILM is stained during vitreous surgery. This potentially selects the more significant ERMs for analysis. Absent strips of ILM often provide a convenient area to begin the membrane peeling. It is hypothesized that the avulsion of the ILM may be the inciting event in the subsequent development of an epiretinal membrane based on histologic evidence of ERM growth from areas of perivascular ILM absence. Eyes with PVDs unassociated with ILM avulsions may be at a lower risk of ERM formation. Ideally the clinical identification of ILM avulsions at the time of the vitreous detachment may determine the patient’s risk for ERM development.
Increased Vitreopapillary Traction in Eyes with Small Optic Nerves May Contribute to the Development of Non-arteritic Ischemic Optic Neuropathy

Tongalp Tezel, MD
New York, NY

Purpose: To investigate the role of vitreopapillary traction in the development of non-arteritic ischemic optic neuropathy (NAION) and to determine which anatomical features of the small discs make them susceptible to the development of optic nerve perfusion defects.

Methods: Anatomical features of the vitreopapillary interface was studied in 32 eyes with NAION using SD-OCT. High-resolution horizontal raster scans centered at the optic disc were obtained and analyzed using an image analysis software. Results were compared with two control groups consisting of age, sex and refraction-matched non-NAION patients with small optic discs (Control Group I: disc diameter:<1.1 mm and cup/disk ratio <0.2, 31 eyes) and individuals with normal sized optic disks (Control Group II, disc diameter:1.5-1.8 mm, 32 eyes).

Results: The rate of PVD over the macula was similar among study groups (NAION: 62.5%, Control I: 61.3% and Control II: 65.6%, p=0.93). However, posterior hyaloid remained attached over small discs at a significantly higher rate (NAION: 81.2%, Control I: 83.9% and Control II: 43.7%, p=0.0005). This was due to a higher rate of strong focal vitreopapillary adhesions (=vitreopapillary tufts) on small discs compared to normal sized discs (NAION: 72.2%, Control I: 58.7% and Control II: 19.1%, p=0.007). The optic density of these vitreopapillary tufts and their proximity to the underlying vessels suggested perivascular glia as their main contributor. Blood vessels under these vitreopapillary tufts were often distorted in NAION patients, indicating that vitreopapillary traction transduced by these tufts is strong enough to contort the vessel wall. Vitreopapillary tufts in eyes with NAION were gathered mostly just above the optic nerve vessels (NAION: 69% vs Control I: 3%, p=0.00001) and were associated with schisis of the optic nerve head glial matrix.

Conclusions: Small discs with small cups have stronger vitreopapillary attachments due to higher amounts of vitreopapillary tufts. As a result, a strong anteroposterior tractional force is exerted on a relatively smaller optic nerve surface by synergetic vitreous gel, especially after the release of the posterior hyaloid from the macula. This transduced mechanical force on the blood vessels can contort vessel wall, disrupt of the blood flow and make them amenable to thrombosis.
**Purpose:** To describe the early spectral-domain optical coherence tomography (SD-OCT) changes after spontaneous vitreomacular traction (VMT) release.

**Methods:** A retrospective single center case series was performed examining patients with recent onset spontaneous VMT release based on SD-OCT imaging. Patients were included if the time interval between the pre-VMT and post-VMT SD-OCT imaging was less than 3 months. Outcome measures included mean change in visual acuity and SD-OCT analysis of the changes in the vitreoretinal interface and retinal abnormalities pre-VMT to post-VMT release.

**Results:** A total of 13 eyes from 12 patients at a mean age of 67 years were included in the study. On average, the interval between the pre-release and post-release encounters was 30 ± 21.6 days (median, 28 days). Mean logMAR visual acuity pre-VMT release was 0.26 ± 0.25 (Snellen equivalent, 20/36). After VMT release the mean logMAR acuity improved to 0.10 ± 0.09 (Snellen equivalent, 20/25, \( P = 0.08 \)). The ellipsoid zone had focal areas of disruption in 8 eyes (62%) before release, which resolved in 4 eyes after release (\( P = 0.24 \)). Disruption of the external limiting membrane was present in 7 eyes (54%) before release, which resolved in 5 eyes after release (\( P = 0.097 \)). Intraretinal cysts were present in 11 eyes (85%) before release, and had resolved in 8 eyes after release (\( P = 0.0048 \)). Subretinal fluid was present in one eye (8%) before release, which resolved after release (\( P > 0.99 \)). There were no instances of new or worsening SD-OCT changes observed after spontaneous VMT release.

**Conclusions:** Spontaneous release of VMT did not result in any new or worsening outer retinal changes on early SD-OCT imaging that were not already present beforehand. The majority of these changes, when present, resolved without further intervention during follow-up. No cases of diffuse ellipsoid zone disruption were noted as has been reported in ocriplasmin-induced VMT release. Moreover, patients recovered or maintained excellent visual acuity without any instances of severe vision loss. As a result, our findings lend support to the theory that the retinal dysfunction and anatomic abnormalities noted after ocriplasmin-induced VMT release are less likely to be due to the mechanical release itself and more likely to be due to a pharmacologic effect.
Efficacy and Safety Outcomes for Ocriplasmin Intravitreal Injection from Multiple Prospective Clinical Trials (MIVI-TRUST, OASIS, and ORBIT)

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Purpose: Ocriplasmin 125 µg has been studied in several large, prospective clinical studies. MIVI-TRUST were the 2 Phase III clinical trials that compared ocriplasmin to placebo injection and was used to obtain regulatory approval in 53 countries to date. OASIS was a Phase IIIb clinical trial that compared ocriplasmin to sham injection and was designed to follow patients for 24 months. ORBIT was a Phase IV observational study designed to collect real-world clinical data on ocriplasmin use in the United States.

Methods: Altogether, 1151 patients with symptomatic vitreomacular adhesion (VMA) were enrolled in the clinical trials. Patients were treated with a single injection of ocriplasmin 125 µg and were followed for 6 to 24 months. The primary endpoint of all 3 studies was pharmacological VMA resolution at 1 month.

Results: VMA resolution at 1 month was 26.5% in the MIVI-TRUST trials. Several patient baseline characteristics (including no epiretinal membrane (ERM), focal adhesions ≤1500 µm, and full thickness macular holes ≤400 µm) were identified to increase ocriplasmin efficacy. The OASIS and ORBIT studies confirmed these findings, with efficacy at approximately 40-60% at 1 month in these patients without ERM, with focal adhesions and with small macular holes. The safety profile for all studies was consistent, with the most common adverse drug reactions (ADRs) being vitreous floaters and photopsia. Most ADRs were non-serious, mild in severity, and occurred between 0 to 7 days post-injection.

Conclusions: Efficacy results from these large, prospective clinical trials illustrate the importance of patient selection when treating with ocriplasmin, and support a consistent safety profile between studies.
Macula Society Collaborative Retrospective Study of Ocriplasmin for Vitreomacular Traction

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Purpose: To assess anatomic and visual outcomes of ocriplasmin for treatment of vitreomacular traction (VMT).

Methods: Macula Society members were surveyed online to retrospectively collect data on patients receiving ocriplasmin for VMT. Clinical findings, optical coherence tomography (OCT) parameters, change in visual acuity, and adverse events were collected online using standardized forms.

Results: A total of 223 eyes (223 patients) with VMT received ocriplasmin. Of these, 208 eyes (208 patients) had a follow-up of at least 4 weeks and those serve as the group for analysis. At baseline, of the 208 eyes, a full-thickness macular hole (MH) was present in 75 eyes (36%) and a lamellar hole was present in 41 eyes (20%). VMT adherence was focal (<1500 µ) in 179 (86%) eyes, broad in 9 eyes (4%) and not reported in 20 (10%) eyes. Follow-up ranged from 4 weeks to 18 months. Of the 204 eyes with at least one visit by 12 weeks, vitrectomy (PPVx) was performed in 12 (6%) by 4 weeks and in 31 (15%) by 12 weeks. Sixty-four eyes (31%) underwent vitrectomy by the last visit. VMT resolved in 83 of 191 (44%) eyes by 12 weeks with ocriplasmin alone; VMT resolved in 148 (74%) eyes by the last visit, including eyes undergoing PPVx. Among eyes with a MH at baseline and at least one visit up to the specified time point, MH closure was achieved with ocriplasmin alone in 10 of 65 eyes (15%) by one week, 26 of 74 eyes (35%) by 4 weeks and 30 eyes (40%) at the last visit. Including eyes that underwent PPVx, at the last visit, 65 eyes (87%) had MH closure. There was no association between rate of closure and MH size. Overall mean change in visual acuity at the last recorded visit compared to the baseline visual acuity was -0.06±0.40 logMAR, which represents a small improvement in vision (P = 0.03). Among the 198 participants with at least one visual acuity measurement, at the last visit visual acuity improved by at least 2 lines in 69 eyes (35%) and by at least 3 lines in 54 eyes (27%). Visual acuity decreased by at least 2 lines in 35 eyes (18%) and by 3 lines in 27 eyes (14%) at the final visit. Complications included photopsias (15%), dimness of vision (14%), decreased color vision (10%), MH development (5%), macular RPE atrophy (2.7%), retinal detachment (1.9%) and retinal tear (1.4%). No cases of endophthalmitis were reported.

Conclusions: Ocriplasmin resulted in release of VMT in 45% of eyes and closure of MH in 40% without PPVx with stable or improved visual acuity in many eyes but with a visual acuity decrease in approximately 20%. Reported adverse events were not infrequent and suggest caution when considering use of ocriplasmin.
PHARMACOLOGIC CLOSURE RATE OF FULL THICKNESS MACULAR HOLE WITH OCRIPLASMIN

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PURPOSE: To analyze a single center’s experience with ocriplasmin for pharmacologic full-thickness macular hole (FTMH) closure associated with vitreomacular traction (VMT).

METHODS: Single center retrospective study of 33 eyes that received intravitreal ocriplasmin for symptomatic FTMH with VMT. VMT release, FTMH closure, visual acuity changes, and anatomical characteristics on spectral domain optical coherence tomography (SD-OCT) were analyzed.

RESULTS: All eyes injected with ocriplasmin had focal VMT. FTMH size measured ≤250 µM in 18/33 (55%) eyes, 250-400 µM in 11/33 (33%) eyes, and >400 µM in 4/33 (12%) eyes. Nonsurgical closure of FTMH was achieved in 12/33 (36%) eyes, and 20/33 (61%) eyes had VMT release. On average, eyes achieved pharmacologic FTMH closure within 20 days (range 4-32 days, with one occurring at 76 days) and pharmacologic VMT release within 16 days (range 3-76 days). Of eyes that had FTMH closure, 9/12 (75%) eyes had baseline FTMH size ≤250 µM and 3/12 (25%) eyes had baseline FTMH size of 200-400 µM. Subsequent vitrectomy for FTMH closure was performed in 20/21 (95%) eyes at an average of 50 days (range 12-182 days) after receiving ocriplasmin. Mean logMAR best-corrected visual acuity (BCVA) improved from 0.90 (20/159) at baseline to 0.40 (20/50) at final follow-up (p<0.0001, mean 13.4 months follow-up). Overall average FTMH diameter in eyes that did not experience pharmacologic closure did not vary significantly from time of injection (293 µm) to 1 month follow-up (326 µm). Ellipsoid changes occurred in 16/33 eyes (48%), resolving in all eyes at an average of 35 days (range 10-87 days). At final follow-up (mean 13.4 months), 29/33 (88%) of patients experienced an increase of two or more lines of vision, while 25/33 (76%) experienced an increase in three or more lines of vision. Out of 33 patients, none experienced a decline in two or more lines of vision at time of final follow-up.

CONCLUSIONS: In clinical practice, ocriplasmin achieved VMT release in 61% of treated eyes, with a 36% closure rate for FTMH. All 33 patients in this series experienced stability or improvement in vision at final follow-up, and ocriplasmin was not associated with widening of FTMH.
Macular Hole Enlargement after Ocriplasmin Injection for Full-thickness Macular Hole

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Purpose: Ocriplasmin, approved as a pharmaceutical agent to promote vitreolysis of vitreomacular adhesion (VMA) and enable macular hole (MH) closure, may have adverse events, such as macular hole enlargement with failure to close the macular hole. Herein, we report a consecutive series of eyes with full-thickness macular holes (FTMH) treated with intravitreal ocriplasmin in order to assess the frequency and long-term visual impact of macular hole enlargement after ocriplasmin injection.

Methods: Retrospective review of 22 eyes with symptomatic VMA and FTMH associated with vision loss and anatomic macular distortion. Each eye was treated with a pars plana injection of ocriplasmin (125mcg in 0.1cc) and assessed at 1 week and 1 month post-injection using OCT, with a minimum follow-up of 6 months.

Results: Initial enlargement in MH width after injection occurred in 64% of FTMH eyes. 50% of stage 2 holes and 88% of stage 3 holes enlarged. 100% of eyes with MH enlargement required surgical MH closure versus 12.5% in those without MH enlargement (p=0.001). MH enlargement was not significantly associated with differences in age, VMA width, MH width, photopsia, dyschromatopsia or MH stage. Mean pre-injection visual acuity (VA) was no different between eyes with or without MH enlargement post-injection. Mean follow-up (FU) was 19.7 months. Visual acuity was significantly worse in MH-enlarged eyes than in eyes without MH enlargement at all stages of FU (p<0.02). At 6 months, VA was 20/37 for eyes without MH enlargement versus 20/94 in eyes with MH enlargement (p=0.016). At 12 months, VA was 20/46 for eyes without MH enlargement versus 20/117 in eyes with MH enlargement (p=0.021). At last FU, VA was 20/35 for eyes without MH enlargement versus 20/91 in eyes with MH enlargement (p=0.002).

Conclusions: Ocriplasmin may effectively achieve vitreomacular separation in eyes with symptomatic VMA and FTMH. However, MH enlargement may increase the likelihood of requiring surgical intervention and negatively impact final VA. An understanding of potential complications and appropriate patient expectations are vital in the management of symptomatic VMA with ocriplasmin.
**Lamellar Macular Hole: Two Distinct Clinical Entities?**

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**PURPOSE:** To investigate whether lamellar macular holes can be divided into different subgroups.

**METHODS:** In this institutional study, clinical charts and Spectral-Domain Optical Coherence Tomography (OCT) images of 102 eyes of 90 consecutive patients diagnosed with lamellar macular hole were reviewed.

In OCT imaging, the presence of lamellar macular hole was defined according to the following findings: presence of irregular foveal contour, separation of the layers of the neurosensory retina, and the absence of full thickness macular defect.

Mean outcome was the morphological and functional characterization of different subtypes of macular hole.

**RESULTS:** Two different subtypes of lamellar macular hole were identified: tractional and degenerative. The first type, tractional, was diagnosed in 43 eyes, and was characterized by the schisic separation of neurosensory retina between outer plexiform and outer nuclear layers. It often presented with an intact ellipsoidal layer and was associated with tractional epiretinal membranes and/or vitreo-macular traction. The second type, degenerative, was diagnosed in 48 eyes, and its distinctive traits included the presence of intra-retinal cavitation that could affect all retinal layers. It was often associated with non-tractional epiretinal proliferation and a retinal “bump”. Moreover, it often presented with early ellipsoidal zone defect and its pathogenesis, although chronic, and progressive remains poorly understood.

Finally, 11 eyes shared common features with both tractional and degenerative lamellar macular holes and were classified as mixed lesions.

**CONCLUSIONS:** Degenerative and tractional lamellar macular holes are two distinct clinical entities. A revision of the current concept of lamellar macular holes is needed.
Yellow Micropulse Laser vs. Photodynamic Therapy in Eyes with Chronic Central Serous Chorioretinopathy Results of the Pan American Collaborative Retina Study (PACORES) Group

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PURPOSE: To compare the functional and anatomical outcomes of eyes with chronic central serous chorioretinopathy treated with yellow micropulse (MP) laser vs. photodynamic therapy (PDT).

METHODS: A multicenter retrospective comparative study of 53 eyes treated with yellow MP laser and 30 eyes treated with PDT. MP laser treatment consisted of a duty cycle of 5%, the spot size varied from 100 to 200 µm, power varied from 320 to 660 mW and the pulse duration was 200 ms. PDT treatment consisted of half dose verteporfin (3mg/m2) infused over 15 min followed by laser activation for 40 seconds. Spot sizes varied from 400 to 2000 µm.

RESULTS: At baseline, the mean age (40.3±9.2 vs. 43.9±13.3 yrs), mean duration of symptoms prior to treatment (9.8±11.9 vs. 20.8±27.5 months), mean central macular thickness (429±73 vs. 470±170 µm), mean subfoveal choroidal thickness (329±94 vs. 297±38 µm) and mean best corrected visual acuity (logMAR 0.29±0.28 vs. 0.44±0.40) did not differ statistically between the MP and PDT groups respectively. At 12 months, the best corrected visual acuity was logMAR 0.19±0.25 in the MP group (p<0.0001 compared to baseline) and 0.47±0.37 in the PDT group (p=0.4820 compared to baseline); the CMT in the MP group was 284±66 (p<0.0001 compared to baseline) and 247±84 µm (p<0.0001 compared to baseline) in the PDT group; and the subfoveal choroidal thickness in the MP group was 429±70 (p=0.0937 compared to baseline) and 335±70 µm (p<0.0001 compared to baseline) in the PDT group.

CONCLUSIONS: Both PDT and MP are effective in restoring the macular anatomy. However it appears that yellow MP laser has a more beneficial effect in visual acuity than PDT.
Analysis of Intravitreal Levels of Neurotrophins in Diabetic Retinopathy

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Purpose: Diabetic retinopathy is a disease of progressive vascular-neurodegeneration. The neurotrophin family includes nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4). Neurotrophins are a group of growth factors that play a critical role in the development, survival, maintenance, and repair of the nervous system, as well as play essential roles in angiogenesis and fibrosis through action of their receptor, p75NTR. Hypoxic conditions cause an upregulation of the neurotrophin receptor, resulting in an upregulation of proangiogenic factors. Knockdown of the neurotrophin receptor has been shown to restore the upregulation of pro-angiogenic factors, causing a nearly one-third reduction in local vascular endothelial growth factor (VEGF) levels. Neurotrophin levels have been shown to be elevated in vitreous samples in animal studies with induced proliferative diabetic retinopathy, however human studies are lacking. We assayed the human vitreous in an attempt to further investigate the effect of diabetic retinopathy on several neurotrophin levels.

Methods: Prospective study comparing various intravitreal neurotrophin levels in patients with diabetic retinopathy compared to patients without diabetes. The indications for vitrectomy were rhegmatogenous and tractional retinal detachment, non-clearing vitreous hemorrhage, and epiretinal membrane peel. Quantitative analysis was determined using neurotrophins ELISA.

Results: A total of 50 vitreous samples from 50 eyes were collected. 22 patients had diabetic retinopathy and 28 samples were collected from non-diabetic controls. Of patients with diabetic retinopathy at the time of vitrectomy, 3 had mild non-proliferative diabetic retinopathy, 4 had moderate non-proliferative diabetic retinopathy, 3 had severe non-proliferative diabetic retinopathy, and 12 had proliferative diabetic retinopathy. Our analysis showed that neurotrophins, including NGF, BDNF, NT-3, NT-4, CNTF, and GDNF, were present in all vitreous samples of diabetic retinopathy eyes and each at a lower concentration in non-diabetic eyes. There was a significant increase in levels of NGF (p=0.0001), BDNF (p=0.0091), NT-3 (p<0.0001), NT-4 (p=0.0001), CNTF (p=0.0001), and GDNF (p=0.0079) in eyes with diabetic retinopathy compared to non-diabetic eyes.

Conclusions: Our study is the first to show the elevated presence of various neurotrophins in the human vitreous in diabetic retinopathy.
ASSOCIATION BETWEEN BASELINE CHARACTERISTICS AND CHANGES IN DIABETIC RETINOPTHACY SEVERITY SCALE (DRSS) SCORE: ANALYSES FROM THE VISTA AND VIVID STUDIES

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PURPOSE: To evaluate the influence of baseline characteristics on improvement of DRSS scores at week 100 compared with baseline.

METHODS: VISTA and VIVID were phase 3 trials randomizing 466 and 406 DME patients, respectively, to receive intravitreal aflibercept injection (IAI) 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks following 5 monthly doses (2q8), or macular laser photocoagulation. Change in DRSS score was an exploratory endpoint at week 100. The aim of this ad hoc analysis was to determine, using observed data, what factors influenced ≥2-step improvement in DRSS scores at week 100. Factors considered were baseline age, gender, race, HbA1c level, duration of diabetes, best-corrected visual acuity (BCVA), central retinal thickness (CRT), and baseline DRSS score. Regression analysis was used to determine the impact of these factors.

RESULTS: In the integrated VIVID and VISTA studies, 10.2%, 34.7% (p = .0018), and 38.5% (p < .001) of laser, 2q4, and 2q8 patients, respectively, experienced a ≥2-step improvement in DRSS score at week 100 compared with baseline. Baseline DRSS score was the only factor significantly associated with ≥2-step DRSS score improvement (p < .0001). Age, gender, race, HbA1c level, duration of diabetes, BCVA and CRT did not have an impact on the ability to gain ≥2-step improvement in DRSS score. 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.

CONCLUSIONS: Overall, a significant proportion of patients in the VIVID and VISTA trials experienced at least a 2-step improvement in DRSS score at week 100. Baseline DRSS score was the most significant identified factor associated with ≥2-step improvement in DRSS score at week 100.
Visual and Anatomic Outcomes Before and After Cataract Surgery in Patients Treated for Diabetic Macular Edema (DME) in the VISTA and VIVID Studies

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Purpose: To evaluate the effect of cataract surgery on visual and anatomic outcomes in patients with DME treated with intravitreal aflibercept injection (IAI) or laser in VISTA and VIVID.

Methods: VISTA and VIVID, two similarly designed phase 3 trials, treated 461 and 404 DME patients, respectively, with IAI 2 mg q4 weeks (2q4), IAI 2 mg q8 weeks following 5 monthly doses (2q8), or laser through week 100. Starting at week 24, if rescue treatment criteria were met, IAI patients received laser, and laser patients received IAI 2q8 (following 5 monthly doses). Best-corrected visual acuity (BCVA) and central retinal thickness (CRT) were assessed monthly for two years. A post-hoc analysis evaluated the impact of cataract surgery on BCVA and CRT in the laser and combined IAI groups. Only patients who did not receive rescue treatment were included in this analysis.

Results: Cataract surgeries were performed in the study eye of 27 and 54 laser and IAI patients, respectively. The corresponding numbers after excluding patients who received rescue therapy were 16 and 49 surgeries. At the first study visit post-op, the mean BCVA gains from the last visit pre-op was 9.3 letters (69.4 vs. 60.2 letters) for laser patients and 10.1 letters (67.3 vs. 57.2 letters) for IAI patients. The corresponding gains at the first study visit at least 30 days post-op were 8.5 letters (70.0 vs. 61.5 letters) for laser patients and 12.4 letters (69.4 vs. 57.0 letters) for IAI patients. At the first study visit post-op, the mean CRT changes from the last visit pre-op was -3.4 µm (409.6 vs. 413.0 µm) for laser patients and +53.3 µm (356.2 vs. 302.9 µm) for IAI patients. The corresponding changes at the first study visit at least 30 days post-op were +22.9 µm (417.1 vs. 394.2 µm) for laser patients and +55.9 µm (359.4 vs. 303.5 µm) for IAI patients.

Conclusions: Overall, visual gains were observed in patients treated with laser or IAI following cataract surgery. Despite a modest increase in CRT, BCVA gains were numerically higher for patients treated with IAI as compared to laser in this short-term post-hoc analysis.
Change in Retinal Perfusion Status in Patients Treated for Diabetic Macular Edema (DME) in the VISTA Study

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Purpose: To evaluate change from baseline in retinal perfusion status in patients with DME treated with intravitreal aflibercept injection (IAI) or macular laser in VISTA.

Methods: VISTA, a double-masked, randomized, active-controlled phase 3 trial, treated 461 DME patients with IAI 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks following 5 monthly doses (2q8), or laser through week 100. Starting at week 24, if rescue treatment criteria were met, IAI patients received laser, and laser patients received IAI 2q8. Retinal perfusion status was evaluated by fluorescein angiography based on presence or absence of retinal non-perfusion in each quadrant by an independent, masked reading center. Post hoc analyses assessed perfusion status through week 100 as well as change from baseline in perfusion status: improvement (decreased number of quadrants with non-perfusion) or worsening (increased number of quadrants with non-perfusion). Laser patients who received IAI rescue treatment were censored at time of rescue.

Results: At baseline, the proportion of patients with zero quadrants of non-perfusion in the laser, 2q4, and 2q8 groups were 17%, 28%, and 23%, respectively. At week 100, 6%, 43%, and 35% of patients in the laser, 2q4, and 2q8 groups, respectively, demonstrated zero quadrants of non-perfusion. Improvement in perfusion status from baseline at week 24 was observed in 3%, 27%, and 20% of the patients in the laser, 2q4, and 2q8 groups, respectively. Corresponding proportions at week 100 were 15%, 45%, and 40%. Worsening in perfusion status from baseline at week 24 was observed in 15%, 12%, and 10% in the laser, 2q4, and 2q8 groups, respectively. Corresponding proportions at week 100 were 25%, 9%, and 9%.

Conclusions: A greater proportion of DME patients treated with IAI demonstrated the absence of retinal non-perfusion at week 100 compared to those treated with laser. Additionally, IAI-treated patients demonstrated greater improvement and less worsening of retinal perfusion compared to laser treated patients.
Randomized Trial Comparing Ranibizumab Monthly to Treat and Extend with and without Angiography-guided Laser for DME: TREX-DME 1 Year Outcomes

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Purpose: To compare the efficacy of a treat & extend algorithm using ranibizumab 0.3 mg with and without angiography-guided macular laser photoocoagulation to monthly dosing of ranibizumab 0.3 mg for center-involving diabetic macular edema (DME).

Methods: This is a multicenter, prospective, randomized trial of 150 eyes randomized 1:2:2 into one of three cohorts: Monthly (n=30), TREAT and Extend without macular laser photoocoagulation (TREX; n=60), and treat and extend with angiography-Guided macular LAser photoocoagulation (GILA; n=60). In the TREX and GILA cohorts, eyes underwent 4 monthly injections of 0.3 mg ranibizumab followed by a treat & extend algorithm based on disease activity. Eyes in the GILA cohort also received angiography-guided macular laser photoocoagulation at month 1 and again every 3 months if microaneurysm-associated leakage was present.

Results: Baseline demographics, including duration of diabetes, insulin usage, body mass index, retinopathy severity, best corrected visual acuity (BCVA), and central retinal thickness (CRT) were well balanced between the cohorts. 137 eyes (91%) completed the 1 year end-point visit. At 1 year, the mean BCVA improved by 8.6, 9.6, 9.5 letters in the Monthly, TREX and GILA cohorts, respectively (p=0.8). Likewise, CRT improved by 123, 146 and 166 µm, in the Monthly, TREX, GILA cohorts, respectively (p=0.47). The mean number of macular laser treatments in the GILA cohort at 1 year was 2.9 (range=1-4). Treatment burden, defined as the number of injections through 1 year, was significantly reduced in TREX (10.7) and GILA (10.1) compared to the Monthly cohort (13.1, p<0.001). Furthermore, there was a trend towards statistical significance between the mean maximum interval at month 12 for the TREX and GILA cohorts (8.1 versus 9.2 weeks, respectively; p=0.104). There were no cases of endophthalmitis, and the total incidence of Anti-Platelet Trialists’ Collaboration (APTC) events was 4.0%.

Conclusions: This large, prospective, randomized trial, found that treat & extend dosing of ranibizumab 0.3 mg with and without angiography-guided macular laser photoocoagulation significantly decreased treatment burden while providing similar visual and anatomic outcomes compared to monthly dosing at 1 year.
Predicting Visual Acuity Response to Anti-VEGF DME Therapy in Protocol I: A Post-hoc Analysis of Outcomes in Patients with Limited (<5 Letter) and Intermediate (5-9 Letter) Response at 12 Weeks

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Purpose: In pivotal anti-VEGF randomized trials, 30–50% of DME patients failed to have optimal vision response, gaining <10 letters at 2-3 years. Early prediction of anti-VEGF response may facilitate timely consideration of additional therapies, for patients unlikely to achieve optimal BCVA response over time. This analysis assessed long-term BCVA outcomes at years 1-3, in patients with limited or intermediate BCVA response to ranibizumab at week 12.

Methods: A post-hoc analysis of the DRCRnet Protocol I data was conducted that included DME patients randomized to ranibizumab+deferred or prompt laser. Patients were stratified by observed BCVA response at week 12 into three cohorts: <5 letters, 5-9 letters, and ≥10 letters improvement. Visual acuity outcomes, measured by mean BCVA change from baseline (CFB) and proportion of ≥10-letter gainers at 1 and 3 years, were evaluated.

Results: Three-hundred-forty patients met inclusion criteria. At week 12, 135 (39.7%) patients showed limited early response (<5 letters improvement), 79 (23.2%) patients had intermediate early response (5-9 letters improvement), and 126 (37.1%) patients had strong early response (≥10 letters improvement). Differences in mean BCVA CFB at week 12 (-0.3, +6.9 and +15.2; p<0.001) remained evident at week 52 (+2.8, +8.2 and +16.5, p<0.001) and week 156 (+3.0, +8.2 and +13.8; p<0.001). Controlling for potential confounders, a significant association remained between BCVA response at week 12 and BCVA response at weeks 52 and 156 (p<0.001 for both). The majority of limited and intermediate early responders (77.0% and 55.7%) failed to gain ≥10 letters from baseline by week 52, with mean BCVA CFB at week 156 for these patients of 1.2 and 4.8 letters, respectively. Moreover, among intermediate early responders, 27.8% regressed to <5 letters improved from baseline by week 156.

Conclusions: Long-term BCVA response to ranibizumab in DME can be predicted after 12 weeks. In this analysis, 71.1% of limited early responders failed to show strong BCVA response at study end. In these patients, additional therapies with alternative modes of action may be considered early. Intermediate early responders were more likely to show strong response by study end (48.1%), but there remains an unmet need for a substantial proportion of these patients.
Quantifying Microvascular Density and Morphology in Diabetic Retinopathy Using Spectral Domain Optical Coherence Tomography Angiography (SD-OCTA)

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Purpose: To quantify changes in retinal microvasculature in diabetic retinopathy (DR) using SD-OCTA.

Methods: Retrospective, cross-sectional, observational study of healthy and diabetic adult subjects with and without DR. Retinal microvascular changes were assessed using SD-OCTA images and an intensity-based optical microangiography (OMAG) algorithm. A semi-automated program was used to calculate indices of microvascular density and morphology in non-segmented and segmented SD-OCTA images. Microvascular density was quantified using skeleton density (SD) and vessel density (VD) while vessel morphology was quantified as fractal dimension (FD) and vessel diameter index (VDI). Statistical analyses were performed using the Student’s t-test or analysis of variance with post hoc Tukey Honest Significant Difference tests for multiple comparisons.

Results: Eighty-four eyes with DR and 14 healthy eyes were studied. Spearman’s rank test demonstrated a negative correlation between DR severity and SD, VD, and FD, and a positive correlation with VDI (rho = -0.767, -0.7166, -0.768, and +0.5051, respectively; P < 0.0001). All parameters showed high reproducibility between graders (ICC = 0.971, 0.962, 0.937, and 0.994 for SD, VD, FD, and VDI respectively). Repeatability (k) was greater than 0.99 for SD, VD, FD, and VDI.

Conclusions: Vascular changes in DR can be objectively and reliably characterized using SD, VD, FD and VDI. In general, decreasing capillary density (SD and VD), branching complexity (FD), and increasing vascular caliber (VDI) were associated with worsening DR. Changes in capillary density and morphology were significantly correlated with diabetic macular edema. OCTA of the central 3mm of the macula may serve as a useful biomarker of diabetic retinopathy severity.
Distribution of Hemorrhages and/or Microaneurysms (H/Ma) Identified on Ultra-wide Field (UWF) Retinal Images and the Risk of Progression Over 4 Years

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Purpose: To determine the association between distribution of hemorrhages and/or microaneurysms (H/Ma) identified on ultra-wide field (UWF) retinal images and risk of diabetic retinopathy (DR) progression over 4 years.

Methods: Single-site prospective 4-year longitudinal study. Eyes with no to moderate nonproliferative DR (NPDR) on ETDRS photography were evaluated. ETDRS photos and UWF imaging were acquired using standardized protocols at the same visit. H/Ma counts in ETDRS fields and in UWF areas not covered by ETDRS photos were performed. A ratio of H/Ma counts outside to H/Ma counts within the ETDRS fields was calculated, with a ratio >1.4 representing 75th percentile and termed a predominantly peripheral H/Ma distribution (PPL-HMA), with ≤1.4 termed posterior distribution (Post-HMA). Follow-up ETDRS photos were acquired and evaluated at 4 years.

Results: One hundred twenty-six eyes were evaluated [24 (19%) no DR, 48 (38%) mild and 54 (43%) moderate NPDR]. Similar numbers of H/Ma were identified in ETDRS photos compared to the same ETDRS area in UWF images (ETDRS 43 vs. UWF-ETDRS 49, p<0.100). Additional 21 H/Ma (50% increase) were identified in the peripheral-UWF fields, suggesting greater H/Ma severity in 16 (13%) eyes. Follow-up 4 year ETDRS photos were acquired in 37 (77.1%) eyes with mild and 43 (79.6%) eyes with moderate NPDR. Among eyes with mild NPDR, 9 (24.3%) had PPL-H/Ma and 28 (75.7%) Post-HMA. DR severity progression (≥2 step) with PPL-HMA was 22.2% (2 eyes developed PDR, H/Ma ratio 3.45 and 2.73) vs. 0% with Post-HMA. Among eyes with moderate NPDR, 23 (53.5%) eyes had H/Ma count ≥100 while 20 (46.5%) eyes had <100. With H/Ma counts of ≥100, ≥2 step progression was 39.1% compared to 5% in eyes with H/Ma count <100 (p=0.008).

Conclusions: UWF images identify ~50% more H/Ma than ETDRS photos, suggesting more severe H/Ma severity in ~13% of eyes. More peripheral H/Ma and higher counts were associated with greater progression. If these early findings are validated in larger studies, H/Ma counts and peripheral:posterior H/Ma ratios may prove to be sensitive markers of DR progression.
Safety and Efficacy of Intravitreal Ranibizumab for Diabetic Macular Edema in Eyes Previously Treated with Intravitreal Bevacizumab: A Randomized Dual-arm Comparative Dosing Trial. The REACT Study

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**PURPOSE:** Anti-VEGF therapy has emerged as a first-line therapy for the management of DME. Limited studies have evaluated the impact of switching between anti-VEGF agents. The purpose of this study was to examine the impact of switching to ranibizumab from bevacizumab in treatment-resistant DME.

**METHODS:** REACT is an IRB-approved investigator sponsored study. Key inclusion criteria included persistent foveal fluid on SD-OCT, a minimum of 6 bevacizumab injections within 12 months, a minimum of 2 bevacizumab injections within 10 weeks, and a minimum of 1 bevacizumab within 6 weeks of enrollment. All eyes had a best corrected ETDRS visual acuity (BCVA) from 20/25 to 20/320 in the study eye. Subjects were randomized between 2 groups: monthly ranibizumab (Group 1) and a treat-and-extend ranibizumab (Group 2) after 3 monthly mandated injections. The overall study cohort was assessed as well as within the 2 groups. Key outcome measures included mean change in BCVA, mean change in central subfield thickness (CST) on OCT, proportion of eyes gaining at least 10 letters, proportion of eyes gaining at least 15 letters, proportion of eyes losing at least 15 letters, and number of injections. The study duration was 12 months.

**RESULTS:** Twenty-seven eyes were enrolled (15 in group 1 and 12 in group 2). The mean number bevacizumab injections prior to enrollment was 8.6 (range: 6-20). For the overall cohort, the mean change in BCVA was +4.5 letters (p = 0.02). Eleven percent of eyes gained 3 lines or more, 19% gained 2 lines or more, and 4% of eyes lost 3 lines or more. There was a significant reduction in CST of 100 microns (p = 0.005). The mean number of injections was 9.8. There were no differences between the two groups for any of the key parameters. Three subjects (11%) experienced serious adverse events, including an ischemic stroke and 2 hospitalizations.

**CONCLUSIONS:** Switching to ranibizumab in eyes previously treated with bevacizumab resulted in both functional and anatomic improvements. There was no difference between parameters when comparing treat-and-extend and monthly treatment regimen.
Ranibizumab (0.3 mg) for Persistent Diabetic Macular Edema After Recent, Frequent and Chronic Bevacizumab: 1 Year Rotate Trial Results

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Purpose: To evaluate the safety and efficacy of 0.3 mg ranibizumab in eyes with persistent DME after recent, chronic and frequent bevacizumab.

Methods: Open-label, prospective study of 0.3 mg ranibizumab for eyes with persistent DME after bevacizumab. Thirty eyes from 22 patients were randomized in a 1:2 ratio to a Sustained group (12 monthly mandatory intravitreal 0.3 mg ranibizumab injections), or a PRn group (6 monthly mandatory intravitreal 0.3 mg ranibizumab injections, followed by criteria-based PRn dosing).

Results: At baseline, mean best-corrected visual acuity was 63 ETDRS letters (20/63) in both groups and mean baseline CST was 400um and 453um in the Sustained and PRN groups, respectively. At 12 months, mean best corrected visual acuity was 70 ETDRS letters (Snellen equivalent 20/40) in both groups and the mean CST was 307um and 331um in the Sustained and PRN groups, respectively. Average visual acuity gain was 6.5 letters overall with a gain of 6.7 and 6.4 in the Sustained and PRN groups, respectively (p= 0.466). At M12, the mean overall decrease in CST thickness was 116um overall, with 92 um and 127 um decrease in the sustained and PRN groups respectively (p=0.259). Adverse events included 2 deaths, one patient with multiple comorbidities (renal failure, cirrhosis, and pulmonary congestion secondary to right heart failure), myocardial infarction in one patient, elevated blood pressure (2 patients), and mild posterior subcapsular cataracts in 2 eyes. No endophthalmitis, retinal tears, detachments, or vitreous hemorrhages were observed.

Conclusions: Ranibizumab 0.3 mg may provide additional efficacy in eyes with persistent DME after bevacizumab, and demonstrated improved visual and anatomic outcomes in patients with DME. No statistically significant differences in outcomes were evident between the two dosing regimens.
Conversion to Aflibercept after Prior Anti-VEGF Therapy for Persistent Diabetic Macular Edema

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Purpose: To evaluate the short-term functional and anatomic outcomes of patients with persistent diabetic macular edema (DME) who were converted from bevacizumab and/or ranibizumab to aflibercept.

Methods: Retrospective, interventional, noncomparative, consecutive case series. Only eyes treated with at least 4 consecutive injections of ranibizumab/bevacizumab spaced 4-6 weeks apart prior to conversion and with at least 2 aflibercept injections afterward were considered for inclusion. Pertinent patient demographic, examination, and treatment data were extracted from clinical charts and tabulated for analysis.

Results: Fifty eyes of 37 patients were included. Eyes received a mean of 13.7 bevacizumab/ranibizumab injections prior to conversion, followed by 4.1 aflibercept injections over 4.6 months of subsequent follow-up. The mean logMAR visual acuity at the pre-switch visit was 0.60 ± 0.43 (Snellen equivalent, 20/80). This improved to 0.55 ± 0.48 (Snellen equivalent, 20/70) by the second visit after conversion, corresponding to a mean logMAR change of -0.05 ± 0.22 (P = .12). The average central macular thickness from the pre-switch spectral-domain optical coherence tomography scan was 459.2 ± 139.2 µm. This significantly improved to 348.7 ± 107.8 µm by the second visit following conversion, reflecting a mean decrease of 112 ± 141 µm (P < .0001). The mean intraocular pressure (IOP) recorded at the pre-switch visit was 15.1 ± 3.3 mm Hg. At the second follow-up after converting to aflibercept, the IOP averaged 14.9 ± 3.2 mm Hg, with a mean decrease of 0.2 ± 3.0 mm Hg (P = .63).

Conclusions: Conversion to aflibercept for persistent DME resulted in significant anatomic improvements. While trends towards improved visual acuity and reduction in IOP were observed, these were not statistically significant.
**Short-term Results of Fluocinolone Acetonide Intravitreal Implant for Diabetic Macular Edema in Highly Treated Eyes**

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**Purpose:** To determine the efficacy of 0.19 mg fluocinolone acetonide intravitreal implant on best-corrected visual acuity (BCVA), central retinal thickness (CRT) on optical coherence tomography, and intraocular pressure (IOP) in a cohort of treatment experienced patients with diabetic macular edema (DME).

**Methods:** Patients treated with fluocinolone acetonide for DME were identified at a retina only group practice. A retrospective chart review was performed. To be included, patients needed to receive a single fluocinolone acetonide implant, and have had prior treatment with one or more agents for DME (including bevacizumab, ranibizumab, triamcinolone or dexamethasone steroid implant). Data collected included age, gender, prior drug exposure, agent employed for steroid challenge, BCVA, CRT, and IOP prior to and subsequent to fluocinolone acetonide.

**Results:** Twenty-three eyes of 18 patients were included in the study cohort. The mean age was 69. Fourteen patients were female and four were male. Prior treatments included: 2 focal laser photocoagulation (13 eyes), 5 prior bevacizumab treatments (3 eyes), 11 prior ranibizumab treatments (11 eyes), 2 prior aflibercept treatments (1 eye), 3 prior intravitreal triamcinolone acetonide 4.0mg/0.1ml (iVTA) treatments (14 eyes), 1 prior sub-Tenon triamcinolone acetonide 40mg/1.0ml treatments (2 eyes), and 5 prior intravitreal dexamethasone steroid implants (21 eyes). Twenty-two of the 23 eyes were steroid challenged with intravitreal dexamethasone implant, and one eye was challenged with intravitreal triamcinolone acetonide. Average time of follow up was 169 days (range of 84-287 days) after fluocinolone acetonide. Average logMAR visual acuity was 0.566 at baseline and 0.51 at last follow up (P = 0.440). Average IOP was 17.65 mmHg at baseline and 17.96 mmHg at last follow up (P = 0.814). Average CRT was 404.61 µm at baseline and 286.43 µm at last follow up (P = 0.007).

**Conclusions:** Exposure to fluocinolone acetonide resulted in a statistically significant improvement in CRT in highly treatment experienced eyes with DME. There was no statistically significant change in intraocular pressure at the last follow up with prior negative steroid challenge. Nine-month follow up and an expanded cohort of 26 eyes are anticipated at the time of The Retina Society 2016 Annual Meeting.
Ranibizumab Induces Regression of Diabetic Retinopathy (DR) in Over 75% of Patients with Highest-risk Non-proliferative Diabetic Retinopathy (NPDR), Independent of Examined Baseline Characteristics

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**Purpose:** In RIDE and RISE, ranibizumab induced DR disease severity regression in a majority of patients with highest-risk NPDR at baseline (ETDRS diabetic retinopathy severity scale [DRSS] levels 47/53). We examined macular non-perfusion (MNP) outcomes and baseline predictors of DR improvement in these patients.

**Methods:** In the randomized phase III RIDE/RISE studies, patients with DR and DME (N=759) received monthly sham or ranibizumab (0.3-mg or 0.5-mg) injections for 24 months. Our retrospective analysis evaluated MNP status and DR outcomes over time in ranibizumab-treated patients with highest-risk NPDR (ETDRS-DRSS 47/53) at baseline. Potential baseline predictors of DR severity improvements were also examined.

**Results:** At baseline, 33% of patients had highest-risk NPDR and they were equally distributed among treatment groups. Over 75% of these patients treated with ranibizumab experienced ≥2-step DR improvements at months 12 and 24 compared with <12% of sham-treated patients. At month 24, <3% of ranibizumab-treated patients experienced ≥2-step DR worsening compared with 10% of sham-treated patients. Among patients with highest-risk NPDR at baseline, the proportion of patients with MNP remained relatively stable over time in both ranibizumab arms but increased in the sham arm. At baseline, 35.9%, 27.1%, and 28.9% of patients in the in ranibizumab 0.3-mg, ranibizumab 0.5-mg, and sham arms, respectively, had MNP (P=0.469). At month 24, respective rates of patients with MNP were 29.4%, 31.4%, and 57.8% (P=0.007). In patients in with highest-risk NPDR at baseline, baseline mean central foveal thickness (CFT), BCVA, and duration of diabetes were similar in patients who experienced ≥2-step DR improvement at month 24 and those who did not. These baseline characteristics were not predictive of ≥2-step DR improvement at month 24 (P>0.5).

**Conclusions:** Among RIDE and RISE patients with highest-risk NPDR at baseline, ranibizumab treatment resulted in statistically significant and clinically meaningful DR severity improvements in >75% of patients. In ranibizumab-treated patients, the proportion of patients with MNP remained stable throughout the trial, while MNP rates increased in sham-treated patients. DR reversal was independent of baseline values for CFT, BCVA, and diabetes duration, suggesting that these baseline characteristics may not be important when making treatment decisions for patients with DR with DME.
The Clinical Importance of Changes in Diabetic Retinopathy Severity Score

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Purpose: To investigate the clinical importance of changes in diabetic retinopathy severity score (DRSS) in eyes treated with intravitreal ranibizumab.

Methods: Post-hoc analysis of the Phase 3 RIDE/RISE studies of ranibizumab for the treatment of DME.

Results: The majority (57%) of eyes treated with ranibizumab experienced at least a 1 step improvement in DRSS from baseline to month 24. 40% had no change and 3% had DRSS worsening. Eyes with DRSS improvement or stability had a greater mean BCVA letter score change than eyes with DRSS worsening (+15.1, +14.2, +11.3, and +11.2 letters for ≥3-step, ≥2-step, 1-step improvement and no DRSS change, respectively) compared with +5.0 letters in patients who had any DRSS worsening. A BCVA letter score gain of ≥15 was more common in patients with a ≥2 or ≥3-step DRSS improvement (51.9% and 44.6%, respectively) compared with those with a 1-step DRSS improvement, no change, or worsening (37.9%, 39.6%, and 26.7%, respectively). A loss of ≥15 in BCVA letter score was more common in patients with any DRSS worsening (13.3%) compared with patients who had stable or improved DRSS (0 to 2.8%). Resolution of macular edema was more common in patients with DRSS improvement: 84.2%, 87.7%, and 92.3% of patients with 1-step, ≥2-step, and ≥3-step improvement in DRSS achieved CFT ≤250 µm, compared with only 65.2% and 53.3% of patients who had no DRSS change or any DR worsening.

Conclusions: Eyes with greater degrees of improvement in DRSS had superior functional and anatomic outcomes when compared with eyes that had lesser degrees of DRSS improvement or DRSS worsening. These findings suggest that change in DRSS is a clinically important outcome and a measure of treatment effectiveness which should be evaluated in future studies in diabetic eye disease.
Efficacy of Ranibizumab in Eyes with Diabetic Macular Edema and Macular Nonperfusion

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Purpose: To describe the relationship between macular nonperfusion (MNP) and vision outcomes in patients with diabetic macular edema (DME) treated with ranibizumab or sham in RIDE/RISE.

Methods: This was a retrospective subanalysis of RIDE/RISE, 2 randomized, controlled phase 3 studies that evaluated the safety/efficacy of ranibizumab 0.3 mg or 0.5 mg vs sham for treating DME. Presence and area of MNP were evaluated in study eyes (intent-to-treat) with BCVA and fluorescein angiogram data (pooled ranibizumab 0.3 mg and 0.5 mg, N=438; sham, N=228). MNP area was calculated as total disc areas (DA) of capillary loss on subfields of the ETDRS grid in the fundus fluorescein angiograms corresponding to field 2 of 7-field fundus photographs. Changes from baseline to Month (M) 12 and M24 in MNP status (worsening, no change, or improvement) and BCVA change by MNP status were evaluated.

Results: The proportion of ranibizumab-treated eyes with MNP remained stable through M24, but increased in sham-treated eyes (baseline, M12, M24, respectively: 26.9%, 20.1%, 25.2% for ranibizumab vs 26.3%, 35.5%, 43.1% for sham). Mean MNP area (DA) was similar for the two arms over time (baseline, M12, M24, respectively: 0.23, 0.17, 0.18 for ranibizumab vs 0.17, 0.22, 0.27 for sham). Eyes with MNP had lower mean baseline BCVA in both treatment arms (present vs absent, ranibizumab: 53.7 vs 58.0 letters; sham: 56.0 vs 57.9 letters). In the ranibizumab arm, mean BCVA gain from baseline at M12 and M24 was higher in study eyes with vs without MNP (M12, +14.6 vs +10.3 letters, P=0.0004; M24, +16.0 vs +12.1 letters, P=0.008). With ranibizumab, ≥2-step DR improvement was seen as early as M3 (n=51) and increased over time (n=117 at M24), regardless of change in MNP status.

Conclusions: Ranibizumab-treated eyes of DME patients with baseline MNP do not experience an increase in MNP area over sham; have worse baseline vision but gain more vision than those without baseline MNP, resulting in similar vision at M12/24; and achieve ≥2-step DR improvement regardless of MNP status. In conclusion, this analysis shows that DME patients with MNP at baseline benefit greatly from treatment with ranibizumab and should not be excluded from therapy.
Potential Beneficial Effect of Low Dose Danazol in Combination with Renin Angiotensin Inhibitors in Diabetic Macular Edema: Results of the Optimeyes Trial

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Purpose: To evaluate the efficacy and safety of low-dose danazol in diabetic macular edema (DME). In addition, to identify target patient populations in terms of Body Mass Index (BMI) and potential interactions or synergies between this medication and other systemic medications.

Methods: Phase 2 trial evaluating danazol 0.5mg, and 1mg vs placebo in patients with different body mass indices over a 12 week period, in terms of best corrected visual acuity (BCVA) improvements and reduction of OCT central field thickness (CFT).

Results: Four hundred twenty-five eyes were randomized into 3 groups. Patients were further randomized by body mass indices. Patients with body a mass index of 27-31 kg/m² showed 3.9 letter improvement in the both the .05mg group and 3.4 letter improvement in the 1.0 mg group vs 1.5 letter improvement in sham, (p=.01). In addition the 0.5 mg group had a decrease in CFT of 45.2um vs 0.4um in sham (p=0.06). Subset analyses with patients taking renin angiotensin (RAS) inhibitor medications showed a mean improvement of 6 letters in 0.5mg, 4 letters in 1.0 mg and 1.1 letters in sham (p=0.02). In addition, the OCT CFT was reduced 49um in the 0.5mg group vs an increase of 10.2ug in the sham (p=.03).

Conclusions: These data suggest low-dose danazol combined with RAS inhibitors is a painless, safe and efficacious oral treatment for patients with DME, and shows promise as a rescue medication following anti-VEGF therapy failure. A phase 3 trial, with low-dose danazol formulated for all BMIs is planned for the beginning of 2017.
North Carolina Diabetic Retinopathy Telemedicine Network

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Purpose: Retinal tele-screening with remote expert interpretation is an emerging strategy for providing diabetic retinopathy (DR) evaluations in the primary care setting and is especially useful in reaching patients living in rural and underserved areas. The purpose of this study was to identify patient characteristics associated with DR and retina specialist referral.

Methods: In a 2-year cross-sectional study, patients were recruited from 5 Area Health Education Center (AHEC) primary care clinics which serve rural and underserved populations across North Carolina. 1787 patients with diabetes mellitus (DM) received retinal screening photographs with remote expert interpretation by a single retina specialist to determine the presence and severity of DR. Participants included patients aged 18 years or older with Type I or Type II DM who presented to these 5 clinics for their routine diabetes care. Of these patients, 1661 with complete data were included in the statistical analysis.

Results: Of 1661 patients, 1323 (79.7%) had no DR, 183 (11.0%) had DR that did not require referral to a retina specialist, and 155 (9.3%) had DR that required referral. Older patients (OR = 1.28) and African American patients (OR = 1.84) had greater odds of referral when compared to those who were Caucasian and/or younger by 10 year increments. Patients with higher HbA1c levels (OR = 1.19) and longer duration of diabetes (OR = 1.76) had increased odds of having DR that required referral. Stroke (OR = 1.65) and kidney disease (OR = 1.59) were the comorbid conditions most associated with DR and referral in our study population.

Conclusions: When implemented in the primary care setting, telemedicine is a successful intervention to increase the reach of DR screening in patients with diabetes who otherwise face access barriers to proper and timely eye care. In this study, we found that while a relatively small percentage of patients with DM ultimately required the expertise of a retinal specialist, without the telemedicine network, these rural and underserved patients may not even have had access to eye care. Telemedicine can facilitate efficient, effective retinal care delivery to those patients in greatest need.
Outcomes after Failed Pneumatic Retinopexy for Retinal Detachment

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Purpose: To provide visual and anatomic outcomes for patients with retinal detachment (RD) who failed primary pneumatic retinopexy (PR).

Methods: This retrospective single-center, consecutive case series included patients with recurrent or persistent RD after primary PR. Three secondary procedures were compared including repeat PR, pars plana vitrectomy (PPV), and combined scleral buckle/pars plana vitrectomy (SB/PPV). The main outcome measures were anatomic reattachment and visual acuity (VA) at 1 year.

Results: Of a total of 423 primary PR’s performed for RD, this study included 73 cases that failed. The overall single surgery anatomic success rate for the secondary procedure was 75%; the final success rate at one year was 100%. There was no statistically significant difference in success rates between repeat PR (63%), PPV (76%), and SB/PPV (88%). Improvement in visual acuity was similar at one year between all three groups. Visual acuity at one year was similar between eyes undergoing PPV and SB/PPV (LogMAR VA 0.47 [20/59] for PPV and LogMAR VA 0.52 [20/66] for SB/PPV, p = 0.75). Visual acuity at one year was better for those without macular involvement at the time of secondary procedure compared to eyes whose maculae detached (LogMAR VA 0.29 [20/39] vs LogMAR VA 0.73 [20/106], p < 0.005). Fifty percent of PR failures underwent a secondary procedure within 1 week of primary PR; 80% occurred within 1 month.

Conclusions: Anatomic success rates for these procedures after failed PR were lower than their published success rates for primary RD—failed PR may select for RDs inherently more difficult to reattach. The anatomic success rate trended greater with SB/PPV and PPV, respectively, but VA improvements were similar for each. The suitable secondary procedure depends on patient factors and surgeon preference.
Macular Hole after Pars Plana Vitrectomy for Rhegmatogenous Retinal Detachment

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PURPOSE: To report the clinical features, possible associations and treatment outcomes of patients with macular hole after pars plana vitrectomy (PPV) for rhegmatogenous retinal detachment (RD) at a university based referral center.

METHODS: Retrospective consecutive case series (2009 to 2014). Patients with diabetic tractional retinal detachments and traumatic retinal detachments were excluded.

RESULTS: In the current study of 15 patients, macular hole was not visible before, during or immediately after RD surgery. The average time from RD surgery to macular hole diagnosis was 119 days (range: 41 - 398 months). No vitreous staining agents were used during the original RD surgery. Possible associations in these patients included 9 (60%) with a history of macula off RD, 9 (60%) with history of recurrent RD, 5 (33%) in eyes with high myopia and 10 (66%) in eyes with concurrent epiretinal membrane.

Macular hole surgery was performed on all eyes. No patients had more than one macular hole surgery. Macular hole closure was accomplished in 11/15 (73%) eyes at last follow up (average 302 days). Of the 11 eyes with macular hole closure, 20/200 or better was achieved in 8 eyes but only 5 eyes achieved 20/80 or better.

CONCLUSIONS: In eyes with macular hole formation after PPV for RD, possible associations include macula off RD, recurrent RD, high myopia and epiretinal membrane formation. Macular hole closure was achieved in the majority of patients but closure was associated with only modest visual improvement. Macular hole formation in these patients implies more than a purely tractional etiology.
Anatomic and Visual Outcomes for Complex Rhegmatogenous Retinal Detachment (RRD) in the Era of Small Gauge Vitreoretinal Surgery

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Purpose: To study outcomes of surgery for complex RRD in the era of small gauge vitreoretinal surgery.

Methods: Consecutive case series. Inclusion criteria: all cases of rhegmatogenous retinal detachment associated with severe PVR, high myopia, and GRT, who underwent PPV and silicone oil tamponade. During the study period the surgical technique included small incision PPV (25G or 23G) in all cases. Exclusion criteria: age <18, follow-up < 3 months, proliferative diabetic retinopathy, open globe injury, and endophthalmitis. Outcome measures included retinal re-attachment and best corrected visual acuity (BCVA).

Results: Sixty-five eyes of 65 patients, mean age 62 years (range 19-90 years), were included in the study. The mean follow-up was 29 months 12 eyes were highly myopic. Giant retinal tear was present in 7 eyes, and PVR grade C or higher in 54 eyes. The retina was reattached with one procedure in 58 (89%) cases. Final reattachment was achieved in 63 (97%) eyes. The BCVA at baseline was $\geq$ 20/40 in 1 (2%) eyes, 20/50-20/100 in 4 (6%) eyes, 20/200-20/400 in 10 (15%) eyes, CF in 25 (38%) eyes, HM in 21 (32%) eyes, and LP in 4 (6%) eyes. At the last follow-up the BCVA was $\geq$ 20/40 in 6 (9%) eyes, 20/50-20/100 in 12 (18%) eyes, 20/200-20/400 in 25 (38%) eyes, CF in 18 (28%) eyes, HM in 2 (3%) eyes, and NLP in 2 (3%) eyes. Twelve eyes had silicone oil in place at the last follow-up.

Conclusions: Small gauge vitrectomy for complex RRD with severe PVR is associated with good outcomes that appear to compare favorably with the historical data from studies with 20 gauge vitrectomy.
Effect of Scleral Buckling on Eyes that have Previously Undergone Lasik Surgery

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Purpose: Vitreoretinal surgeons often default to vitrectomy rather than scleral buckling if an eye has undergone refractive surgery. If the patient is young and phakic, and a pneumatic retinopexy is unlikely to work or has failed, a scleral buckle might be a better choice. But how does buckling affect the final refraction? We have recently reported on the effect of segmental buckling and have expanded our work to include encircling elements. We wished to determine, using a finite element analysis virtual model, how eyes with corneal thinning after LASIK behave with respect to induced myopia, axial length change, and induced astigmatism after routine scleral buckling.

Methods: We modeled a virtual eye similar to one that we had previously used to assess surgical treatments for central retinal vein occlusion, and used finite element analysis. We used experimentally derived elastic properties for human sclera, cornea, retina, lens, zonules, ciliary body and choroid. We assumed that the IOP was 15 mmHg, that there was direct contact between the sclera and the buckling elements, that corneal thinning was at an optical zone radius of 3 mm, and we calculated the anterior and posterior refractive power of the cornea. We assumed that the cornea was thinned by 25% compared to a normal cornea. We performed our analyses using 3 and 6 clock hours of segmental buckling of 3 different buckle heights, and similarly we looked at 3 different encircling band widths and buckle heights.

Results: With a segmental buckle, eyes with a thinned cornea generally underwent less induced myopia and a negligible astigmatic shift compared to eyes with normal thickness corneas. A superiorly located buckle also causes a deformation that tilts the cornea downward. Eyes buckled with encircling bands have a greater induced myopia than when segmental elements are used, but the myopia is often secondary to corneal steepening rather than from an increased axial length.

Conclusions: In an eye having corneal thinning from previous lasik surgery, segmental buckling appears to be a better choice than an encircling band if induced refractive errors are to be minimized.
Persistent Indocyanine Green (ICG) Fluorescence Following Macular Hole Repair

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Purpose: Pars plana vitrectomy with indocyanine green (ICG) stained internal limiting membrane (ILM) peeling is a common procedure in macular hole (MH) surgery. A number of papers, however, report ICG-related retinal toxicity with resulting poorer visual acuity (VA) outcomes despite successful anatomic closure. There has been one case report of persistent ICG fluorescence at 7 months after surgery, indicating possible long term persistence of residual ICG. However, there are no long term studies with larger number of eyes on how long ICG persists in an eye after being used intra-operatively. We aimed to study the duration and pattern of ICG fluorescence and to correlate with optical coherence tomography (OCT) in eyes following MH repair.

Methods: We performed a retrospective studies on 25 eyes that were operated for MH with ICG staining to assist ILM peeling and imaged post-operatively for residual ICG to assess the duration and the pattern of ICG persistence. Serial images were taken at the usual post-operative visits using ICG angiography filter in place and OCT was also obtained.

Results: Mean MH size was 360 um and mean baseline VA was 20/200. Following surgery, all MH were closed and mean final VA was 20/50. Mean days of follow up was 412 days. At last follow up, 12/25 eyes continued to have ICG fluorescence at fovea. The likelihood of persistent fluorescence correlated with the baseline MH size. Among 13 eyes where ICG fluorescence disappeared, it occurred on average of 300 days. Time to disappearance of ICG fluorescence also correlated with the baseline MH size. 14/25 eyes had ellipsoid zone disruption at last follow up.

Conclusions: ICG fluorescence can persist for a long time after surgery, indicating that ICG used intra-op may last longer than previously reported even at lower concentration and ellipsoid zone disruption at fovea is commonly seen even in eyes with MH closure.
Peeling or Not Peeling the Internal Limiting Membrane in Macular Pucker Surgery. A Microperimetric Response

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PURPOSE: To compare functional and anatomical outcomes after idiopathic macular pucker removal between eyes that underwent internal limiting membrane (ILM) peeling and eyes that did not.

METHODS: This multicentric, randomized clinical trial, included 60 eyes of 60 patients affected with idiopathic macular pucker. All the 60 eyes underwent 23-gauge pars plana vitrectomy (PPV), in 30 eyes PPV was associated with ILM peeling (“ILM peeling group”), whereas in 30 eyes PPV was not associated with ILM peeling (“ILM not peeling group”). Retinal sensitivity, frequency of microscotomas, and all the other microperimetric parameters were tested by MP1 microperimetry. Best-corrected visual acuity (BCVA) was investigated with the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Anatomical outcomes were analyzed with spectral domain optical coherence tomography (SD-OCT).

RESULTS: After a 12-month follow-up, the mean retinal sensitivity in the 4° central area showed a greater and faster recovery in the ILM not peeling group than in the ILM peeling group (P = 0.041). The number of absolute microscotomas (0 dB) within the 12° central retinal area was significantly higher in the ILM peeling group than in the ILM not peeling group (P= 0.044).

CONCLUSIONS: The ILM not peeling group seems to show better outcomes than the ILM peeling group as measured by mean retinal sensitivity and number of microscotomas after a 12-month follow-up.
Should Epiretinal Membranes be Peeled before Vision Drops Below 20/40?

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**Purpose:** To evaluate whether pseudophakic patients with symptomatic epiretinal membranes (ERM) and preoperative visual acuity 20/40 or better benefit from early intervention with small gauge vitrectomy and ILM/ERM peeling compared to patients for whom surgery is delayed until visual acuity declines to 20/50 or worse.

**Methods:** Retrospective chart review of a consecutive series of 119 pseudophakic eyes of 113 patients that underwent vitrectomy and ILM peeling for idiopathic epiretinal membrane by multiple physicians within a multi-physician retinal practice. Exclusion criteria included cataracts and any ocular conditions that could potentially limit postoperative outcomes. Primary outcome measure was final best Snellen visual acuity. Secondary outcomes included the proportion of eyes with final visual acuity ≥ 20/40 and potential preoperative prognostic factors for improvement in visual acuity after surgery, including preoperative vision, severity of retinal wrinkling, central macular thickness, and ellipsoid zone status.

**Results:** Twenty-four of 27 (89%) eyes with ≥ 20/40 preoperative vision attained final postoperative vision of ≥ 20/40, while fifty-two of 88 (59%) eyes with preoperative vision ≤ 20/50 attained ≥ 20/40 vision at final postop vision. Postoperative reduction in retinal wrinkling was significantly associated with ≥ 2 lines improvement in visual acuity (p=0.048). The was no significant difference in central macular thickness between patients that gained ≥ 2 Snellen lines and those that gained < 2 lines (p=0.12). Although ellipsoid zone disruption was more common in eyes that failed to gain ≥ 2 lines visual acuity, this difference was not significant. There were no cases of retinal detachment or endophthalmitis.

**Conclusions:** Removal of ERMs before vision drops to 20/50 or worse may increase the likelihood of attaining final postoperative vision of 20/40 or better. Larger prospective studies are required to determine the significance of this observation.
Macular Pucker Surgery Outcomes in Good Vision Eyes

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Purpose: To assess outcomes of early surgical intervention of macular puckers when visual acuity is still very good compared to worse visual acuity.

Methods: Patients undergoing pars plana vitrectomy (PPV) for macular pucker/epiretinal membrane with a minimum follow-up of 6 months, and cataract extraction/IOL before final follow up follow-up were included. Excluded were eyes with co-morbidities affecting visual acuity (e.g. CRVO, BRVO, DME, exudative AMD, etc.). Eyes grouped by preoperative visual acuity, 20/30 or better—“good visual acuity eyes,” 20/40 to 20/60—“contemporary indication for PPV,” 20/70 or worse—“historical indication for PPV.”

Results: Among eyes with good visual acuity, 9 of 9 eyes (100%) had final visual acuity of 20/25 or better. Among eyes with “contemporary indication for PPV” 13 of 27 eyes (48%) had visual acuity of 20/25 or better, and eyes with “historical indication for PPV” 3 of 10 eyes (30%) had visual acuity of 20/25 or better (Chi-Square p=0.005 for 20/25 or better, overall distribution of visual acuity p=0.01).

Conclusions: Earlier intervention of macular puckers with still good visual acuity results in better long term visual acuity outcomes. Measures that assess amount of improvement achieved by surgical intervention are postulated to be less important than best achieved, final visual acuity.
INTERNAL LIMITING MEMBRANE PEELING (ILMP) REABSORBS MACULAR EDEMA (ME) AND IMPROVES VISUAL ACUITY PRECISELY BECAUSE IT IS A RETINAL TRAUMA OF MECHANICAL NATURE

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PURPOSE: ILMP is challenged because it is traumatic. However well-conducted ILMP can reabsorb macular edema (ME). This work aims to study the relationship between adult reactive retinal astrogliosis (ARRA) reactional to trauma and retinal edema (RE) in the entire eye in vivo.

METHODS: Light microscopy and immunohistochemistry studies of Epithelial Growth Factor (EGFR) and Glial Fibrillary Acidic Protein (GFAP) were performed 1) in ten human eyes presenting a retinal injury of mechanical nature (retinal detachment (RD) (two eyes), of biochemical nature (venous occlusion, endophthalmitis) (three eyes), and of mixed nature (five eyes) 2) in two porcine eyes enucleated at Day 15 and 35 after creation of a RD.

RESULTS: In the human eyes in vivo: in case of biochemical injury alone, RE is present, restricted to the external retinal layers; horizontal astrocytes GFAP up-regulation is co-observed; Muller Cells (MC) gliosis is not observed. EGFR is not expressed. In case of RD, there is neither RE nor macular edema (ME); a dramatic MC vertical gliosis spanning from the ILM to the outer limiting membrane (OLM) is obviated; astrocytes gliosis is absent. In case of mixed triggering factors, both gliosis are observed without RE/ME.

In the porcine eyes in vivo: at Day 15, a RE is observed, prevailing in the external layers; a dramatic MC GFAP up-regulation, spanning from the ILM to the external plexiform layer is co-observed; EGFR activation is dramatic, spanning from the ILM to the OLM. At Day 35, RE is no longer present; MC GFAP activation is spanning down to the OLM; EGFR activation is still present, but fainted.

CONCLUSIONS: Recent neuro-sciences data explain why ARRA is mechano-protective and neuro-regenerative. Recent data in wound healing suggest that tearing of MC endfeet basal membranes induces “hybrid” Mesenchymal to Epithelial Transformation which boosts osmotic capacities.

ILMP is a retinal trauma of mechanical nature. It drives ARRA controlled by EGFR pathways. Sequential spatial and temporal MC spanning GFAP adult re-activation, and regenerated MC endfeet basal membranes, induce resorption of RE. Due to its mild intensity, ARRA remains limited to its early homeodynamic beneficial phase and to minor collateral damage. ILMP is a (non pharmaceutical) therapeutical manipulation of EGFR.
MANAGEMENT OF FOCAL VITREOMACULAR TRACTION WITH PNEUMATIC VITREOLYSIS

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PURPOSE: To present a case series for investigating the outcomes of pneumatic vitreolysis (intravitreal C3F8 gas injection without a vitrectomy) and limited face-down positioning in the treatment of symptomatic vitreomacular traction (VMT) with or without a macular hole (MH).

METHODS: A retrospective review of eyes with symptomatic VMT treated with 0.3 mL of intravitreal C3F8 gas injection was performed. Treated patients were asked to avoid the supine position until gas resolution. Patients with small stage-2 macular holes (≤ 250 microns) were asked to maintain part-time face-down position during waking hours and continue face-down position as much as possible when sleeping at night.

RESULTS: Forty-six patients (46 eyes) with symptomatic VMT underwent pneumatic vitreolysis between 2010 and 2015. A complete posterior vitreous detachment (PVD) was achieved in 42 eyes (91.3%) at a median of 2.9 weeks after gas injection. Twenty-eight of 32 eyes (87.5%) with VMT only developed a PVD, while all 14 eyes (100%) with a stage-2 MH developed a PVD with MH closure in 9 of the 14 eyes (64.3%). The median pre-operative best spectacle-corrected visual acuity (BSCVA) was 20/50, and the median BSCVA was 20/35 at last visit. The mean follow-up time was 12.5 months. There were reduced rates of PVD associated with pneumatic vitreolysis for eyes with broad VMT (>2 disc areas) (25% success) and eyes with thick cellophane membrane (66.7% success). There were few adverse events. One eye with initial VMT only developed a full-thickness MH, and one eye with initial VMT only developed a retinal detachment despite release of VMT. Both eyes were successfully repaired with a vitrectomy and the final VA was 20/30 for both eyes.

CONCLUSIONS: Intravitreal C3F8 gas injection alone with limited face-down positioning appears to be a viable treatment option for resolving focal VMT, and closing select stage-2 MH with few complications. More studies are needed to elucidate the indication, benefits and risks of pneumatic vitreolysis.
Optical Coherence Tomography-guided Short-duration Face-down Positioning after Vitrectomy for Macular Hole

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Purpose: To compare the results of pars plana vitrectomy (PPV) for macular hole (MH) with face down positioning of one day with optical coherence tomography (OCT) MH closure confirmation (short duration group), compared to strict face down positioning for 10 days (traditional group).

Methods: A retrospective review of all eyes that underwent PPV for MH by one surgeon from 8/1/2011 to 9/28/2015 were included. Patients were excluded if they had other visually significant pathology besides cataract. Baseline patient age, gender, phakic status, visual acuity (VA), and duration of MH were recorded. Characteristics of surgery including performance of internal limiting membrane (ILM) peel and tamponade agent were recorded. VA, phakic status, and whether OCT was performed and demonstrated MH closure were recorded for one day, one week, on month, three months, and final follow-up after PPV. VA was converted to LogMAR for statistical analysis. A two-tailed T-test was used to compare baseline characteristics, VA at one month and final follow-up, and final phakic status. The primary outcome measure was closure of MH at one month after PPV.

Results: Thirty-three consecutive eyes of 31 patients underwent PPV followed by strict face down positioning for 10 days. Then 10 consecutive eyes of 9 patients underwent PPV for MH with face down positioning for one day. The groups were similar with respect to age, gender, duration of MH, phakic status, and size of MH. All patients underwent PPV with ICG-assisted ILM peel with gas or air tamponade. One patient in the short duration group had recurrence of MH at one week after PPV requiring additional surgery (which closed the hole). Closure at one month after PPV was achieved in 9/10 eyes in the short duration group compared to 33/33 eyes in the traditional group (p=0.23) One patient in the traditional group had recurrence of MH at postoperative month three but did not undergo further surgery. LogMAR VA at one month was 0.78 (Snellen 20/120) and 0.60 (Snellen 20/80) in the short duration and traditional group respectively (p=0.38) and final visual acuity was 0.41 (Snellen 20/50) and 0.36 (Snellen 20/46) (p=0.74).

Conclusions: Using OCT imaging as a guide, shorter duration of face-down positioning following PPV for MH appears effective and safe with comparable success rates and VA outcomes at one month and final follow-up to those obtained with strict 10-day face down positioning. Further investigation with larger sample size is indicated to substantiate these findings.
**Autologous Neurosensory Retinal and Choroidal Free Flap for Closure of Refractory Large Macular Holes**

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**Purpose:** To evaluate the structural and functional outcomes of the autologous neurosensory retinal or choroidal free flap technique for closure of refractory large macular holes (MH).

**Methods:** Retrospective review of patients undergoing an autologous neurosensory retinal free flap (n=4) or combined autologous neurosensory retinal and choroidal free flap (n=1) for refractory full thickness MH at the Duke Eye Center. Surgical technique comprised of a bimanual approach to harvest a neurosensory retinal flap from the mid-periphery that was transferred over the MH, covered with perfluorocarbon liquid and then exchanged for silicone oil or gas tamponade.

**Results:** A total of 5 procedures were performed on 4 eyes with one patient undergoing a repeat autologous neurosensory retinal free flap. Tamponade used was silicone oil (n=4) or C3F8 gas (n=1) followed by 1 week of face down positioning.

Indications for surgery were refractory myopic MH (n=2), myopic MH retinal detachment (n=1) and large refractory MH following prior MH surgery. Mean age was 65.6 ± 9 years. Average preoperative MH size was 1215 ± 257 µm (range 1060-1600 µm). Mean number of prior retinal surgeries related to the MH was 2.75 (range 1 - 5). Mean spherical equivalent where available was -13.75 diopters. Three eyes were phakic and one was pseudophakic. Mean postoperative follow up was 6.75 ± 2.9 months.

Visual acuity improved from 1.6 ± 0.73 to 0.98 ± 0.55 logMAR (p=0.08) at final follow-up. Complete MH closure was achieved following 3/5 surgeries. Among the two cases that did not close, MH size reduced from 883.5 to 442.5 µm with improvement in visual acuity. Complications encountered were flap displacement in 2/5 surgeries. Optical Coherence Tomography (OCT) - Microperimetry co-localization (n=1) showed improvement in microperimetry amplitudes and partial restoration of outer retinal layers. Intraoperative OCT (n=1) demonstrated retinal flap stability during silicone oil removal.

**Conclusions:** Autologous neurosensory retinal and choroidal free flaps are a viable option for refractory large (>1000 µm) MH and MH related retinal detachment with good structural and functional outcomes. Flap dislocation is the most common complication.
Displacement of Submacular Hemorrhage with Subretinal Air. Initial U.S. Experience

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PURPOSE: To present the initial experience of using subretinal air to displace submacular hemorrhage (SMH) with anatomical and functional outcomes.

METHODS: Retrospective consecutive chart review of patients who underwent displacement of SMH with subretinal air at 5 sites in the US. None of the surgeons had prior experience with using subretinal air. Data included preoperative and postoperative visual acuity (VA) at predetermined time points, technique, and complications. Description of SMH included cause, duration, extent and thickness at fovea, presence of subretinal pigment epithelial hemorrhage, extent of displacement, additional use of subretinal tissue plasminogen activator (tPA), bevacizumab, and gas tamponade.

RESULTS: Twenty-four eyes of 24 patients were included (11 males with a mean age of 77.6 +/- 10.8 years). Etiology included exudative age related macular degeneration in 19 (79%), polypoidal choroidal vasculopathy in 4 (16.7%), and trauma in 1 (4.16%). Fourteen of 24 patients (58.3%) were on anticoagulation, 8 (57%) on aspirin 81mg, 4 (28.6%) on warfarin, and 2 (14.3%) on clopidogrel. Submacular hemorrhage was located only subretinal in 6 (25%), subRPE in 2 (8.3%), and combined in 16 (66.7%). All patients underwent vitrectomy with injection of subretinal tPA and air in all (100%), with additional bevacizumab only in 18 of 24 patients (66.7%). Of the 24 patients, tamponade in the vitreous cavity included SF6 gas in 14 (58.3%), air in 8 (33.3%), C3F8 gas in 1 (4.12%), and silicone oil in 1 (4.12%). The subretinal component of SMH was successfully displaced in all cases (100%). There was residual sub-RPE heme in 2 cases (8.3%). Preoperative LogMAR visual acuity was 1.95 +/- 0.4 and improved to 1.13 +/- 0.6 (p=0.0001) at 3 months and 1.16 +/- 0.15 at final visit ranging from 5 to 28 months.

CONCLUSIONS: Combined subretinal air and tPA is an effective technique to successfully displace SMH to a wide extent. Complications are similar to those reported with displacement with subretinal tPA alone.
FELLOWSHIP RESEARCH AWARD

PROTECTIVE EFFECT OF MESENCHYMAL STEM CELL DERIVED EXOSOMES IN A MODEL OF RETINAL ISCHEMIA

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PURPOSE: Exosomes derived from human mesenchymal stem cells (hMSCs) cultured under hypoxic and serum-free conditions contain proteins and growth factors that promote angiogenesis. This study investigated the effect of intravitreal administration of these exosomes using a murine model of retinal ischemia.

METHODS: Oxygen-induced retinopathy (OIR) was induced by exposing one week old male C57BL/6J mice to 5 days of 75% hyperoxic conditioning, and then returned to room air. At 12 days of age, the right eye of mouse was injected intravitreally with saline (Group 1, n=4) or exosomes derived from hMSCs (Group 2, n=4) and compared to control mice of same age grown under room air (No OIR) and injected intravitreally with saline (Group 3, n=4). After 2 weeks, fluorescein angiography (FA) and phase variance optical coherence tomography angiography (pvOCTA) were used to assess retinal perfusion. The eyes were harvested after euthanasia for histologic analysis. The extent of retinal vascular preservation was quantitated histologically by counting vascular nuclei on the retinal surface.

RESULTS: hMSC-derived exosomes induced vascular preservation in a mouse model of OIR, as determined in vivo by FA and pvOCTA. Retinal thickness was significantly reduced in saline-injected controls as compared exosomes-treated eyes in the OIR model, as determined by OCT (111.1±7.4 µm in Group 1; 132.1±11.6 µm in Group 2; p<0.001). Histological analysis demonstrated that hMSC-derived exosomes inhibited neovascularization as compared to saline-injected controls (7.75±3.68 neovascular nuclei per section in Group 1; 2.68±1.35 neovascular nuclei per section in Group 2, p<0.001). No immunogenicity was detected and no ocular/systemic adverse effects were noted during the two week follow-up.

CONCLUSIONS: Intravitreal injection of exosomes derived from hMSCs was well tolerated without immunosuppression and decreased the severity of retinal ischemia in this murine model. Exosomes are easily manufactured and stored, and allogeneic use is possible. Intravitreal exosome therapy is an appealing novel non-cellular approach that warrants further exploration in ophthalmology.
Evolution of Vitreoretinal Techniques and Technologies

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The history of vitreoretinal surgery is a story of the interrelated development of a vast array of techniques and evolution of technique-driven technology. Partnerships between surgeons and engineers are a crucial driver of this extraordinary process.

**Vitreous Removal:** Robert Machemer developed pars plana vitrectomy to eliminate the need for keratoplasty and operate with a closed system with controllable intraocular pressure. Machemer did the first clinical cases of pars plana vitrectomy and was central to the development of a systematic approach to vitreoretinal surgery and a distinct vitreoretinal surgery subspecialty. A vitreous cutter with infusion and aspiration was developed and used clinically in Japan prior to development of vitrectomy in the United States but this was published in the Japanese literature and apparently not known in the United States. Anton Banko patented a vitreous cutter including aspiration and infusion prior to the development of the VISC by Jean Marie Parel and Machemer but never commercialized the device. Banko developed the fluidics for the initial phacoemulsification machine for Charles Kelman, had knowledge of mechanized lens removal systems invented by Kelman prior to the application of ultrasound, and saw vitreous often during the development of clinical phacoemulsification. Jean Marie Parel developed the VISC, fiberoptic endoillumination, and the solenoid operated MPC vertical scissors working with Machemer. Nicholas Douvas developed the RotoExtractor which, like the VISC, was a full-function, large incision, rotary cutter but incorporated an oscillatory mode in an attempt to address the vitreous winding problem of the VISC. Conor O’Malley and Ralph Heinz developed 3-port vitrectomy with a 20 gauge (0.89mm) system as well as a lightweight, reusable, bellows-driven, pneumatic, axial cutter driven by the Ocutome 800 console (Berkley Bioengineering, 1972). I developed the disposable diaphragm axial cutter working with Carl Wang and later invented the first dual actuation, limited rotary action cutter with InnoVision, a company I started.

**Drainage of Subretinal Fluid and Surface Tension Management:**
I invented internal (through the retinal break) drainage of subretinal fluid to address the many complications of trans-scleral drainage: incarceration, bleeding, and incomplete drainage. I developed simultaneous internal fluid-air exchange, now just called fluid-air exchange, to eliminate the problems of sequential exchange: hypotony, incomplete exchange, and having a needle in a deflated eye. I developed air-gas exchange and air-silicone exchange to produce a complete exchange of air for so-called tamponade substances without fluctuation in intraocular pressure. Brooks McEwen developed the air pump produced a continuous source of air at a controllable infusion pressure which replaced using a syringe for fluid-air exchange. Carl Wang and I developed the first power gas injector and first power silicone injector. I invented vacuum cleaning using a straight cannula with a fingertip side port to control fluid egress (flute needle) but soon switched to Conor O’Malley’s better technique of extrusion, using the console aspiration system and foot pedal to control fluid egress. David McLeod and Peter Leaver combined the John Scott
technique of injecting silicone oil without vitrectomy with my fluid-air exchange, internal drainage of subretinal fluid, and endophotocoagulation technique; creating the currently utilized paradigm. Gary Abrams developed the concept of using an iso-expansive gas concentration which was ideal for my technique of fluid-air exchange and internal drainage of subretinal fluid followed by air-gas exchange. The use of iso-expansive gas-air mixtures produced near full gas fill without producing elevated intraocular pressure or post-op small bubbles. Stanley Chang developed the critical idea of using perfluorocarbon liquids to unfold giant breaks, as well as draining subretinal fluid and stabilizing the retina during PVR membrane dissection.

RETINOPEXY AND HEMOSTASIS: Machemer utilized both monopolar diathermy and endocryopexy; both of which had significant hazards. I developed endophotocoagulation for retinopexy, hemostasis, and panretinal photocoagulation and adapted the technique to three-port vitrectomy. Endophotocoagulation eliminated the need for conjunctival incisions to apply cryopexy. My first system used the Zeiss xenon source while my first commercial system used Patrick O’Malley’s Log III photocoagulator xenon source; subsequently Maurice Landers, Jay Fleischman, and I simultaneously and independently developed endophotocoagulation systems using an argon laser source, later Yasuo Tano developed the near-IR diode laser source and finally several companies developed 532 nm, diode pumped sources, frequency upconverted laser sources.

EPIRETINAL MEMBRANE REMOVAL: Machemer developed membrane peeling using a bent needle. Conor O’Malley developed the pic for membrane peeling which was safer because it did not have sharp point. I developed end-grasping forceps membrane peeling to enable safe, one-step epiretinal membrane without the need for needles, pics, or viscodissection. Many surgeons refer to this technique as pinch peeling. I developed diamond-coated membrane peeling forceps and conformal forceps which afforded a better purchase than earlier forceps designs. I developed scissors segmentation to divide adherent, epiretinal membranes that could be peeled into separate epicenters to reduce tangential traction. I developed scissors delamination of epiretinal membranes to completely remove adherent epiretinal membranes without utilizing dangerous membrane peeling in high adherence diabetic TRD cases. Machemer developed relaxing retinotomy at the same time I developed retinectomy which mean was defined as removing all tissue anterior to a circumferential incision in the retina. Machemer and I independently and simultaneously developed subretinal surgery.

FLUIDICS: The VISC and RotoExtractor used an assistant-operated syringe to produce vacuum. Conor O’Malley’s Ocutome 800 provided the first foot pedal controlled aspiration although it was on-off, not linear control. I developed linear suction control for The Ocutome 8000 working with engineers at Coopervision after they had acquired Berkley Bioengineering, the developers of the Ocutome 800. Linear suction was developed to enable proportional control of vacuum by the surgeon rather than control by the circulator. Carl Wang subsequently left CooperVision to start the original MidLabs with me. I worked with Wang and his engineers to develop the disposable, 20-gauge, pneumatic, hourglass shaped axial cutter, higher cutting rates and faster aspiration fluidics.

SYSTEMS INTEGRATION: In the mid-80s I started InnoVision and invented the Ocular Connection Machine, the forerunner of the Alcon Accurus and subsequently the Alcon Constellation. The OCM began the revolution of system integration, a steadily increasing number of functions in one console under unified control using a graphical user interface.
and single foot pedal control. The OCM had a xenon light source, servo-controlled IOP, global functions, a smart key graphical user interface, tool ID, a tubing management system incorporated into a sterile articulated arm, the dual actuation InnoVit which eliminated spring return produced 1500 cuts/minute, push prime, and proportional diathermy all of which were ultimately implemented on the Alcon Constellation. The Constellation uses RFID instead of the more primitive tool ID system on the OCM. The Accurus included global functions, a smart key driven graphical user interface, a halogen light source, power silicone injector, fragmenter driver electronics, power scissors and ultimately supported 23G and 25G vitrectomy as well as 2500 cuts/minute vitrectomy. The OCM and the Constellation utilized a very small venturi driven aspiration chamber continuously emptied by a peristaltic pump to allow very fast response time to foot pedal command. In addition to IOP compensation, global functions, a smart key graphical user interface, tool ID, a tubing management system incorporated into a sterile articulated arm, dual actuation, and proportional diathermy described above the Constellation has variable duty cycle control, auto-gas fill, auto-stopcock for fluid air exchange, dual xenon illumination sources, power silicone injector, and supports 10,000 cuts per/minute.
Ultra-wide Field Retinal Imaging in the Staging and Management of Sickle Cell Retinopathy

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Purpose: To determine whether ultra-wide field (UWF) retinal imaging changes the staging or management of sickle cell retinopathy compared to clinical examination.

Methods: This IRB-approved, single institution, prospective, observational study included 34 consecutive new patients with sickle cell disease seen in the investigators’ clinics. Patients with prior treatment for sickle cell retinopathy, other retinal vascular disease (e.g. diabetic retinopathy) or inadequate view for imaging were excluded. All patients underwent dilated fundus examination as well as UWF pseudo-color fundus photography (FF) and fluorescein angiography. A standardized questionnaire form requiring Goldberg staging and treatment recommendation per eye was completed by the investigators in a staged approach after 1) clinical examination, 2) FF and 3) FA. Primary outcomes were difference in retinopathy stage and the percentage of eyes with change in management across all 3 levels of evaluation.

Results: Sixty-eight eyes of 34 patients (17 men/women, mean age 30.8 years) were included. 26 patients were genotype SS (76.5%), 6 SC (17.6%), and 2 \( \beta \)-thalassemia (5.9%). By examination alone, the majority of eyes (42 eyes, 61.8%) were staged as no/non-proliferative retinopathy versus proliferative retinopathy (7 eyes/10.3% stage I, 11 eyes/16.2% stage II, 5 eyes/7.4% stage III, 3 eyes/4.4% stage IV, 0 eyes stage V). Based on FA, only 3 eyes (4.4%) were staged as no/non-proliferative retinopathy, with the majority stage II (51 eyes, 75.0%), or above (8 eyes/11.8% stage III, 3 eyes/4.4% stage IV, 0 eyes stage V). The average stage difference was 0.62 between FF and examination, 0.62 between FF and FA, and 1.24 between exam and FA. Scatter laser or pars plana vitrectomy was recommended for 7 eyes (10.3%), but in no case did the addition of FF or FA change treatment decisions.

Conclusions: UWF imaging detects a higher stage of sickle cell retinopathy compared to clinical examination alone in a cohort of sickle cell patients without prior treatment or known retinopathy stage. However, in no case did imaging change management. UWF can be considered in addition to clinical exam to accurately stage sickle cell retinopathy.
Late-phase Fluorescein Angiographic Findings which Predict Capillary Dropout and Subsequent Drug Treatment which can Lead to Capillary Preservation

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Purpose: To demonstrate that indistinct capillary margins in the late-phase of the fluorescein angiogram in either the periphery or posterior pole causing retinal edema (LAPPEL) is an angiographic sign preceding capillary dropout in retinal vascular diseases and may represent a time when this capillary damage may be reversed by using a drug which increases intraretinal endothelial cell adhesive proteins and preserves capillary integrity.

Methods: It is known that steroids in tissue culture can increase the production of intraretinal endothelial cell adhesive proteins Claudin 5 and VEcadherin. We have shown that in human retinal endothelial cell (HREC) tissue culture that Norrin can do the same and may do so in larger amounts. We also have shown in gene expression studies intra-HREC adhesive proteins are increased by Norrin even higher in the face of exposure to VEGF. We have seen in familial exudative vitreoretinopathy (FEVR) indistinct capillaries preceding capillary loss which resulted in the need for ablative laser therapy. To test the hypothesis that less-destructive drug therapy to repair these leaky, sick capillaries might reverse these changes, we treated two patients with FEVR who had LAPPEL lesions. Both patients were treated with topical steroid and NSAID, and one was treated with intravitreal triamcinolone. Both patients had indistinct vessels encroaching into the foveal area and showed a subsequent reduction in vision—both to 20/80 in their better-seeing eye. They both also showed thickening of the fovea on OCT. No anti-VEGF agents were used.

Results: Following treatment, OCT thickness was reduced. Fluorescein angiographic findings reversed and vision improved in both patients to 20/20 in one and 20/40 in the other. Only two injections have been done over 12 months and topical drops continued in both patients to date.

Conclusions: The LAPPEL lesion seems to be a fluorescein angiographic precursor of capillary dropout and these changes may be able to be successfully reversed without anti-VEGF, with fewer injections, or even with topical medication. We hope drugs such as Norrin which increase intraretinal endothelial cell adhesive proteins and modulate Wnt signaling may achieve the same results without the side effects of steroids.
Norrin Regulates Vascular Development and Capillary Regeneration

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Purpose: The advent of anti-VEGF therapy has greatly improved suppression of pathologic vascular changes, however, it does not address the progressive capillary loss that is seen with many retinal diseases. The Wnt-signaling pathway allows for a unique opportunity to rescue injured retina by modulating vascular regeneration. This study aims to evaluate the mechanisms by which Wnt-signaling directs vascular recovery.

Methods: A mouse model of Oxygen-Induced Retinopathy was used to create hypoxic injury and monitor recovery of capillary networks. Animals were treated with intravitreal injections of saline, norrin (Wnt-signaling activator), or aflibercept (anti-VEGF). The fellow eye served as a control. Retinal endothelial cell (REC) cultures treated with VEGFa were used to evaluate the effect of norrin, aflibercept, or corticosteroid on tight junction integrity. Gene expression arrays and western blots were performed to uncover the pathways activated during treatment response.

Results: Treatment with norrin results in a statistically significant reduction of retinal avascular area compared to control eyes. Conversely, aflibercept significantly increases the area of avascular retina (low and high dose) at post-natal day (P) 17 and the delayed vascular growth corresponds to decreased ERG amplitudes (P21 and P42) and structural changes in the retinal layers that persist (P42) despite vascular recovery. Furthermore, norrin treatment promotes modulated angiogenesis and improved capillary bed formation. This action is, in part, due to norrin’s ability to regulate tight junction formation and direct endothelial budding. REC cultures treated with norrin demonstrate both an anti-VEGF effect as well as an anti-inflammatory effect, noted in the gene and protein expression arrays.

Conclusions: Modulation of Wnt-signaling allows for improved capillary formation and regeneration in the retina. It acts both as a modulator of VEGF and inflammatory mediators and may be helpful in the management of retinovascular diseases.
Late-stage Management of Macular Edema Secondary to Retinal Vein Occlusion: Collective Analyses of the BRAVO, CRUISE, HORIZON, and SHORE Studies

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Purpose: To understand the time course of therapeutic response, stability of improvements after switching to PRN therapy, and rates of disease quiescence in patients with RVO treated with ranibizumab.

Methods: BRAVO/CRUISE were 12-month (M) phase 3 studies of ranibizumab for macular edema due to branch or central RVO (BRVO/CRVO), respectively; the HORIZON open-label extension followed ~60% of these patients at least every 3M for an additional ≥12M. SHORE was a 15-M, phase 4 study that compared monthly versus PRN ranibizumab in BRVO/CRVO patients. Taken together, 729 ranibizumab-treated patients (380 BRVO/349 CRVO) were given monthly injections for at least 6-7M and then switched to PRN treatment based on pre-specified BCVA/OCT criteria.

Results: Response time course: Rapid anatomic improvements were seen after 1 ranibizumab injection, with >200-µm reductions in mean retinal thickness. In ranibizumab 0.5 mg-treated patients, the median time to first gain of ≥15 ETDRS letters from baseline was 4.0M in BRAVO, 5.2M in CRUISE, and 2.1M in SHORE. Stability with PRN therapy: In SHORE, 80% of patients qualified to switch to PRN treatment by M8. During the PRN phase, BCVA gains were maintained with a mean 0.3-letter change in SHORE, 0.1 in BRAVO, and −1.0 in CRUISE. In SHORE, there was no significant difference in the slope of BCVA change from M7-15 between PRN (n=86) and monthly dosing (n=85; P=0.509). Rates of disease quiescence: With PRN treatment, 18.6% and 4.0% of BRVO patients (BRAVO/SHORE) and 6.9% and 11.1% of CRVO patients (CRUISE/SHORE) achieved disease quiescence according to BCVA/OCT-based retreatment criteria and required no additional ranibizumab injections. During the second year of follow-up of BRAVO/CRUISE patients in the HORIZON-OLE, 34.2% and 19.9% of BRVO/CRVO patients, respectively, did not require further injections; mean BCVA was stable in BRVO patients, but limited decline was observed in some CRVO patients.

Conclusions: For patients with RVO and macular edema, rapid vision improvements can be seen with ranibizumab treatment; 3-line vision improvements may take as long as 5 months. After monthly treatment producing significant visual gains, switching to PRN treatment produced visual stability. Disease resolution with no further treatment occurred more commonly in year 2.
LONG-TERM OUTCOMES OF EYES WITH MACULAR EDEMA SECONDARY TO CENTRAL RETINAL VEIN OCCLUSION (CRVO) TREATED WITH INTRAVITREAL BEVACIZUMAB. RESULTS OF THE PAN AMERICAN COLLABORATIVE RETINA STUDY (PACORES) GROUP

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PURPOSE: Report the 5 year outcomes of eyes with cystoid macular edema (CME) secondary to CRVO treated with intravitreal bevacizumab pro re nata (prn).

METHODS: Multicenter retrospective case series of 65 eyes. Main outcome measured was change in best corrected visual acuity (BCVA) at 5 years of follow-up. Secondary measures included central macular thickness (CMT) and total number of injections at 5 years.

RESULTS: Mean age of this cohort was 63.2 yrs and included 32 male patients. Patients had a mean follow up of 66.1 ± 8.8 months. At baseline, 11 pts had POAG, 42 had HTN, 24 were diabetic, 1 had a prior stroke and 6 had a prior myocardial infarction (MI). At 5 years, the mean BCVA improved from 1.40 ± 0.64 at baseline to 1.04 ± 0.70 logMAR (p<0.0001). At baseline, 3 eyes had a BCVA of ≥20/40, 7 eyes had between <20/40 and >20/200, and 55 eyes ≤20/200. At 5 years, 11 eyes had ≥20/40, 17 eyes had between <20/40 and >20/200 and 37 eyes ≤20/200 (p=0.022). At 5 yrs, 34 (52.3%) eyes had a gain of ≥3 lines, 23 (35.4%) eyes remained within 3 lines and 8 (12.3%) eyes had a loss ≥3 lines of BCVA. CMT improved from 614 ± 237 µm to 300 ± 130 µm (p<0.0001). At 5 yrs, 38 (58.5%) eyes had a completely dry SD-OCT. Patients received a total of 7.3 ± 4.8 (range 1-19) injections. On average, patients were injected 3.8 ± 1.9 (range 1-9) times in the first year, 1.7 ± 1.3 (range 0-4) in the second year, 0.9 ± 1.2 (range 0-5) in the third year, 0.5 ± 1.1 (range 0-5) in the fourth and 0.5 ± 1.3 (range 0-5) in the fifth year. None of the eyes developed endophthalmitis, retinal detachment or uveitis. Neovascular glaucoma developed in 4 (6.1%) eyes. During the 5 yr follow-up, 2 patients developed a stroke, 3 a MI and 1 died.

CONCLUSIONS: Intravitreal prn bevacizumab appears to be effective long term in reducing macular edema and improving visual acuity in eyes with CME secondary to CRVO.
Combination Therapy of Ranibizumab Plus Laser-induced Chorioretinal Anastomosis for Central Retinal Vein Occlusion

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Purpose: To assess the efficacy and safety of a combined treatment for patients with macular edema from central retinal vein occlusion (cRVO) consisting of intravitreal ranibizumab and a laser induced chorioretinal anastomosis (L-CRA).

Methods: Fifty-eight patients with CRVO were randomized 1:1 to receive either sham L-CRA plus intravitreal ranibizumab 0.5mg (29 patients) or L-CRA plus ranibizumab 0.5mg (29 patients). The L-CRA/sham was attempted at 2 sites at baseline with monthly injections of ranibizumab in both groups from month 1-6. From month 7-12 both groups both groups received monthly prn ranibizumab as required. Outcome measures included change from baseline in best corrected visual acuity (BCVA) and central foveal thickness (CFT) measured by masked assessors and also the number of injections required in the prn phase according to predetermined reinjection criteria.

Results: A successful L-CRA was created in at least one site in 24 of 29 patients in the combination group (82.8%) (17 patients with 2 sites and 7 patients with 1 site). The mean number of injections required in the prn phase was 2.3 in the ranibizumab plus sham L-CRA vs 1.5 for the ranibizumab plus L-CRA group (p=0.02). For the group of ranibizumab plus functioning L-CRA (24 patients) the injections decreased to 1.2 (p=0.005). The mean difference in BCVA from baseline for the 3 groups was an increase of 3.8 letters for the ranibizumab/sham group (p=0.36), 10.8 for the ranibizumab/total L-CRA group (p<0.001) and 14.7 for the ranibizumab/functioning L-CRA group (p<0.001). Of the potential 58 sites small new vessel development at was seen at 10 sites (17%), 5 of which regressed spontaneously and the remaining 5 were treated with sectorial laser peripheral to the L-CRA site. Three patients developed minor macular traction from avascular fibrous tissue proliferation treated with a vitrectomy as per protocol. No patient developed significant retino-choroidal neovascularization requiring vitrectomy surgery.

Conclusions: Combining the treatments of ranibizumab with an L-CRA results in improved visual acuity outcomes and lessens the need for repeated injections for patients with CRVO. The procedure is associated with a risk of fibrous proliferation and new vessel formation however this is manageable with careful follow-up and prompt treatment.
Oral Niacin as a Modulator for Central Retinal Vein Occlusions

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Purpose: Niacin, a well-established treatment for hyperlipidemia, is known to induce vasodilation. Patients with chronic central retinal vein occlusions (CRVO) and refractory cystoid macular edema (CME) have been observed to spontaneously improve when placed on systemic niacin therapy for hyperlipidemia. Similarly, when treatment was withdrawn, affected eyes developed increased retinal hemorrhages and recurrent CME, suggesting reversibility of effect. This study evaluates the effects of oral niacin on CRVO and associated ocular complications.

Methods: A prospective, single center, non-randomized, interventional case series of niacin for CRVO was conducted. Best-corrected visual acuity (BCVA), central macular thickness (CMT), and ocular complications were analyzed in 50 patients with CRVO over the course of 1 year. Eight patients were controls. The main outcome measures of this study included BCVA and CMT measurements after 1 year of oral niacin (500 mg TID) therapy, proportion of eyes experiencing improvement of 15 or more letters of vision, and incidence of ocular complications secondary to CRVO.

Results: The mean initial logMAR BCVA was 0.915, and improved on niacin to 0.745 (P=0.12), 0.665 (P=0.02) and 0.658 (P=0.03) after 3, 6, and 12 months of follow-up, respectively. At baseline, mean CMT was 678.9 µm, and improved to 478.1 µm (P=0.001), 388.6 µm (P<0.001), and 317.4 µm (P<0.001) for the same time points. The control group had a mean initial logMAR BCVA of 1.023, which gradually deteriorated to 1.162 (P=0.36) after 12 months, and baseline CMT of 700.0 µm at baseline, which gradually improved to 490.9 µm (P=0.06) after 12 months. Panretinal photocoagulation for neovascularization was required in 5 patients (13.2%) receiving niacin and 3 (37.5%) of the controls.

Conclusions: Niacin is associated with statistically significant functional and anatomic improvements in patients with CRVO. Niacin-induced vasodilation may potentially hasten collateral vessel formation and dilate choroidal vessels. Future investigations will help ascertain whether there is a role for niacin as an adjunct therapy to intravitreal injections in the management of CRVO.
GENETIC RISK FACTORS FOR RADIATION VASCULOPATHY

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PURPOSE: To do a genome-wide scan for polymorphisms associated with risk of vision loss from radiation complications in an extremely discordant cohort of patients treated with proton beam irradiation for choroidal melanoma.

METHODS: We identified a cohort of 126 patients at high risk of radiation complications due to tumor location within 2 disc diameters of the optic nerve and/or fovea who provided a blood sample to the Massachusetts Eye and Ear Uveal Melanoma Biorepository. Controls (n=76) were defined as patients with visual acuity 20/40 or better 3 years after treatment. Cases (n=50) were selected as patients with visual acuity 20/200 or worse due to radiation papillopathy or retinopathy 3 years after treatment. Genotyping of these samples was performed utilizing the a chip which includes 2.5 million single nucleotide polymorphisms encompassing both common and rare DNA variation.

RESULTS: Hypertension (OR 0.267, p=.0009), visual acuity at diagnosis of choroidal melanoma (OR=1.031, p=.002), tumor distance to fovea (OR=0.341, p=6.52E-05), tumor distance to optic disc (OR=0.481, p= 5.41E-05), height of tumor (OR=1.704, p= 0.0069), tumor within 2DD of both the fovea and optic disc (OR=9.956, p = 1.07E-06) were associated with poor visual acuity (20/200 or worse).

Single SNP analysis was performed controlling for the risk factors identified using stepwise regression and the first PC. While this analysis determined that there were 74,529 nominally significant SNPs (p<.05), there were no SNPs that reached genome-wide significance (p < 5E-08). The SNPs reaching the highest significance level (p < 1E-04) were kgp9816892 (rs11678387), an intergenic SNP located on chromosome 2 (p=4.43E-05) shown to increase risk of poor vision; kgp8928416 (rs8133945), an intergenic SNP located on chromosome 21 (p=6.67E-05) shown to decrease risk of poor vision; and rs16921196, a SNP located on chromosome 8 in the gene XKR4 (p=7.60E-05) shown to increase risk of poor vision.

CONCLUSIONS: Visual loss from radiation vasculopathy after treatment for choroidal melanoma is not only related to tumor location, but may be influenced by hypertension and possibly genetic factors.
Novel Classification System for Combined Hamartoma of the Retina and Retinal Pigment Epithelium

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Purpose: To develop an anatomical classification scheme for combined hamartoma of the retina and retinal pigment epithelium (CHRRPE) and specify recommendations for follow-up interval.

Methods: Retrospective review of patients with CHRRPE who were examined over a 7-year period (2008 – 2015). The clinical presentation, fundus examination and optical coherence tomography (OCT) were analyzed. Diagnosis of CHRRPE was based on clinical features of lesions, including: vascular changes, epiretinal component and pigmentation, as well as associated systemic syndromes, including neurofibromatosis.

Results: Lesions were classified based on location, fundus features and OCT findings. Lesion location: posterior pole including macula and peripapillary—Zone 1; mid-periphery—Zone 2; and far-periphery—Zone 3. Associated fundus findings: retina flat—Stage 1; retinal traction and/or retinoschisis—Stage 2; and retinal detachment—Stage 3. OCT findings: epiretinal component only—A; partial retinal involvement—B; and complete retinal and RPE involvement—C. Complete ophthalmologic evaluation, including fundus examination, fundus photography, and OCT, is recommended at least every 6 months for patients under 12 years of age, with more frequent follow-up in patients with: lesions in the posterior pole (Zone 1) or with retinal traction, retinoschisis, or retinal detachment (Stage 2 and 3). Surgical intervention is recommended in patients with vision loss secondary to macular traction or retinal detachment.

Conclusions: A new clinical classification system is proposed for evaluating and managing patients with CHRRPE. Zone and stage of CHRRPE lesion will assist with determining follow-up interval and surgical intervention. In addition, application of a uniform classification scheme will facilitate assessment and comparison of findings across different studies.
Germline BAP1 Mutation in Familial Uveal Melanoma: Report of 26 New Families

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Purpose: Familial uveal melanoma (UM) is very rare with 100 cases reported in the literature. This study sought to estimate the frequency of BAP1 mutations in familial UM.

Methods: We report 31 families with familial UM that underwent BAP1 sequencing. This includes 26 previously unreported families. In addition, we conducted a literature review highlighting 117 familial UM families.

Results: In this study, 5/31 (16%) families with familial UM were positive for germline BAP1 mutation. The frequency of BAP1 mutations in familial UM is estimated to be about 21%. Familial UM families reported in the literature appear to have high rates of breast cancer, cutaneous melanoma, lung cancer, and prostate cancer.

Conclusions: BAP1 is a significant contributor to hereditary UM, though other cancer predisposition genes likely contribute to uveal melanoma risk.
Intra-arterial Chemotherapy in Very Small Infants (< 10 kg) with Retinoblastoma

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Purpose: To review clinical outcomes in very small children (less than 10 kg) with retinoblastoma undergoing intra-arterial chemotherapy (IAC).

Methods: This was a retrospective single center case series. All children undergoing IAC for retinoblastoma who weighed less than 10 kg at the time of first treatment were included in this analysis. Thirty-four catheterizations in eleven eyes of six patients were included for analysis. All children underwent modified IAC with 1-3 chemotherapeutic agents (melphalan, topotecan, carboplatin) and the addition of ultrasound guidance for femoral artery 4-French catheter placement in conjunction with pediatric interventional cardiology given the very small size of these femoral arteries.

Results: The mean patient weight at the time of initial treatment was 8.8 kg. Nearly every eye had advanced disease (International Classification Group B:1; C: 4; D: 6). All but one child had tandem (simultaneous bilateral) treatment. All eyes were salvaged with no eyes lost to enucleation or requiring external beam radiation. At least one form of additional local therapy was used in each case including laser, cryotherapy, and intravitreal chemotherapy. The median number of IAC cycles required for salvage was 2.5. Vitreous hemorrhage developed in two eyes but cleared 3-6 weeks later with one intravitreal bevacizumab injection. No patients were hospitalized for neutropenic fever. No intraoperative complications occurred during IAC. No metastatic disease or secondary cancers developed during the study period.

Conclusions: In this series IAC was both safe and effective in very small infants despite previously reported concerns with groin access and efficacy. Ultrasound guidance for femoral access lead to successful catheterization in all cases. Patients in this cohort required fewer catheterizations and received lower total doses of chemotherapy than previously published series of larger children with similar staged disease, indicating that immature tumors in the eyes of these young children may actually be better responders to IAC than tumors in older children.
Association Between Choroidal Nevus Risk Factors and Gene Expression Profile Prognostic Class

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Purpose: Clinical features associated with growth of choroidal nevi are increasingly being used to discriminate between large choroidal nevi and small choroidal melanomas in order to decide whether to treat such borderline choroidal melanocytic tumors. The purpose of this study was to determine the association between these clinical features and a validated gene expression profile (GEP) classifier that accurately predicts metastatic risk in choroidal melanocytic tumors.

Methods: Fine needle aspiration biopsy and GEP testing was performed on 145 borderline choroidal melanocytic tumors. Each tumor was assigned a GEP of Class 1 (low metastatic risk) or Class 2 (high metastatic risk). The status of the following favorable and unfavorable clinical features was recorded for each tumor: thickness, internal reflectivity, proximity to disc, subretinal fluid, orange lipofuscin pigment, drusen, RPE atrophy and fibrous metaplasia.

Results: The GEP classification result was Class 1 in 120 cases and Class 2 in 25 cases. None of the clinical features was significantly associated with GEP classification. The only near-significant association was between increasing tumor thickness and the Class 2 GEP (Fisher exact test, P=0.07).

Conclusions: Clinical features associated with growth of choroidal nevi do not correlate well with a validated prognostic instrument for predicting metastatic risk in choroidal melanocytic tumors. The use of these clinical risk factors to make treatment decisions in patients with borderline choroidal melanocytic tumors outside of a clinical trial setting needs to be reassessed.
Mushroom Shaped Choroidal Lesions other than Melanoma

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PURPOSE: There is a general belief that a mushroom shaped fundus mass is highly suggestive, or even pathognomonic, of a uveal melanoma.

METHODS: We reviewed the charts of patients referred to an Ocular Oncology Service with lesions that had a mushroom shape clinically and with ultrasonography in which melanoma was a diagnostic consideration but who proved on further evaluation to have lesions other than uveal melanoma. We also reviewed the literature on other similar cases.

RESULTS: A total of 14 conditions, other than melanoma, demonstrating a mushroom configuration were identified. Those seen personally by the authors included adenocarcinoma of the retinal pigment epithelium, metastatic lung carcinoma to the choroid, late recurrence of retinoblastoma, ciliary body leiomyoma and a mycotic retinal abscess. Those shared with us by colleagues and/or cited in the literature included metastatic lung cancer, metastatic thyroid cancer, ciliary body schwannoma, choroidal hemangioma, age related macular degeneration, mycotic fungal abscess, retinal vasoproliferative tumor, solitary fibrous tumor of sclera, and idiopathic fibrovascular proliferation.

CONCLUSIONS: Most tumors in the ocular fundus that demonstrate mushroom configuration prove to be melanoma. However, there are well-established exceptions that show a mushroom configuration clinically and with ultrasonography and prove to be non-melanoma conditions. Clinicians should be aware of these mushroom shaped pseudomelanomas in order to make an accurate diagnosis and avoid misdirected management.
Tumor Regression Patterns Based on Gene Expression Profile Testing Radiotherapy for Uveal Melanoma: A Multicenter Study

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**PURPOSE:** Gene expression profile (GEP) testing of uveal melanoma (UM) can segregate these tumors into 2 main Classes based on survival probability. The purpose of this study is to determine the relationship between GEP status and UM tumor height regression following plaque brachytherapy (PBT).

**METHODS:** A retrospective, multi-center study was undertaken with UM patients entered from 9 major Ocular Oncology centers from across the United States. Eligible adult patients had UM treated by I-125 PBT, had a concurrent tumor biopsy at the time of surgery, and had a GEP test result from January 1, 2010 through June 30, 2014. Baseline overall group and GEP Class-specific demographic characteristics were obtained. Mean and percentage (%) change in tumor height was reported at 3-, 6-, 9-, 12-months. Statistical analysis was performed using Wilcoxon rank sums, Fisher’s exact test, and Kaplan-Meier analysis with p<0.05 held as significant.

**RESULTS:** A total of 353 eyes of 353 patients were eligible with a median follow-up of 2.1 years (range 0.5 to 5.3 years). GEP status divided the cohort into Class 1 (n=247) and Class 2 (n=106) UM tumors. Mean age and baseline UM dimensions were greater in Class 2 patients (p<0.006). Class 2 tumors, compared to Class 1, were thicker at all time points (p<0.001). However, the percentage reduction in tumor height from baseline was significantly greater in Class 1 vs. Class 2 tumors, respectively, at 3- (17.5% vs. 11.8%, p=0.007) and 6-months (26.8 vs. 17.1%, p=0.007) but not at 9- (p=0.26) and 12-months (p=0.57) after treatment. In UM with baseline apical height between 3mm to 8mm, greater % reduction was noted in Class 1 tumors at 3-, 6-, and 9-months (p<0.04 for each).

**CONCLUSIONS:** Class 1 tumors show a significantly greater percentage reduction in tumor height at early time points within the first year of treatment than Class 2 tumors. In COMS Medium size tumors, these reductions are noted for 9 months after treatment. This is the largest study to date that demonstrates a correlation between UM tumor height reduction and lower risk Class 1 GEP status.
Optical Coherence Tomography Angiography of the Macula after Plaque Radiotherapy of Choroidal Melanoma. Comparison of Irradiated versus Non-irradiated Eyes in 65 Patients

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Purpose: To study macular capillary density and foveal avascular zone (FAZ) in the superficial and deep capillary plexuses following plaque radiotherapy of choroidal melanoma using optical coherence tomography angiography (OCTA).

Methods: Retrospective analysis of 65 consecutive patients with choroidal melanoma. All patients were treated with standard dose I-125 plaque radiotherapy and imaged with OCTA. A comparison of irradiated versus nonirradiated (control) eyes was performed.

Results: The mean patient age was 55 years (median 56, range 12-81 years). Underlying medical diseases included diabetes mellitus (4/65, 4%) or hypertension (25/65, 38%), but no patient demonstrated disease-related retinopathy. The mean pre-treatment melanoma diameter was 11 mm (median 11, range 4-20 mm) and mean thickness was 5 mm (median 5, range 2-13 mm). At mean follow-up of 46 months after plaque radiotherapy, the most frequent finding on OCTA (irradiated eye) was non-perfusion in the superficial capillary plexus (19/65, 29%) and deep capillary plexus (20/65, 31%), followed by loss of choriocapillaris within tumor margins (11/65, 17%). The FAZ showed significantly larger mean area (irradiated vs nonirradiated eye) in the superficial plexus (0.961 mm² vs 0.280 mm², p < 0.0001) and deep plexus (1.396 mm² vs 0.458 mm², p < 0.0001), even in eyes without any clinical evidence of radiation maculopathy (superficial 0.278 mm², p=0.03; deep 0.454 mm², p=0.02). Parafoveal capillary density (superficial and deep) was decreased in all irradiated eyes (p<0.001). This difference was preserved after subgroup analysis of eyes with (p<0.001) or without (p<0.001) clinical or OCT evidence of radiation maculopathy. These findings could be more significant as some eyes were excluded from measured analysis due to uninformative OCTA image distortion from advanced cystoid macular edema (5/65, 8%), profound macular non-perfusion (5/65, 8%), and tumor-related image distortion (3/65, 5%).

Conclusions: OCTA demonstrated significant enlargement of the FAZ and decreased parafoveal capillary density of both superficial and deep capillary plexuses in eyes following plaque radiotherapy of choroidal melanoma, even in eyes with no clinical evidence of radiation maculopathy.
**Prognostic Value of Vascular Congestion In Mushroom-shaped Uveal Melanomas, Treated with Proton Beam Irradiation**

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**PURPOSE:** To evaluate the prognostic value of vascular congestion observed on panoramic ICG angiography (ICG-A) in mushroom-shaped uveal melanomas treated with proton beam irradiation.

**METHODS:** Between 2007 and 2013, 712 uveal melanoma patients were examined with panoramic (150°) FA and ICG-A, using the HRA2 camera and Staurenghi lens, before proton therapy. Of those cases, 202 were mushroom-shaped, of which 41 presented vascular congestion, i.e. a dilated vascular network at the top of the tumor on ICG-A. Their treatment results (minimal follow-up: 3 years) were compared to a control group of 41 mushroom-shaped melanoma cases without vascular congestion, but with a similar mean LTD (15.3 vs 15.8mm), thickness (8.4 vs 8.1mm), distance to disk (in contact in 24% vs 29%), extent of retinal detachment (≥3 quadrants in 24% vs 22%), visual acuity (≤0.1 in 22% vs 27%) and number of patients lost to follow-up (35% vs 32%).

**RESULTS:** At the last follow-up examination, the retinal detachment had resolved in 15% of cases, was ≤1 quadrant in 11%, 2 quadrants in 11%, and ≥3 quadrants in 63% against respectively 71%, 21%, 4% and 4% in the control group. Intraocular pressure was ≥28mmHg in 41% of cases against 14% in the control group. Visual acuity was ≤0.1 in 89%, 0.16-0.5 in 7% and ≥0.6 in 4% of cases against 71%, 25% and 4% in the controls. Neovascular glaucoma and vitreous hemorrhage were present in 52% and 41% against 14% and 4% in the control group. Secondary enucleation was performed in 22%, but none of the controls.

**CONCLUSIONS:** A vascular congestion on panoramic ICG-A in mushroom shaped uveal melanomas indicates a worse prognosis following proton beam irradiation of uveal melanomas. The efficacy of transvitreal tumor excision and/or intravitreal anti-VEGF and steroid injections in preventing complications and improving eye retention and visual function has not been yet clearly defined.
Survival in a Large Cohort of Patients with Metastasis from Uveal Melanoma

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Purpose: We previously evaluated survival after metastasis (Gragoudas ES et al. Ophthalmology, 1991) in a small group of patients with uveal melanoma treated by proton irradiation. The current project was undertaken to examine survival after metastasis in a larger series of patients with long-term follow-up.

Methods: We evaluated 3067 patients with uveal melanoma treated between 1982 and 2009. Data regarding metastasis were collected through active patient follow-up or medical records obtained from patients’ referring physicians. Survival rates after metastasis were calculated using the Kaplan-Meier method.

Results: Metastasis was diagnosed in 614 patients (20%); median time to metastasis after proton irradiation was 3.4 years. Median survival after metastasis diagnosis was 3.8 months. Ten percent of patients survived 1.5 years or more. Hepatic metastases were diagnosed in all but 49 patients (8%). The one year survival rate was 20%, and after 3 years, only 4% of patients with metastasis were alive. Fifty-two percent of patients with extrahepatic metastasis were alive at one year in contract to 22.5% of patients with hepatic metastasis. Treated patients (n=323) experienced a better outcome than untreated patients, with 29% alive at 1 year after diagnosis of metastasis compared to 5% of untreated patients. Median survival was 6 months for patients who received treatment compared to 1.5 months for patients who did not receive treatment. Chemotherapy was the most common treatment (44%) followed by treatment with more than one modality, e.g., radiation, surgery (35%).

Conclusions: Similar rates of survival were observed in this report compared to our earlier report, suggesting that advances in treatment leading to meaningful improvements in survival have not been realized.
Vision Loss Following Episcleral Brachytherapy: A Risk Calculator

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Purpose: To generate a risk calculator for vision loss following episcleral brachytherapy for uveal melanoma.

Methods: All patients with primary ciliary body or choroidal melanoma treated with iodine-125 or ruthenium-106 episcleral brachytherapy between January 1, 2004, and December 30, 2013 were included. Univariate and multivariable Cox proportional hazards were used to determine the influence of baseline patient factors on vision loss. Kaplan-Meier curves (log rank analysis) were used to estimate freedom from vision loss. Bootstrap resampling was performed to bias correct this estimate.

Results: Three hundred-eleven patients were included in the study (median follow up 36 months). At presentation, visual acuity was better than or equal to 20/50 and better than or equal to 20/200 in 199 and 289 patients, respectively. By Kaplan-Meier analysis, vision less than 20/200 at 3 years was not associated with sex, diabetes, systemic hypertension and hypercholesterolemia (p value > 0.05) but was associated with history of ocular co-morbidities, type of isotope (Ruthenium 106 or Iodine 125) and initial visual acuity (> or ≤ 20/50) (p value < 0.05). By multivariable analysis, age, largest basal diameter, total radiation dose to the fovea and optic disc, and initial visual acuity worse than 20/50 were predictive of vision loss less than 20/200. The concordance index for the full dataset was 0.77. Using this data, an online risk calculator was developed to predict vision loss following episcleral brachytherapy.

Conclusions: Vision prognostication tool presented herein needs to be validated by independent datasets. Such a tool may improve counseling of patients that are being evaluated for episcleral brachytherapy. At risk individuals identified by this tool, could be considered for inclusion into trials exploring prevention or treatment of radiation retinopathy and alternative therapies of uveal melanoma.
Vitreoretinal Surgical Management of Uveal Melanoma: Unique Intraoperative Findings and Outcomes

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**Purpose:** To report the surgical indications, operative findings and outcomes for microincisional vitrectomy surgery management of uveal melanoma. This series focuses on improving anatomic and visual outcomes for patients with uveal melanoma while maintaining excellent local tumor control. This study will discuss the impact of molecular tumor profiling on defining personalized treatment strategies incorporating tumor characteristics and gene classification.

**Methods:** IRB approved retrospective review of all uveal melanoma eyes undergoing MIVS surgery between 2012 and 2015. 342 eyes underwent MIVS utilizing a standardized surgical approach including 23/25 gauge valved trocar surgery, membrane peeling, endolaser tumor treatment, 25 gauge multi-pass FNAB, and intravitreal TA with a minimum follow-up of 6 months. Preoperative testing including quantitative a- and b-scan echography, sdOCT and widefield tumor imaging. Patients were followed with comprehensive ophthalmic evaluation, best corrected VA, IOP, tumor imaging, and targeted intravitreal anti-VEGF/TA at 4-16 week intervals. Reported outcomes include Kaplan-meier analysis of metastasis free survival, globe retention, radiation maculopathy/optic neuropathy, VA, IOP, and recurrent/progressive retinal detachment.

**Results:** Three hundred forty-two eyes were followed for a mean of 23 months (6-49 months). Pre-operative VA (mean) was 20/250 (20/25-LP). Unique intraoperative findings included tight vitreo-tumoral traction (329 eyes, 96%), tumor associated subretinal fluid/focal detachment (311 eyes, 91%), vitreous hemorrhage (20 eyes, 6%) and rhegmatogenous retinal detachment (13 eyes, 4%). No eyes were enucleated during the study window. 321 eyes received intravitreal bevacizumab or triamcinolone acetonide during the study period. Mean VA at 6 months was 20/70, at 1 year was 20/60 and at 2 years was 20/60. Mean IOP at 2 years was 15.6mmHg. 9 eyes (2.6%) underwent additional surgery with silicone oil tamponade for progressive retinal detachment. 2 eyes (0.5%) had clinical tumor progression and received supplemental 125Iodine brachytherapy. 22 patients developed melanoma associated metastatic disease and 6 patients died.

**Conclusions:** Advanced microincisional vitrectomy surgery (MIVS) improves both anatomic and visual outcomes for patients with uveal melanoma. Primary MIVS with endolaser tumor ablation and FNAB molecular tumor genomic testing may enable personalized tumor management by altering primary radiotherapy, incorporating novel adjunctive treatment, and focusing systemic oncologic screening. The intraoperative recognition of both focal subretinal fluid and tight vitreo-tumoral traction may be critical in understanding melanoma associated long-term complications including ischemia, radiation retinopathy/optic neuropathy, vitreous hemorrhage and ultimately progressive visual loss. Advances in MIVS surgery, intravitreal pharmacotherapy and intraoperative imaging have the potential to improve the quality of life for patients with uveal melanoma.
VISUAL BENEFIT OF IODINE-125 BRACHYTHERAPY WITH VITRECTOMY AND SILICONE OIL FOR LARGE CHOROIDAL MELANOMA: 1-TO-1 MATCHED CASE-CONTROL SERIES

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PURPOSE: Radiation treatment for large tumors is controversial due to high risk of local treatment failure and poor visual outcome. Having initially reported the iodine-125 radiation-attenuating effect and clinical benefit of silicone oil 1000 centistokes, we wanted to further elucidate the potential advantage of this technique for vision in larger sized melanoma.

METHODS: Patients diagnosed with a choroidal melanoma and for whom a 23 mm diameter iodine-125 plaque was constructed (largest size at our center) were included if there was at least one year follow-up. A one-to-one matched case-control comparison was performed to determine the effect of vitrectomy and silicone oil 1000 centistokes on visual acuity, ocular complications and metastatic outcome. Cases that underwent 23 mm diameter iodine-125 plaque with vitrectomy and silicone oil 1000 centistokes were matched to control patients who underwent plaque alone, with respect to tumor size and duration of follow-up.

RESULTS: 20 cases and 20 controls with choroidal melanoma treated with a 23 mm plaque were identified with average follow-up of 20.9 months. Average tumor height of cases was 7.8 mm (3.0 to 12.1 mm) and in controls, 7.9 mm (3.2 to 11.0 mm) (P=0.85). Average tumor greatest basal diameter of cases was 16.4 mm (14.0 to 20.9 mm) and in controls, 17.5 mm (14.0 to 21.3 mm) (P=0.05). Excluding patients with NLP vision, the final LogMAR vision was 0.83 in case patients and 2.06 in control patients (P=0.0064); the change from pre-treatment to last follow-up LogMAR vision in cases was 0.70 and 1.62 in controls (P=0.019). Of good vision results, 65% of cases and 25% of controls achieved vision >20/200 (P=0.025). Of poor vision results, 35% of cases and 80% of controls achieved vision <20/200 (P=0.0053), and 5% of cases and 35% of controls achieved LP or NLP vision (P=0.044). 39 of the 40 eyes (98%) achieved local tumor control at last follow-up. Metastasis was not statistically different between groups.

CONCLUSIONS: Iodine-125 for the treatment of mostly large choroidal melanoma is effective at achieving local tumor control at our center. Furthermore, combining brachytherapy with vitrectomy and silicone oil 1000 centistokes for radiation attenuation significantly improves vision over plaque alone. This report describes further evidence of visual advantage of radiation attenuation in eyes with uveal melanoma.
Safety and Efficacy of 25G Vitrectomy with Needle Biopsy of Choroidal Melanoma for Gene Expression Profiling (GEP) During Brachytherapy

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Purpose: To assess the safety and efficiency of 25g pars plana vitrectomy (PPV) with needle biopsy for choroidal melanoma.

Methods: Retrospective review of 67 consecutive eyes (67 patients) undergoing brachytherapy and 25g PPV. All patients also had choroidal melanoma biopsy with a 25g sharp 1.5” needle through the trocar during 25g PPV. Intraocular pressure was increased for approximately one minute and endolaser was applied to biopsy site for all patients to control for hemostasis.

Results: Adequate biopsy sample was obtained in 67/67 (100%) eyes for gene expression profiling (GEP). Early postoperative vision was stable or improved in 66/67 (98.5%) eyes due to ability to control hemostasis. Only 2/67 (2.98%) developed a complication (1 cataract, 1 transient vitreous hemorrhage) over a mean 16 (range 6-36) month follow-up.

Conclusions: 25g PPV with needle biopsy of choroidal melanoma during brachytherapy is an effective method for GEP assay allowing for controlled hemostasis, stable or improved visual acuity, and few complications.
Prevalence of Drusen and Conversion to Neovascular Age-related Macular Degeneration in Fellow Eyes in the HARBOR Study

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Purpose: To evaluate the prevalence of drusen types at baseline and the conversion to neovascular age-related macular degeneration (nAMD) based on FA and SD-OCT findings in fellow eyes of the HARBOR study population. The Age-Related Eye Disease Study 2 (AREDS2) demonstrated that in the subgroup of patients with bilateral large drusen and late AMD in one eye at baseline, 35.5% progressed to nAMD over a median of 4.9 years of follow-up.

Methods: Retrospective analysis of the 24-month, phase 3, randomized, double-masked, active-treatment controlled HARBOR study focusing on the fellow eyes that had drusen (hard or soft) at baseline without the presence of nAMD. Fellow eye conversion was defined as presence of CNV on FA and any fluid identified on SD-OCT defined as presence of subretinal fluid, cystoid space, intraretinal fluid, pigment epithelial detachment, or central subfield thickness $\geq 275$ µm at any post-baseline visits.

Results: In HARBOR, 352 fellow eyes had drusen without any nAMD at baseline. Of these, 28 (8%) eyes had hard drusen and 324 (92%) eyes had soft drusen. At 24 months, eyes with soft drusen had a higher rate of conversion to CNV than eyes with hard drusen (19% vs 4%, respectively). While the proportion of eyes with hard drusen at baseline was small, 92% of them developed soft drusen by 24 months. All fellow eyes that converted to nAMD had intermediate/large drusen at baseline. Eyes with a quantity of $>6$ intermediate/large drusen had a higher rate of conversion to nAMD than eyes with $0$--$5$ intermediate/large drusen at baseline.

Conclusions: In HARBOR, the majority of fellow eyes had soft drusen at baseline and 19% of these eyes converted to nAMD by 2 years. All fellow eyes that converted to nAMD had intermediate/large drusen at baseline with increased rate of conversion in eyes with $>6$ intermediate/large drusen. Most eyes with hard drusen at baseline converted to soft drusen over 2 years. These findings confirm that the type, quantity, and size of drusen appear to play a role in subsequent conversion to nAMD and should help guide clinicians to identify eyes that require vigilant monitoring.
Type 1 versus Type 3 Neovascularization in Pigment Epithelial Detachments Associated with Age-related Macular Degeneration after Anti-VEGF Therapy in the EVEN Study: Post-hoc Analysis of a Prospective Study

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Purpose: To evaluate the functional and anatomic response of type 1 and type 3 neovascularization in pigment epithelial detachments (PED) associated with treatment-naïve, neovascular age-related macular degeneration in a 12-month period.

Methods: EVEN is a multi-centered, prospective, interventional study. Eligible eyes underwent an intravitreal aflibercept injection protocol with 6 monthly loading doses followed by injections every 2 months. Visual acuity (VA) and morphologic features of the PEDs were compared at baseline and follow-up intervals between eyes with type 1 versus type 3 neovascularization.

Results: Thirty-six eyes from 36 patients were analyzed. At 12 months, type 1 eyes showed a $4.5 \pm 23$ ETDRS letter gain ($p=0.1665$), and type 3 eyes showed a $14 \pm 11$ ETDRS letter gain ($p=0.0072$), resulting in a 9.2 greater letter gain in type 3 eyes ($p = 0.0707$). Both type 1 and 3 eyes showed a decrease in PED size, subretinal fluid (SRF) volume, and subretinal hyper-reflective material volume (SRHRM) at month-12; however, type 3 eyes had a greater reduction in PED size and SRHRM. Both type 1 and type 3 lesions demonstrated geographic atrophy (GA), but type 3 lesions showed a greater incidence and rate of progression of the GA. Type 1 eyes with intraretinal fluid and type 3 eyes with SRF had worse VA than their counterparts at baseline. Simple linear regression modeling showed that PED size, SRF volume, and SRHRM were not predictive of VA; however, central retinal thickness was found to be predictive of final VA for type 1 eyes. Eyes that sustained RPE tears had greater baseline PED volume, maximal PED height and SRF volume. Type 1 eyes required an average of 1.636 (range 1-4) injections to eliminate exudation, which was greater than type 3 eyes that required an average of 1.143 (range 1-2) injections ($p=0.0251$).

Conclusions: Aflibercept monotherapy was highly effective for vascularized PEDs, but baseline and follow-up anatomical and functional outcomes differed according to neovascular subtypes. The more favorable response of type 3 eyes with less injections than type 1 eyes suggests differentiation of neovascular subtypes at baseline diagnosis may allow for a more tailored and optimal therapy.
Correlation of Optical Coherence Tomographic Hyperreflective Foci with Visual Outcomes after Treatment in Age-related Macular Degeneration and Polypoidal Choroidal Vasculopathy

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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 anti-vascular endothelial growth factor (VEGF) injection in neovascular age-related macular degeneration (nAMD) and polypoidal choroidal vasculopathy (PCV).

Methods: We retrospectively reviewed the medical records of 44 patients with nAMD and 44 patients with PCV. The number of HF were counted according to the location of HF on SD-OCT: neurosensory retinal layer, outer retinal layer and subretinal layer. Statistical correlation between final visual acuity (VA) and pre- and post-treatment OCT parameters including number of HF, the status of external limiting membrane (ELM) and inner segment ellipsoid zone (EZ) was evaluated.

Results: Number of HF in all retinal layers was reduced in nAMD and PCV after treatment. In multivariate regression analysis, final VA was associated with baseline VA (p=0.028), number of subretinal HF (p=0.046) and EZ disruption length (p=0.009) in nAMD. In PCV, final VA was associated with baseline VA (p=0.001), number of subretinal HF (p=0.001) and pigment epithelial detachment thickness (p=0.034). The baseline number of subretinal HF was correlated with final foveal thickness (FT), thickness of subretinal fluid and choroidal neovascularization in nAMD (p=0.002, p<0.001, p=0.009, respectively). In PCV, baseline number of subretinal HF was correlated with final FT, EZ and ELM disruption length (p=0.027, p=0.010, p=0.020, respectively).

Conclusions: The number of HF at subretinal layer on spectral domain optical coherence tomography at baseline might predict the final visual acuity after treatment in nAMD and PCV.
**En-face Spectral Domain Optical Coherence Tomography in Polypoidal Choroidal Vasculopathy**

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**PURPOSE:** Polypoidal choroidal vasculopathy (PCV) is a subtype of type I subretinal neovascularization that is more anti-VEGF resistant and may require alternative treatments including photodynamic therapy. Indocyanine green angiography (ICGA) is the main imaging modality for diagnosis, but is not always available or utilized. Optical coherence tomography (OCT) is widely available and non-invasive. En-face spectral domain optical coherence tomography (SD-OCT) may provide an alternative, and more widely available means to diagnose PCV to guide treatment decisions.

**METHODS:** A retrospective consecutive case series of 100 eyes (84 patients) diagnosed with PCV by ICGA were examined with en-face SD-OCT. The PCV complex imaged by ICGA was compared to the image obtained by en-face SD-OCT. Maximal visualization on en-face SD-OCT was obtained with scans directed below the retinal pigment epithelium with a slab thickness of 25-33 microns on the 512 x 128 macular cube scan. Evaluation was performed on: 1) the ability to diagnose PCV by the characteristic configuration of the branching vascular network and polypoidal dilations; 2) the size and extent of the PCV lesion.

**RESULTS:** The PCV complex was better visualized on ICGA in 45 eyes, on en-face SD-OCT in 44 eyes, and equally seen in 11 eyes. The size of the PCV complex was larger on en-face OCT in 65 eyes, larger on ICGA in 23 eyes, and equal in size in 12 eyes. Twenty eyes had a retinal pigment epithelial detachment (RPED) present. In patients with a RPED, lesion extent was larger on en-face SD-OCT in 17 eyes and on ICGA in 3 eyes. On en-face SD-OCT, the PCV complex was visualized as a dilated, irregular vascular structure with hyperechogenic borders and polypoidal vascular dilations as previously initially visualized on ICGA.

**CONCLUSIONS:** En-face SD-OCT imaging provides a topographical image that visualizes the typical features of the PCV complex and provides a means for diagnosis of PCV utilizing a non-invasive and widely available technology. It confirms the location of the PCV complex between the RPE and Bruch’s membrane. This technology potentially allows for broader recognition of PCV and guide for treatment alternatives to anti-VEGF therapies.
**Changes in Dark Adaptation and Structure by Optial Coherence Tomography in Age-related Macular Degeneration**

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**Purpose:** Visual acuity is a limited functional endpoint for age-related macular degeneration (AMD), as it remains largely unchanged until late stage AMD. Impairment in night vision and a prolonged time of rod-mediated dark adaptation (DA) has been described in early AMD. This study aimed to identify structural parameters associated with time to dark-adapt in AMD.

**Methods:** Cross-sectional, prospective study, including patients with AMD and a control group. All participants underwent ophthalmologic examination; color fundus photographs (CFP); spectral-domain OCT with enhanced-depth imaging protocol; and dark adaptation testing (extended protocol) in both eyes. AMD staging was based on the AREDS CFP grading system. A software program was developed to map the DA 2º testing spot (at 5º on the superior retina) on the OCT b-scans and to obtain the mean retinal and choroidal thickness in the same area. Two independent graders evaluated the b-scans corresponding to this spot and recorded the presence of several AMD-associated abnormalities. Univariate and multivariate multilevel mixed effect linear models (accounting for correlated outcomes between 2 eyes) were used for analyses.

**Results:** We included 82 eyes: 10 controls, 10 with early AMD, 47 with intermediate and 15 with late AMD. The mean age of the four study groups was 61.3 ± 8.2, 71.3 ± 13.4, 69.2 ± 4.9 and 69.7 ± 5.6 years, respectively. The median rod intercept time (RiT) of the control eyes was 4.4 minutes. AMD eyes presented a median RiT of 7.0, 18.1 and 20 minutes for early, intermediate and late disease, respectively. AMD severity stage was an independent predictor of RiT in the univariate and multivariate analyses (p≤ 0.002), with intermediate and late eyes presenting a significantly impaired RiT as compared to early AMD and control eyes (p≤0.002). Similarly, the presence of any structural abnormalities in the mapped OCT areas corresponding to the DA testing spot was significantly associated with a prolonged RiT in the univariate and multivariate assessments (p<0.001 for both). Multivariate analysis revealed that reduced retinal thickness (β=-0.07, p=0.020) and the presence of drusen (β=2.92, p=0.023) in the mapped regions were significantly associated with a prolonged RiT.

**Conclusions:** Our preliminary work demonstrates a structure-function correlation in AMD.
**Adjunctive Indocyanine Green Angiography-directed Verteporfin Photodynamic Therapy for the Treatment of Persistent Disease Activity in Neovascular Age-related Macular Degeneration**

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**PURPOSE:** 1) Identify rates of persistent disease activity (PDA) in neovascular (NV) AMD following loading-dose treatment (three consecutive monthly intravitreal injections) with aflibercept; and 2) assess efficacy of adjunctive indocyanine green angiography (ICGA)-directed verteporfin photodynamic therapy (PDT) for the treatment of PDA in spite of anti-VEGF therapy in patients with NV AMD.

**METHODS:** 1) prospective observational open-label single-arm study of newly diagnosed NV AMD patients undergoing loading dose with aflibercept (n=49); and 2) prospective open-label single-arm study of adjunctive ICGA-directed verteporfin PDT for treatment of PDA in spite of anti-VEGF therapy (n=16). Study groups were stratified by pre-anti-VEGF treatment ICGA subtype. Response to treatments (anti-VEGF and adjunctive PDT) was assessed by clinical exam, OCT, and fluorescein angiography (FA) and classified as either “PDA” (unresolved OCT fluid, FA leakage, FA lesion growth, hemorrhage, or progressive fibrosis), or quiescent, using a categorical disease activity scale.

**RESULTS:** Moderate / severe PDA occurred in 24.5% of patients following aflibercept loading-dose treatment, including evidence of progressive disease (lesion growth, worsened hemorrhage) in 8.2% of patients. In comparison, the rate of moderate / severe PDA was 36.4% in a comparator observational cohort of NV AMD undergoing loading-dose with bevacizumab. Moderate / severe PDA occurred most frequently in patients with ICGA morphologic subtype of branching arteriolar vascular complex (BAVC). Among cases that were quiescent following aflibercept loading-dose, disease reactivation (fluid, hemorrhage, lesion growth) on extension beyond 6 weeks treatment interval occurred in 25% of patients, and these cases were comprised of BAVC and polypoidal choroidal vasculopathy (PCV) subtypes on ICGA. Patients with PDA undergoing ICGA-directed PDT were comprised of ICGA subtypes of BAVC (56.2%), PCV (18.8%), and choroidal leak syndrome (25%). Treatment success of adjunctive PDT, defined as NV AMD disease quiescence at 6-months post-PDT, was achieved in 68.8% of eyes with prior PDA on anti-VEGF monotherapy.

**CONCLUSIONS:** PDA in spite of anti-VEGF remains a significant problem in NV AMD, particularly for those patients with BAVC subtype on ICGA. ICGA-directed verteporfin PDT, which produced sustained resolution of PDA in a majority of patients, should be considered as a secondary, adjunctive treatment option for NV AMD patients with PDA.
Impact of Anti-VEGF Therapy on Photoreceptor in Patients with Exudative Age-related Macular Degeneration

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Purpose: Anti-VEGF therapy is widely used for patients with exudative age-related macular degeneration (AMD). It has been known that VEGF plays an important role in maintenance of photoreceptor as well as vascular complications (angiogenesis and vascular leakage). Various experiments have reported that VEGF inhibition could affect photoreceptor survival. In this study, we examined the impact of anti-VEGF therapy on photoreceptor in patients with exudative AMD.

Methods: Prospective observational cohort study. Consecutive 194 patients with AMD were included. 183 patients received anti-VEGF therapy, whereas eleven patients did not receive any treatment. All patients underwent a full ophthalmologic examination including spectral-domain optical coherence tomography (SD-OCT) and prototype adaptive-optics scanning laser ophthalmoscopy (AO-SLO) (Canon Inc.) during follow-up. AO-SLO images focused on the photoreceptor layer were recorded in the area without any pathological lesion at every visit. The present study examined cone density in each image to estimate the temporal change of the photoreceptors.

Results: During this study, there was no apparent adverse event in enrolled patients. Analyzable AO-SLO images could be obtained from 35/183 (19.1%) in anti-VEGF therapy-treated group (16 patients; intravitreal ranibizumab, 19 patients; intravitreal aflibercept) and 10/11 eyes (90.9%) in untreated group at the first examination. In both untreated and treated groups, the cone densities at three, six, twelve and eighteen months later did not significantly differ from one at the first examination. The ratio of cone density (treated/untreated) at three, six, twelve and eighteen months later were 0.99, 1.00, 1.01 and 1.05, respectively.

Conclusions: Current methods of anti-VEGF therapy may have no effect on healthy photoreceptor in patients with exudative AMD.
Evaluation of Choroidal Perfusion with Rapid-scan Plane Wave Ultrasonography

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Purpose: We have demonstrated, in a pilot IRB study, that sildenafil is useful in treating macular degeneration, in support of the hypothesis that macular degeneration is significantly related to choroidal ischemia. In this study, we used a new technique, ultra high-speed plane-wave ultrasound to evaluated changes in choroidal blood flow following sildenafil administration.

Methods: We scanned the eye of normal subjects before and 1 and 2 hours after administration of 40 mg of sildenafil. A research ultrasound imaging system was used with a 128-element 18 MHz linear array probe. The system was programmed in Matlab to perform compound coherent plane-wave imaging, with 10,000 B-scans acquired at 10 angles per second. Images depicting retrobulbar and choroidal flow were produced in post-processing and power-Doppler amplitude (a measure of perfusion) for the choroid characterized. Ultrasound intensity was within FDA guidelines.

Results: Choroidal perfusion (systolic, diastolic and mean) increased significantly from baseline at one and two hours.

Conclusions: Documentation of the effects systemic PDE-5 inhibitors on choroidal ischemia in macular degeneration can be enhanced with direct measurement of choroidal perfusion rather than solely by alterations in choroidal thickness by EDI-OCT. It can also be of value in studying the effects of choroidal perfusion in other conditions.
Maculopathy in Patients with Monoclonal Gammopathy of Undetermined Significance

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Purpose: To describe retinal findings, laboratory values, and treatment response of patients with pre-malignant immunogammopathy presenting with exudative maculopathy.

Methods: We retrospectively reviewed the medical and ocular histories, ocular examination findings, retinal imaging, ocular disease course, and laboratory findings in 4 patients with exudative maculopathy associated with monoclonal gammopathy of undetermined significance (MGUS).

Results: Six eyes of four patients (2 men and 2 women aged 59-80 years) demonstrated neurosensory macular detachments with treatment-resistant submacular fluid and vitelliform deposits. No eyes demonstrated signs of significant hyperviscosity retinopathy. Fluorescein angiography showed no leakage in any involved eye. Laboratory evaluation revealed IgG kappa MGUS in 3 patients and kappa light chain MGUS in one patient. Two patients had elevated free light chain ratios, an MGUS feature consistent with a higher risk of malignant transformation. Three patients were resistant to multiple treatment modalities, including anti-VEGF injections, photodynamic therapy (PDT), topical dorzolamide, and/or systemic eplerenone. One patient responded to PDT; however, laboratory evaluation revealed decreasing serum IgA over the same time interval. Over follow-up ranging from 29 to 108 months, two patients underwent malignant transformation, one to Waldenstrom’s macroglobulinemia and one to multiple myeloma. The patient who developed multiple myeloma was successfully treated with a bone marrow transplant, but suffered a relapse in which recurrent subretinal fluid preceded hematologic laboratory abnormalities by several months despite frequent testing.

Conclusions: Exudative maculopathy without fluorescein leakage and unresponsive to conventional treatment may suggest an underlying immunoproliferative disorder. Given the propensity for pre-malignant monoclonal immunogammopathies to transform into malignant disease with time, serum protein analysis should be considered in patients with atypical or treatment-resistant serous macular detachment.
The National Eye Institute Visual Function Questionnaire-25 Responsiveness to Changes in Area of Geographic Atrophy in Patients with Age-related Macular Degeneration

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Purpose: The National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) has been shown to be valid and reliable in patients with geographic atrophy (GA) from age-related macular degeneration (AMD). The present study examined the responsiveness of the NEI VFQ-25 to GA area growth in patients with advanced AMD.

Methods: In a post hoc analysis of data from Mahalo, a randomized, sham-controlled, phase 2 trial that evaluated lampalizumab for GA secondary to AMD, the NEI VFQ-25 was interviewer-administered at baseline, 6, 12, and 18 months. Only US subjects were included in this analysis (n=100). Treatment arms were combined for these analyses. Responsiveness of the NEI VFQ-25 was assessed by analysis of covariance, controlling for age, gender, and corresponding NEI VFQ-25 baseline scores. Patients were grouped according to whether the growth in GA area from baseline to 18 months was <2.75 mm² or ≥2.75 mm² (2.75 mm² growth being the median change for the entire cohort). Results are presented for the overall composite, near-activity, and distance-activity subscales, pre-defined secondary endpoints of interest in the ongoing lampalizumab phase 3 trials.

Results: For patients with GA area growth <2.75 mm² (n=37), the mean (SD) changes in NEI VFQ-25 score from baseline to 18 months were −0.2 (9.7), −0.3 (12.8), and 1.8 (15.8) for composite, near-activity, and distance-activity scores, respectively. For patients with GA area growth ≥2.75 mm² (n=42), the mean (SD) changes in NEI VFQ-25 score were −5.1 (12.7), −5.8 (19.9), and −6.4 (19.4) for the composite, near-activity, and distance-activity scores, respectively. The differences in NEI VFQ-25 scores between patients with <2.75 mm² versus ≥2.75 mm² GA area growth were −4.9 (p=0.04), −5.5 (p=0.03), and −8.2 (p=0.04) for the composite, near-activity, and distance-activity scores, respectively.

Conclusions: On average, visual function measured by the NEI VFQ-25 composite, near-activity, and distance-activity scores declined more for patients with GA area growth ≥2.75 mm² versus <2.75 mm². These data demonstrate the responsiveness of the NEI VFQ-25 to change in GA area and support the use of the overall composite, near-activity, and distance-activity scores as outcome measures in clinical trials of patients with GA.
A Simple Optical Coherence Tomography-based System for Scoring the Risk of Progression in Eyes with Intermediate Age-related Macular Degeneration

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PURPOSE: To develop and assess the prognostic value of a simple clinically-practical OCT-based scoring system for intermediate non-neovascular AMD.

METHODS: In this retrospective study, we analyzed 98 consecutive patients who had intermediate non-neovascular AMD in at least one eye, featuring at least one large drusen, but no atrophy or evidence of choroidal neovascularization (CNV) at baseline (a total of 119 eyes met these criteria). A minimum of 6 months of follow-up data was also required. All eyes were imaged with a Cirrus HD-OCT using a 512x128 cube (6x6mm) centered on the fovea. Each eye was scored based on three SD-OCT criteria: drusen volume (DV) ≥ 0.03mm³ (provided automatically by the Cirrus advanced RPE analysis), presence of intraretinal hyperreflective foci (iHRF), and presence of hyporeflective cavities (IHC) within drusen. Presence of each criteria was assigned one point and summed for both eyes, resulting in a total score (TS) of 0 to 6 for each patient. If one eye already had evidence of choroidal neovascularization or RPE atrophy, it was automatically given 3 points. The correlation of baseline TS with progression to AMD by the last follow-up visit was evaluated with logistic regression analysis.

RESULTS: Mean follow-up was 28.50±15.80 (6-64) months. At the patient level, the rate of progression was 40.8% (40/98), with a steady increase in the likelihood of progression with increasing scores (P<0.001; odds ratio [OR], 2.99; 95% confidence interval [CI], 1.88-4.74). At the eye level (N=119 eyes with intermediate AMD at baseline), the progression rate was 39.5% (47/119). When assessing the importance of individual sub-criteria, only iHRF and IHC were statistically significant (DV, P=0.777 OR=0.86 [CI] 0.31-2.39; IHRF, P<0.001 OR=0.077 [CI] 0.02-0.29; IHC, P=0.001 OR=0.17 [CI] 0.06-0.48) predictors of progression.

CONCLUSIONS: A simple scoring system relevant to prognosis for intermediate AMD, and practical for use in a busy clinic, can be developed using SD-OCT criteria.
Prevalence and Natural History of Asymptomatic Macular Neovascularization in Non-exudative Age-related Macular Degeneration Diagnosed using Optical Coherence Tomography Angiography

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Purpose: To characterize the prevalence and natural history of subclinical type 1 neovascularization in asymptomatic eyes with intermediate age-related macular degeneration (iAMD) using swept source optical coherence tomography angiography (SS-OCTA).

Methods: Consecutive patients with asymptomatic iAMD in one eye and neovascular AMD in their fellow eye underwent prospective, IRB-approved, research SS-OCTA imaging. En face images were reviewed for the presence of macular neovascularization (MNV) in the non-exudative eye. The en face slab used for the detection of MNV extended from the outer retina to the choriocapillaris (ORCC). A novel projection artifact removal algorithm was applied to these en face flow images for better visualization of the MNV contained within the ORCC slabs. A novel quantitative algorithm was then applied to the artifact-free flow images to obtain area measurements of the neovascular lesions. In a subset of patients, fluorescein angiography (FA) and indocyanine green angiography (ICGA) were available to confirm the presence and size of MNV.

Results: Eighty consecutive patients with iAMD in one eye and neovascular AMD in their fellow eye were imaged with SS-OCTA between August 2014 and March 2016. Of the 80 dry AMD eyes images, 11 (13.8%) were found to have subclinical MNV in the eye with non-exudative AMD. Three of the eyes underwent FA and ICGA imaging, and ICGA confirmed the presence of plaques with the same size and at the same location as the MNV detected using OCTA. Follow-up imaging of these three eyes demonstrated minimal changes in the size and configuration of the MNV over periods ranging from 5 to 11 months without detection of exudation by OCT imaging. Follow-up of the remaining 8 eyes with MNV is ongoing.

Conclusions: SS-OCTA identified type 1 MNV in asymptomatic eyes with iAMD. The ability to detect MNV and measure its complexity and size over time was enhanced by the use of novel algorithms that removed projection artifacts and measured the neovascular area. Our improved ability to rapidly and non-invasively identify these neovascular lesions in eyes with iAMD suggests the need for a new classification system that distinguishes between neovascular and non-neovascular “dry” AMD.
Evaluating Intravitreal Brimonidine Tartrate Drug Delivery System (Brimonidine DDS) in Patients with Geographic Atrophy in a Phase 2 Study

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Purpose: Although the pathogenesis of geographic atrophy (GA) is not fully understood, protection of retinal pigment epithelium and photoreceptors from cell death may help slow progression of retinal degeneration and curb vision loss. Brimonidine, an alpha2-adrenergic agonist, has demonstrated neuroprotective activity in animal models such as retinal ischemia and blue light-induced retinal phototoxicity. The effectiveness, safety and tolerability of Brimonidine DDS, an intravitreal implant comprised of brimonidine in a slow-release matrix, was evaluated in the treatment of GA.

Methods: This phase 2, multicenter, randomized, double-masked study included patients with bilateral GA attributable to age-related macular degeneration, no evidence of choroidal neovascularization, and best-corrected visual acuity (BCVA) between 70 and 35 letters (Snellen equivalent 20/40-20/200). Patients were randomized (2:2:1) to receive Brimonidine DDS 200 µg or 400 µg, or sham treatment in the eye with worse BCVA (Study Eye) at Baseline and Month 6, with follow-up until Month 24. The primary efficacy endpoint was change in GA area from baseline at Month 12.

Results: One hundred thirteen patients received intravitreal Brimonidine DDS 200 µg or 400 µg, or sham treatment (49, 41, and 23, respectively). Mean change in GA area from baseline was consistently lower in both Brimonidine DDS-treated groups versus the sham group. Mean change in GA area was significantly (P = 0.032) smaller with Brimonidine DDS 200 and 400 µg versus sham at Month 3. Thereafter, reductions in GA lesion area in the Brimonidine DDS-treated groups versus the sham group were observed, but these differences were not statistically significant. Brimonidine DDS was well-tolerated; treatment-related ocular adverse events were predominantly attributed to the injection procedure, the most common being conjunctival hemorrhage and conjunctival hyperemia.

Conclusions: Brimonidine DDS was safe and well-tolerated. The change in GA lesion growth was significantly lower in Brimonidine DDS-treated groups compared with sham at Month 3. Although smaller changes in GA area from baseline were observed with active-treatment versus sham after Month 3, they were not statistically significant and likely related to reduced intravitreal brimonidine concentrations, as suggested by animal data. A second-generation intravitreal brimonidine DDS implant with enhanced vitreal bioavailability is currently being evaluated.
**New Diagnostic Choroidal and Retinal Signs of Type 1 Neurofibromatosis**

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**Purpose:** To evaluate in a large cohort of children affected by neurofibromatosis type 1 (NF 1) the diagnostic performance of two new choroidal and retinal signs.

**Methods:** Five hundred consecutive children (age < 15 years) affected by NF1 and 100 healthy subjects were consecutively included. Each patient underwent genetic, dermatologic, and ophthalmologic examination, to evaluate the presence/absence of each NIH standard diagnostic criterion for NF 1. The presence of NF1-related choroidal abnormalities was investigated using near infrared (NIR) confocal ophthalmoscopy. Fundus multimodal retinal imaging, including fluorescein and indocyanine green angiography, and OCT angiography were performed in patients with NF1-related retinal microvascular abnormalities, also evidenced at NIR ophthalmoscopy.

**Results:** NF 1-related choroidal abnormalities were detected in 297/500 (59.4%) NF1 patients. No healthy subject had choroidal abnormalities. Sensitivity, specificity, and positive and negative predictive values of NF1-related choroidal abnormalities were 0.62, 0.98, 0.97, and 0.45, respectively. Compared with standard NIH criteria, the presence of NF1-related choroidal abnormalities was the third parameter for positive predictive value and the fourth for sensitivity, specificity, and negative predictive value. NF1-related retinal microvascular abnormalities were detected in 27 (5.4%) of NF 1 patients, and in no one healthy subject (p<0.001). These changes consisted of small, tortuous retinal vessels with a “spiral/corkscrew” aspect and originating from retinal veins. The location of NF1-related retinal microvascular abnormalities did not correlate with that of NF1-related choroidal changes. No leakage was detected by any angiographic examination, and OCT angiography showed vascular aspects similar to previously known “ocular phakomatosis” histopathologic data.

**Conclusions:** Choroidal abnormalities, evidenced by a fully non invasive ocular technology, may represent a new criterion for NF 1 diagnosis. Retinal microvascular alterations, a more intriguing retinal aspect of NF 1, represent a fully new aspect of this disorder, strictly correlated to a phakomatosis disorder.
Ultra-wide Field Autofluorescence in ABCA4 Stargardt Disease

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Purpose: To report the ultra-wide field autofluorescence (UWF-FAF) patterns in Stargardt disease (STGD) and genotype/phenotype correlations on UWF-FAF.

Methods: UWF-FAF images were captured that produced high resolution images of the ocular fundus with up to a stated 200-degree field. Four independent graders evaluated images. Electronic medical records were reviewed for demographics, clinical exam and additional ancillary data including electroretinograms (ERG) when available.

Results: UWF-FAF was performed on 58 eyes of 29 patients. Mean age was 46 ± 15 years (range 22-73). Review of images revealed the presence of peripheral (outside the 55 degree view of standard non-widefield FAF imaging) alterations on UWF-FAF in 76% of eyes. Overall, the UWF-FAF pattern was classified as type I in 24% eyes (14/58), type II in 24% (14/58) and type III in 52% (30/58). The most common genetic mutations were c.2588G>C (6/29 patients, 20.7%), c.5882G>A (5/29 patients, 17.2%) and c.4222T>C/c.4918C>T (3/29 patients, 10.3%).

Conclusions: UWF-FAF reveals peripheral changes in the majority of patients with STGD. Peripheral fundus autofluorescence changes may offer the potential to better correlate specific genotypes with phenotypic manifestations of the disorder, and as such may have implications for diagnosis.
Features of Posterior Staphylomas Analyzed by Ultra-wide Field Optical Coherence Tomography and 3D Magnetic Resonance Imaging

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**Purpose:** To determine the incidence and types of posterior staphylomas in a large series of patients with pathologic myopia by multimodal imaging including wide-field fundus imaging, three-dimensional magnetic resonance imaging (3D MRI), and ultra-wide field OCT.

**Methods:** A total of 1,060 eyes of 541 patients with high myopia (axial length > 26.5 mm) in at least one eye were analyzed. We focused on pigmentary abnormalities along the presumed edge of staphylomas in wide-field fundus images in determining the presence and types of staphyloma. 3D MRI analyses of the eye shape as well as ultra-wide field OCT using a prototype machine were also performed.

**Results:** Posterior staphyloma was detected in 552 of 1060 eyes (55%) in images. Wide macular type was the most common (79%), followed by narrow macular (15%), then peripapillary (3%), then inferior, and finally nasal. In the eyes examined by all of 3D MRI, and wide-field OCT, the results of the three examinations were highly correlated for the presence and types of staphyloma. Ultra-wide field OCT images using a prototype machine clearly visualized the entire figure of the posterior segment even in eyes with wide staphyloma in a 3 dimensional way.

**Conclusions:** Posterior staphyloma was found in 55% of eyes with pathologic myopia. Wide macular was the most common, although there were much more variations in the shape of staphylomas than had been previously believed. Ultra-wide field OCT is considered to be a novel and powerful tool to examine the shape of the posterior staphyloma.
Choroidal Changes Associated with Serous Macular Detachment in Eyes with Staphyloma or Dome-shaped Macula

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Purpose: To study the choroidal abnormalities in eyes with dome-shaped macula (DSM) or posterior staphyloma (PS) and their relationship to serous retinal detachment (SRD).

Methods: An observational, retrospective, cross-sectional, multi-center study of consecutive myopic patients demonstrating PS or DSM. Group 1, 28 eyes of 20 patients with DSM and PS associated with SRD was compared to Group 2, 30 eyes of 20 patients, with DSM or PS but without SRD. Radial and enface optical coherence tomography (OCT) scans, were performed and detailed choroidal analysis was performed, cross-sectional, multi-center study of consecutive myopic patients demonstrating PS or DSM.

Results: Group 1 had a thicker mean subfoveal choroidal thickness (161µm versus 92µm, p<0.05) and a greater variation in choroidal thickness (112µm versus 76µm, p>0.05) compared to eyes of Group 2. Focal abrupt changes in choroidal thickness were more commonly seen in Group 1 versus eyes in Group 2 (90% versus 30%, p<0.05). In eyes with SRD, the area of abrupt change in choroidal thickness was located within or at the edge of the SRD in 64% of eyes. In the remaining eyes, the area of abrupt change was within 1500µm of the edge of the SRD. Presence of SRD was always associated with large choroidal vessels (pachyvessels), and 82% had pachyvessels within the area of SRD.

Conclusions: A focal area of increased subfoveal choroidal thickness and an abrupt transition in choroidal thickness, accounted for by dilated choroidal pachyvessels, was seen more commonly in DSM and PS and TDS eyes with SRD than in eyes without SRD and may have a causal role in the pathogenesis of this disorder. Due to significant variations in the appearance of the SRD and the DSM and the retinal and choroidal morphology obtained with OCT scan lines at different orientations in eyes with DSM or PS, a radial scan pattern should be considered as a preferred protocol for imaging in myopic eyes.
OPTICAL COHERENCE TOMOGRAPHY-ANGIOGRAPHIC VASCULAR PERFUSION DENSITY MAPPING FINDINGS IN OPTIC DISC PIT

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PURPOSE: To describe the Spectral-Domain OCT-angiographic findings using vascular perfusion density mapping in eyes with optic disc pit.

METHODS: A retrospective review was performed on the optic nerves of subjects with optic disc pit and normal contralateral eyes with a spectral domain optical coherence tomography system. Split-spectrum amplitude-decorrelation angiography (SSADA) generated optical coherence tomography angiograms of the superficial retinal capillaries, deep retinal capillaries, and choriocapillaris. Skeletonized optical coherence tomography angiograms were used to create color-coded perfusion maps and capillary perfusion density values for each image. Capillary perfusion density values were compared between the optic disc pit eye and the contralateral normal eyes and with clinical staging, and groups were compared using analysis of variance (with a Bonferroni post hoc) and Kruskal-Wallis analyses.

RESULTS: Four optic disc pit eyes and the four contralateral eyes were imaged. Mean patient age was 46, (range 32-67) and mean logMAR visual acuity was 0.4 in optic pit eyes (range 0-0.7) and 0.1 in normal eyes (range 0-0.3). Capillary perfusion density (CPD) values of normal and optic pit discs from each microvascular layer were compared. Kruskal-Wallis analysis revealed that optic disc CPD values were significantly lower than normal eyes for the “inside disc” region of the nerve head microvascular layer (p=0.043); “inferior nasal” (p=0.043), and “temporal” (p=0.021) regions of the radial peripapillary capillary (RPC) microvascular layer. In contrast, Kruskal-Wallis analysis revealed that optic disc CPD values were significantly higher than normal eyes for “inferior temporal” (p=0.021), “superior temporal” (p=0.043), and “nasal” (p=0.021) regions of the choroidal microvascular layer. ANOVA analysis followed up with a Bonferroni post hoc test revealed that optic disc CPD values were significantly lower than normal eyes for the “temporal” region of the RPC microvascular layer (p=0.017). All other optic disc capillary perfusion density value comparisons between normal and optic pit eyes were not statistically significant using both ANOVA and Kruskal-Wallis analyses (p>0.05).

CONCLUSIONS: Quantitative retinal vascular capillary perfusion density mapping demonstrated significant differences in the radial peripapillary capillary and choroidal vasculature between the optic disc pit eyes and the contralateral normal eyes. Thus, OCT-angiography and capillary perfusion density mapping suggests an abnormal vascular supply in optic pit discs, which may contribute to decreased visual acuity in this disease.
DUALING IMAGERS: ADAPTIVE OPTICS SCANNING LASER OPHTHALMOSCOPY FLUORESCIN ANGIOGRAPHY CHALLENGES OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY

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PURPOSE: OCT Angiography (OCTA) is the latest challenge to conventional fluorescein angiography (FA) with higher resolution, noninvasive, quantitative visualization of retinal microvasculature. We compared similarities and differences of OCTA to an even higher resolution FA using Adaptive Optics SLO (AO SLO) in side-by-side tests on healthy and diseased eyes.

METHODS: A dozen eyes, 6 with diabetic retinopathy, retinal vein occlusion, or sickle cell retinopathy and 6 controls were imaged using a commercial system and our laboratory AOSLO-FA. A 10x10° OCTA full vessel layer scan and a 6x6° AOSLO-FA montage centered at the fovea were obtained for each eye. Foveal avascular zone (FAZ) area, perimeter, and acircularity (FAZ perimeter divided by perimeter of circle with equal area) were measured. Vessel density at 3 annular regions of interest (ROI) defined by distance away from the FAZ margin (100, 200, & 300 µm outer diameter) was computed as the total vessel length divided by ROI area. Paired t-tests were used to assess statistical significance. Vessel patterns and deletions of paired images were analyzed for differences.

RESULTS: OCTA revealed many details seen with AOSLO-FA but not on conventional FA. FAZ perimeter, acircularity, and vessel density at all 3 ROIs showed no statistically significant difference. FAZ areas differed slightly but to statistically significant extent (OCTA 0.38±0.27 vs AOSLO-FA 0.38±0.28 mm²; p=0.02). Some vessel segments in AOSLO-FA images were not seen on OCTA and vice versa. While AOSLO-FA has a lateral resolution 10 times better than OCTA (1.3 micron vs. 13 micron) it currently requires intensive post-processing, delaying its clinical utility. Shorter scan times, immediate image reconstruction and the ability to delineate multiple capillary layers in a single scan, make OCTA more clinically available than AOSLO FA. Both techniques are heavily fixation dependent and more vulnerable to media opacities and movement artifacts than conventional FA.

CONCLUSIONS: OCTA of the fovea matched AOSLO-FA in diseased as well as healthy eyes with only minor quantitative and qualitative differences. These comparisons help support the validity of OCTA as a quantitative tool for clinical angiography. Ongoing serial studies with larger numbers of subjects will test its predictive capabilities.
Power Law Flow Patterns in the Choriocapillaris as Imaged by Optical Coherence Tomography Angiography

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Purpose: To characterize the structure of choriocapillaris flow from optical coherence tomography angiography (OCTA) data.

Methods: En face OCTA images 9 microns thick were obtained of the choriocapillaris using an imaging system. Flow voids of any size were counted and measured following automatic local thresholding using the Phansalkar method with a radius of 15 pixels, a method that can compensate for variations in illumination of the sample (ImageJ 1.50i, National Institutes of Health). Data were then analyzed with IBM SPSS version 21. Eyes with drusen or any other defect sufficient to cause shadowing of the choriocapillaris image were excluded.

Results: There were 47 eyes of 33 subjects ranging in age from 24 to 81 years. The voids was found to follow a power law relationship with the form log(area) = Alog(number) + C, where area is the size of the void, A is a constant that varies from one individual to the next, number is the number of voids at any given size, and C is a constant. The slope of the relationship, represented by A, did not vary with age (P=0.15, generalized estimating equations [GEE]) while it was markedly associated with having a history of age-related choroidal neovascularization (CNV) in the fellow eye (P=.008, GEE). As a consequence fellow eyes with a history of CNV were much more likely to have large flow voids (P<.001, GEE) than eyes with no associated CNV in their fellow eye.

Conclusions: Investigation of many biologic systems shows scale invariant patterning that can be described mathematically, and the flow patterns in the choriocapillaris are salient examples. Using this approach a definite difference in eyes with and without fellow eye involvement with CNV was found. This finding may offer insights into the pathophysiologic mechanisms that may precede CNV. Additional research needs to be done to determine if this tool can predict if eyes are at risk for CNV based on their choriocapillaris flow patterns. This methodology employed can easily be incorporated into OCTA instrument software.
Sensitivity and Specificity of Choroidal Neovascularization Detection with Optical Coherence Tomographic Angiography in Age-related Macular Degeneration

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Purpose: To determine the sensitivity and specificity of optical coherence tomographic angiography (OCTA) in the detection of choroidal neovascularization (CNV) in age-related macular degeneration (AMD).

Methods: Thirty-two eyes with treatment naïve CNV, 20 eyes with non-neovascular AMD, and 20 healthy eyes from age-matched controls underwent OCTA with a commercially available high-speed spectral domain OCT. The 3D angiogram was segmented into separate en face views of the inner retinal slab, outer retinal slab, and choroid. Masked graders reviewed the en face angiograms. Abnormal vascular networks in the outer retinal slab served as candidate CNV. The sensitivity and specificity of CNV detection with OCTA was determined for each grader.

Results: Of 32 eyes with CNV, both graders identified 26 true positives with OCTA, resulting in a sensitivity of 81.3%. Four of the six false negatives had large subretinal hemorrhage (SRH) that prevented detection of CNV with OCTA. Of the two other false negatives, one was associated with a large fibrovascular pigment epithelial detachment, and the other had a very small CNV that was difficult to discriminate from shadow graphic projection artifact. The sensitivity improved to 92.9% for both graders if eyes with SRH were excluded. Of 40 eyes without CNV, Grader A identified 37 true negatives for a specificity of 92.5%. One false positive occurred because of motion artifact in an eye with non-neovascular AMD. The other false positive occurred in a region of geographic atrophy where a segmentation error resulted in choroidal vessels present in the outer retinal slab. Grader B identified 38 true negatives for a specificity of 95%. One false positive was associated with motion artifact in a healthy control eye. Both graders identified a false positive that likely represents a subclinical non-exudative CNV. After 15 months of follow-up, this lesion grew slowly with OCTA and was visible with ICGA, but remained dormant clinically.

Conclusions: OCTA has high sensitivity and specificity in the detection of CNV. SRH reduces OCT signal and can interfere with CNV detection. Excluding cases of SRH, sensitivity is above 90%.
Comparison of Optical Coherence Tomography Angiography Biomarkers for Distinguishing Diabetic Subjects with Varying Levels of Retinopathy from Non-diabetic Healthy Controls

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Purpose: To evaluate and compare the sensitivity of current and investigative optical coherence tomography angiography (OCTA) biomarkers for distinguishing eyes with varying levels of diabetic retinopathy (DR) from non-diabetic healthy controls who had undergone OCTA.

Methods: OCTA was performed over a central 3*3 mm macular area using a commercial spectral domain system in patients with diabetes with or without DR and age-matched healthy controls. Sensitivity analysis was performed for the following biomarkers: vascular percentage (VP) obtained by binarization, vessel length (VL) obtained by skeletonization, number of vascular junctions (J), foveal avascular zone (FAZ) area, fractal dimension (FD), and lacunarity (L).

Results: A total of 95 diabetic and 46 age-matched healthy control eyes were included. The following mean values were obtained in the superficial vascular plexus of healthy versus diabetic eyes: VP 53 vs. 47 %, VL 188 vs. 151 mm, J 1504 vs. 1213, FAZ 0.29 vs. 0.44 mm², FD 1.817 vs. 1.812, L 0.222 vs. 0.233. The following mean values were obtained in the deep vascular plexus of healthy versus diabetic eyes: VP 59 vs. 53 %, VL 212 vs. 178 mm, J 1599 vs. 1393, FAZ 0.40 vs. 0.66 mm², FD 1.818 vs. 1.815, L 0.216 vs. 0.225. All indices were statistically different in diabetic versus healthy eyes (P<0.001). However, vascular percentage, vessel length, and number of junctions were all equally superior in detecting diabetic eyes irrespective of state of DR. Area under curve (AUC) values of these indices were >0.92 for superficial and >0.91 for deep vascular networks. Variables obtained through skeletonization, including vessel length and number of junctions, best distinguished healthy eyes, diabetic eyes without DR, and different stages of DR.

Conclusions: OCTA vascular biomarkers consisting of vascular percentage, vessel length, and number of junctions performed better than FAZ area and measures of network complexity in distinguishing diabetic eyes from healthy controls. Vessel length and number of junctions may be more sensitive at differentiating diabetics without retinopathy from those with retinopathy as well as healthy controls.
Intraoperative Ultrahigh Speed Swept Source Optical Coherence Tomography (OCT) for Widefield Imaging, OCT Angiography, and 4D Imaging

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Purpose: Intraoperative optical coherence tomography (OCT) enables non-invasive, high-resolution, depth-resolved imaging during ophthalmic surgical procedures. While commercial intraoperative spectral domain OCT systems can obtain cross-sectional images, ultrahigh speed intraoperative swept source OCT enables densely sampled widefield imaging, repeated scanning for OCT angiography (OCTA), and rapidly acquired volumes for 3D renderings of surgical procedures in real time.

Methods: Imaging was performed on patients undergoing anterior and posterior segment ophthalmic surgery at Tufts Medical Center. The OCT module attached after the objective lens of a surgical microscope to scan the anterior and posterior segments of the eye. The OCT system was powered by a 1050 nm wavelength vertical cavity surface-emitting laser (VCSEL) swept laser source operating at 400,000 A-scans per second. The laser swept through a 75 nm wavelength length for ~9 um axial resolution in tissue and the measured laser output power is below the 1.9 mW safety limit.

Results: 12 x 12 mm², 1000 x 1000 A-scan widefield volumes were acquired in 2.9 seconds before and after the surgical procedure. The pre-operative widefield volumes display the extent of the ocular pathology and the post-operative volumes can gage the results of the operation without the patient leaving the operating room. Each OCTA image, which consisted of 5 repeated OCTA volumes comprising 500 x 500 A-scans, was acquired in 3.6 seconds. OCTA provides non-invasive flow information in the vasculature of the retina during the operation without need for dye injection. 600 x 100 A-scan volumes were repeated acquired at a rate of 5.6 volumes per second to generate 3D renderings over time. These 4D volumes can be used to dynamically monitor the direct interactions of a surgeon’s tool on the tissues of the eye.

Conclusions: Ultrahigh speed swept source OCT offers many additional imaging modalities over standard intraoperative spectral domain OCT systems to provide additional insight during surgical procedures.
Physician-industry Interactions and Anti-VEGF Utilization among U.S. Ophthalmologists

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Purpose: The recent publication of the Physician Payments Sunshine Act provides unparalleled insight into the financial relationship between physicians and the pharmaceutical industry in the United States. Here, we assess the association between industry payments and physician prescribing habits by comparing the utilization of anti-vascular endothelial growth factor (VEGF) intravitreal injections by U.S. ophthalmologists to the industry payments these same physicians received.

Methods: Review of the Centers for Medicare and Medicaid Services (CMS) 2013 Provider Utilization and Payment Data and the CMS-sponsored 2013 Open Payments (Physician Payments Sunshine Act). Ophthalmologists prescribing anti-VEGF injections for all indications were compared by assessing the number and type of injections administered to industry payments received.

Results: 3,011 U.S. ophthalmologists were reimbursed by CMS for 2.2 million anti-VEGF injections in 2013. Of these physicians, 38% also received $1.3 million in industry payments for ranibizumab and aflibercept. Bevacizumab was not marketed by the pharmaceutical industry to ophthalmologists. Analysis showed positive associations between increasing numbers of industry payments to total injection utilization (r=0.24, P<0.001, 95% CI [0.22 – 0.26]), to aflibercept/ranibizumab injection utilization (r=0.32, P<0.001, 95% CI [0.29 – 0.34]), and to percent of injections per provider that were aflibercept/ranibizumab (r=0.27, P<0.001, 95% CI [0.25 – 0.29]). A smaller association was noted between greater number of industry payments and bevacizumab injection utilization (r=0.07, P<0.001, 95% CI [0.04 – 0.09]). Similar associations were found between the total dollars of industry payments received to injection utilization. Subgroup analysis further demonstrated that physicians who received as little as $1-25 in industry benefits were also more likely than those not receiving industry payments to perform a greater percentage of their injections with aflibercept/ranibizumab (P<0.001).

Conclusions: Among ophthalmologists prescribing anti-VEGF medications, there is a positive association between pharmaceutical payments received and increased utilization of aflibercept/ranibizumab injections. As is inherent to the design of correlation studies, this analysis does not determine exposure-outcome or causal relationships.
RAYMOND R. MARGHERIO AWARD PRESENTATION

SPECTRAL-DOMAIN OPTICAL COHERENCE TOMOGRAPHY IMAGING OF THE RETINAL VASCULAR-AVASCULAR JUNCTION IN INFANTS WITH RETINOPATHY OF PREMATURENESS

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PURPOSE: Bedside examination of premature infants at risk for retinopathy of prematurity (ROP) using spectral domain optical coherence tomography (SDOCT), is predominantly performed with en face viewing. Here we present bedside, non-sedated in vivo cross-sectional imaging of retinal microstructures at the vascular-avascular junction in infants with ROP using a handheld SDOCT imaging system.

METHODS: We captured bedside imaging of the vascular-avascular junction in the temporal retina using a SDOCT system in 17 eyes from 10 preterm infants with zone I or II, stage 0 through 4 ROP. B-scan and en face images were analyzed and compared to historical histopathology images.

RESULTS: Distinct inner retinal layers were identifiable posterior to the vascular-avascular junction, while in anterior avascular retina, the inner retinal layer was composed of a single hyperreflective band in stage 0 and stage 1 ROP. A clear ridge structure was observed at the vascular-avascular junction on OCT imaging in stage 2 ROP, and there was prominent preretinal neovascular elevations and significant thickening of the inner retinal layer of avascular retina in stage 3 ROP. Retinoschisis-like changes were observed in eyes with stage 4 ROP posterior to retinal detachment. Outer retinal layers were the same in vascular and avascular retina on OCT imaging. We also visualized small neovascular buds in stage 2 ROP and inner retinal split in stage 3 ROP, both of which were not evident on clinical examination. Regression of preretinal neovascular elevation and progression of retinal vascularization were noted after intravitreal bevacizumab therapy for type I ROP.

CONCLUSIONS: The development of retinal layers at the vascular-avascular junction imaged with bedside non-contact SDOCT is consistent with limited known histopathology. OCT images could be reviewed in vivo over time. These findings provide novel information of the timing and pattern of inner retinal morphology in preterm infants’ eyes with ROP. The ability to visualize temporal and spatial changes in the infant peripheral retina will enable study of neurovascular development during normal and pathological conditions.
J. DONALD M. GASS AWARD

SURVEYING THE PAST AND CHARTING A PATH FORWARD FOR THE SUCCESSFUL TREATMENT OF MACULAR DEGENERATION WITH GENE THERAPY TECHNIQUES

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With recent advances in molecular genetics, the opportunity now exists to explore gene therapy as an alternative treatment approach to ARM. In addition to potentially reducing the treatment burden of frequent injections for the patient and doctor, there also exists the possibility of reducing the associated peaks and valleys in drug concentration that may contribute to untoward complications. This can be accomplished by programming sustained in situ production of relevant therapeutic protein levels by transduction of tissue with the corresponding cDNA. Initial human trial results have been mixed for reasons that have been poorly understood until now.

I present a brief review of the rationale, basic principles and promising results of gene therapy pre-clinical studies that led to the performance of recent human trials using the transgene for sFlt-1 (VEGFR1) which were more mixed and disappointing than expected to many. As a result additional pre-clinical studies were performed using both the sFlt-1 transgene and cDNA for other anti-angiogenic agents to explore whether modifications either in the structure of the secreted protein, the method and site of injection, and alternative vectors and expression cassettes might overcome some of the limitations encountered in the human initial studies.

We discovered that when the sFlt-1 transgene encoded within rAAV2 was injected subretinally beneath the center of the macula, it was possible to nearly completely inhibit the development of experimental choroidal neovascularization in a NHP model induced by high power short duration laser pulses to the macular region. However, when the same transgene and vector were injected in the posterior pole but not under the center of the fovea, the effect was dramatically diminished in a dose dependent fashion. With an alternative novel rAAV vector, optimized by the process of directed evolution for more efficient retina transduction and encoding an enhanced expression cassette for different anti-VEGF transgenes, it was possible to obtain excellent prevention of experimental choroidal neovascularization in the same model, both when the vector was injected beneath the retina away from the center of the fovea and also by a traditional intravitreal non-subretinal route. In contrast, when the same optimized vector and specific promoter coupled to the cDNA for sFlt-1 was injected either intravitreally or subretinally, away from the center of the fovea, the effect was dramatically reduced.

These results provide insight into better understanding the results of prior pre-clinical and early human clinical trials with first generation vectors and promoters as well as the pharmacokinetic and pharmacodynamics differences when cDNA encoding different therapeutic peptides are employed. The design of future gene therapy trials for ARM based upon these new understandings may yield increasingly promising results for this form of therapy for patients with ARM and other retinal diseases.
THE IMPACT OF EXERCISE ON QUALITY OF LIFE AND PROGRESSION OF DISEASE IN RETINITIS PIGMENTOSA

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PURPOSE: Exercise has been found to be neuroprotective in animal models of retinal degeneration. This study aims to evaluate exercise patterns in patients with retinitis pigmentosa (RP) and investigate the effect of exercise on quality of life (QOL) and visual function.

METHODS: Adult patients with RP seen at a single academic center from 2005 to 2014 were identified. Exercise habits were assessed using the Godin Leisure-time Exercise Questionnaire via telephone survey. The SF-36 general health survey, National Eye Institute Visual Function Questionaire-25 (NEI VFQ-25), and Pepper Assessment Tool for Disability (PAT-D) were administered to evaluate QOL. A retrospective chart review was conducted to collect clinical data.

RESULTS: 143 of 496 patients participated in the phone survey (28.8%). The mean age of study participants was 46.9 years. 81 (56.6%) patients were classified as “Physically Active”, and 62 (43.4%) were “Insufficiently Active”. Under the category of clinical disease progression, active patients had a higher initial GVF score than the Insufficiently Active subjects, but this difference did not reach statistical significance (74.8 vs. 60.1, p=0.2552). Final GVF scores were also higher in the Active group, and this difference approached but did not reach statistical significance (78.7 vs. 47.1, p=0.0689). Most notably, Patients with vascular disease (Hypertension, Diabetes and heart disease) had significantly lower GVF scores (46.2 vs. 80.0, p=0.0110). History of smoking, however, was found to have lower GVF scores (69.14 vs. 72.24, p=0.6366) but not statistically significant. Under the category of QOL, active patients scored more favorably on the NEI VFQ-25 (53.3 vs. 45.1, p=0.0104), the physical component summary of the SF-36 (52.9 vs. 47.2, p=0.0022), and the PAT-D (24.34 vs. 30.0, p=0.0096). 66 of 142 respondents were employed (46.5%). Current employment was found to be significantly associated with more favorable scores on the NEI VFQ-25, SF-36 and PAT-D.

CONCLUSIONS: In patients with RP, an active lifestyle is associated with improved QOL. Vascular disease is associated with more advanced visual field loss. More research is warranted to evaluate the influence of exercise on QOL and progression of disease in RP.
Glucose Re-establishes Cone Outer Segment Synthesis and Function in Retinitis Pigmentosa

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Purpose: Retinitis pigmentosa (RP) is a disease caused by genetic mutations in rod photoreceptors that result in their dysfunction and death. However, it is the subsequent loss of cone photoreceptor function (i.e. the development of dormant cones) that is responsible for loss of functional vision. We studied the ability of rod progenitor cell transplants to rescue dormant cones and identified the mechanism of this rescue effect.

Methods: The pig model of P23h retinopathy has a visual streak (i.e. an area of cone dominance) that is analogous to the macula and allows the study of cone photoreceptors function and structure. Porcine embryonic day 65 (E65) normal (i.e. wild-type) rod progenitor cells or rod-differentiated induced pluripotent stem cells (iPSCs) were transplanted into the subretinal space in P23h retinopathy at P60 – a time when there are no rod photoreceptors and there is total loss of cone outer segments (OS). 5x10^5 cells in 50µl was injected beneath the visual streak in the experimental eye, with diluent alone in the control eye. Morphologic studies (light microscopy, immunohistology and electron microscopy) and electrophysiology (multifocal ERG [mfERG]) were performed at 1-3 months post transplantation.

Results: Both E65 rod progenitor cells and rod-differentiated iPSCs when transplanted at P60, when cone OS are lost, resulted in the regrowth of opsin+ cone OS for a radius of 1000µm from the transplant site beneath the visual streak. Additionally, the photopic mfERG was increased in regions surrounding the transplant site correlating with endogenous cone OS restoration. No effect was seen with the sham transplant. Since we have evidence that glucose becomes sequestered in the RPE and is not delivered to photoreceptors in the P23h retina, we injected glucose at a concentration of 280 mM in 50µl beneath the visual streak in the P23h retina at a time when rods are lost and cones retain inner segments but no OS; media was injected in the contralateral eye. After three days we found that opsin+ cone OS were restored in a 1500µm radius from the site of glucose injection but not in the eye with subretinal media.

Conclusions: P23h retinopathy is a pig model of RP with progressive loss of cone function. Transplanted normal (wild-type) rod precursors result in endogenous cone OS synthesis and the return of dormant cone electrophysiologic function. Rod photoreceptor loss appears to limit cone access to glucose which becomes sequestered in the RPE and is not delivered to photoreceptors in the P23H retina. Transplanted rod precursors restore cone access to glucose and subretinal glucose replacement alone reactivates cone OS synthesis and induces enzymes in cone photoreceptors associated with the aerobic metabolism of glucose. Thus, pharmacologic modulation of glucose metabolism in RP may prevent cone dormancy and result in the persistence of cone function in the absence of rod photoreceptors.
The Role of Autophagy in Photoreceptor Degeneration in the P23H Mouse Model of Autosomal Dominant Retinitis Pigmentosa

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Purpose: Mutations in the rhodopsin molecule are a major cause of autosomal dominant retinitis pigmentosa (ADRP). The mechanism by which these mutations result in retinal degeneration is not known. Autophagy is a major intracellular catabolic pathway that contributes to maintenance of cell homeostasis. In this study we examine the role of autophagy in regulating photoreceptor cell death in the P23H mouse of ADRP.

Methods: We modulated autophagy activity in the rod cells both genetically and pharmacologically. For the former, we created a variant of the P23H mouse in which all the rod cells were defective in their capacity to initiate autophagy by crossing the P23H mouse with the Atg5-delta-rod mouse. Pharmacologic activation of autophagy was achieved with temsirolimus, a derivative of rapamycin. Reduction in autophagy flux was achieved with hydroxychloroquine. We assessed the rate of autophagy activation and its effect on retinal degeneration. We also assessed for activation of secondary death pathways under these various conditions.

Results: We predicted that autophagy depletion would result in a more rapid degeneration of the photoreceptors in the P23H mouse, due to a reduction in the capacity to remove the mutant rhodopsin molecule. Paradoxically, we observed that depletion of autophagy activation in the rod cells resulted in a marked reduction of photoreceptor degeneration in the P23H mouse. We observed a state of hyper-autophagy in the P23H mouse, particularly at younger ages. In addition to hyper-autophagy, we also detected up-regulation of apoptosis pathways.

Conclusions: Hyper-autophagy is a major contributor to photoreceptor cell death in the P23H model of ADRP. This novel finding provides a potential therapeutic point of intervention for patients with this form of retinal degeneration.
Distinguishing Retinitis Pigmentosa from Severe Hydroxychloroquine Toxicity

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Purpose: Advanced hydroxychloroquine (HCQ) retinopathy is well known to cause extensive retinal degenerative pathology from pericentral or diffuse retinitis pigmentosa (RP).

Methods: This is a retrospective case series, approved by Stanford Medical School IRB. Patients seen in the past 10 years with severe HCQ toxicity (n=11; ages 32-82) or pericentral RP (n=9; ages 25-83) were included if modern images were available. Pericentral RP was characterized as a limited ring of degeneration, excluding severe visual loss. All patients, except one with RP, had a full field ERG. Most patients had wide-field fundus autofluorescence (FAF) and Goldmann fields.

Results: We initially thought inferior damage might differentiate HCQ and RP, but this was not a sharp discriminator. We thought HCQ damage might be relatively focal, since early toxicity is focal, but HCQ retinopathy was actually very diffuse. Patients with HCQ retinopathy, relative to pericentral RP, showed few fundus spicules, only rarely a foveal FAF glow-ring, and fuzzy rather than sharp borders to the degeneration. In contrast to pericentral RP, the ERG in HCQ retinopathy showed greater rod loss, and much more delayed flicker ERG time-to-peak. Relative to typical RP, HCQ patients had no history of long-standing night blindness, rod and cone involvement was similar, and Goldmann fields were surprisingly well-preserved.

Conclusions: Most of our HCQ patients showed a combination of fundus, field and ERG features that were found only irregularly in pericentral RP. To a large degree these reflect the facts that HCQ retinopathy was a relatively recent event, and HCQ is a systemic metabolic toxin that affects the entire retina. Very severe retinopathy mimics conventional RP, but without long night blindness and with better visual fields.

Occam’s razor argues against implicating a second disease unnecessarily, when there is an obvious history of major HCQ exposure. Furthermore, pericentral RP is a rather rare disease, and diffuse RP would be strangely mild in our older HCQ patients. In theory gene testing could definitively rule out RP, except that present tests are neither sufficiently reliable nor affordable.
LONG-TERM OUTCOMES OF HUMAN EMBRYONIC STEM CELL DERIVED RETINAL PIGMENT EPITHELIAL CELL TRANSPLANTATION FOR RETINAL DEGENERATION

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PURPOSE: To summarize long-term safety data and clinical outcomes of two prospective phase I/II studies assessing safety and tolerability of human Embryonic Stem Cell (hESC) derived retinal pigment epithelial (MA09-hRPE) cell transplantation in patients with atrophic age-related macular degeneration (AMD) and Stargardt disease (SD).

METHODS: Visual acuity (VA) and images of patients participating in two phase I/II open-label, multi-center, prospective clinical trials investigating subretinal injection of hESC-derived RPE cell suspension in patients with atrophic AMD and SD were evaluated.

RESULTS: Patients with severe vision loss (no better than 20/400) due to atrophic AMD (n=10) and SD (n=10) were treated. Mean follow-up is 2.97 years in AMD and 3.14 years in SD arm. No cases of tumor formation, macular edema, secondary glaucoma, retinal detachment, adverse preretinal RPE cell engraftment, vascular occlusion, or obvious rejection have been observed. Fifteen patients (75%) developed increased subretinal pigmentation. Excluding 3 AMD and 6 SD patients who experienced significant cataract progression, mean VA improved by 14.3 letters in the treated and 3.0 letters in the fellow eyes of AMD subjects, and improved by 8.4 letters in the treated eyes but deteriorated by 2.7 letters in the fellow eyes of SD subjects. BCVA improved by ≥15 letters in 2 of 7 (29%) AMD subjects and in 1 of 4 (25%) SD subjects at 24 months.

CONCLUSIONS: These long-term results suggest that hESC-derived RPE cells could provide a safe new source of cells for the treatment of medical conditions caused by tissue loss or dysfunction. Further work to assess efficacy of this treatment modality is warranted.
Comparing iPSC Derived Retinal Pigment Epithelial (RPE) Cell Cultures and Commonly Used RPE Cell Lines: What a Clinician Should Know

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PURPOSE: Many preclinical studies use RPE cell lines in translational experiments. We wish to describe similarities and differences between iPSC derived RPE (iPSc-RPE) cultures and commonly used RPE cell lines.

METHODS: Eleven total induced pluripotent stem cell lines were obtained from the Mayo Clinic BioTrust and cultured in media on coated plates. Differentiation of iPSCs to RPE was performed on coated plates following a 80 day protocol using defined media. Differentiation was assessed using morphologic, biochemical, and functional criteria. Cells were passaged using one of 4 different enzymatic preparations. Cells were then subject to additional passages during which they were switched to DMEM/F12 (70%/30%) containing 1% FBS at 0, 7, 14, or 28 days after plating. After 3 passages, cells were assessed to determine whether they possessed an RPE phenotype based on marker expression, morphology, physiology, and functional characteristics. These cells were compared to ARPE-19 and D407 RPE culture cell lines.

RESULTS: Immunoprecipitation and Western blotting demonstrates that, iPSC RPE, but not iPSCs express RPE65, Best1, and CRALBP, but iPSCs do not. Densitometry of Western blots normalized to b-actin expression demonstrates that RPE65 and Best1 expression increase with time in culture. Morphologically, ARPE-19 (A, B) and D407 cells are not pigmented, while iPSC-RPE exhibit a high level of pigmentation when observed in tissue culture plates or under the microscope Only iPSC-RPE produce a hexagonal monolayer as would be observed of RPE in the eye. Western blot does not detect CRALBP, Best1, or RPE65 protein in either ARPE-19 or D407 cells. All three are expressed by iPSC RPE.

CONCLUSIONS: Morphologically and biochemically, there is a difference between iPSC-RPE and commonly used RPE cell culture lines. Future studies requiring the use RPE cell cultures should also include using iPSC-RPEs.
Phenotypic Matching for Genetic Confirmation of Retinal Dystrophies

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Purpose: Genetic testing is now more readily available for patients with retinal dystrophies, however, interpretation of results can be difficult as mutations are often difficult to be differentiated from polymorphisms. A machine learning program that predicts the most likely gene causative of a patient’s phenotypic profile using input information about patient demographics, electroretinogram (ERG) response, visual field, pattern of inheritance, and fundus autofluorescence (FAF) features can aid the identification of the gene mutation causative of disease.

Methods: Clinical phenotypic data; patient age, sex, ERG response, visual field, family history, FAF imaging, and genetic diagnosis was collected on 152 patients seen at the Kellogg Eye Center. After filtering out mutated genes that affected fewer than 5 patients, 102 patients were usable for machine training purposes. Machine learning algorithms were developed to predict the genes most likely to be mutated and causing the observed clinical features for a given patient. Machine learning used 80/20 training/testing splits of the data. The classification performance compared with that of a baseline classifier.

Results: A prototype has been created that has greater than 60% accuracy for predicting the causative mutated gene for a particular patient’s phenotype. Based on questions related to family history, the prediction accuracy of pattern of inheritance was 72%. This prototype is currently being shown to other retinal dystrophy clinics for helping clinicians encountering diagnostic dilemmas with genetic testing and determining inheritance particularly when a genetic counselor may not be readily available for pedigree analysis. With the continued collaboration of outside institutions, the functionality of the algorithm will be improved.

Conclusions: The generation of this machine learning program provides ophthalmologists with a prediction of a causative mutated gene and likely pattern of inheritance when evaluating a patient with a retinal dystrophy. This may help ophthalmologists refine their clinical diagnosis and identify most relevant genetic testing to order. Additionally, genetic test results can often be difficult to interpret. Programs such as PolyPhen and SIFT help to determine whether or not a variant detected in a gene is truly pathogenic by assessing the molecular characteristics of the variation. Our program realizes the value of phenotypic features and variable expression of gene mutations to further refine the subset of gene mutations most likely to cause the clinical features manifesting in a particular patient.
Orally Delivered, Synthetic Chromophore Therapy for Inherited Retinal Disease Due to Genetic Defects in the Visual Cycle

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Purpose: To study the safety and efficacy of orally-delivered QLT091001 (9-cis-retinyl acetate) in patients with inherited retinal disease diagnosed as retinitis pigmentosa (RP) or Leber congenital amaurosis (LCA) caused by mutations in the RPE65 or LRAT genes (“IRD”).

Methods: Three open-label Phase Ib trials were conducted in patients with IRD caused by autosomal recessive mutations in RPE65 or LRAT (IRD01 and IRD02), or RP caused by an autosomal dominant mutation in RPE65 (RP01). Dosing regimens included a single course (once daily dosing for 7 days) of 10 or 40 mg/m² QLT091001 in IRD01; up to 3 courses of 10, 40 or 60 mg/m² QLT091001 at intervals of ≥1 month in IRD02; and a single course of 40 mg/m² QLT091001 in RP01. Visual function tests included Goldmann visual field (GVF) and standardized best-corrected visual acuity (BCVA) at baseline, days 7-9, 14, 30, 60 and approximately bimonthly thereafter. Safety assessments included ophthalmic and physical examinations, electrocardiograms and laboratory blood work.

Results: Thirty-two patients were enrolled in IRD01, 27 of whom subsequently enrolled in IRD02. Five patients were enrolled in RP01. Ages ranged from 6-67 years. There was 1 withdrawal (by request) from IRD01, and 4 withdrawals from IRD 02; 3 by request and 1 due to intracranial hypertension (ICH), the only serious adverse event seen in these studies. The ICH resolved with appropriate therapy. Common non-serious adverse events were transient and/or reversible. Improved visual function (≥20% increase in GVF area and/or ≥5 ETDRS letter increase in BCVA for at least 2 consecutive visits) was observed in 81% of patients in each of IRD01 and IRD02, and 80% of patients in RP01.

Conclusions: Orally-delivered QLT091001 for IRD demonstrated improvements in visual fields and/or visual acuity in the majority of subjects in the three Phase Ib studies. Adverse events were consistent with the retinoid class. A Phase III placebo-controlled trial is planned to confirm these results.
Pathogenesis in Autoimmune Retinopathy

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Purpose: We investigated cellular immune responses in autoimmune retinopathy (AIR) patients. AIR patients typically present with histories of sudden onset of photopsias, progressive scotomata, abnormal ERGs, visual field losses, no retinal pigment deposits, and autoimmune family histories. Presence of anti-retinal autoantibodies (ARA) in combination with the above findings is considered diagnostic.

Methods: Patients meeting AIR criteria were consented for blood donation. Serum ARAs were evaluated by Western blot, and ELISA. Peripheral blood mononuclear cells (PBMC) were isolated and analyzed by multi-color flow cytometry for markers of lineage and activation of a broad range of T, B and innate lymphocyte subsets. PBMC were cultured for six days with human recoverin protein to test for recall T helper cell responses. Cytokine output was measured by ELISA for interferon gamma (IFNγ) and interleukin-10 (IL-10). An "inflammatory index" was calculated as the ratio of IFNγ/IL-10 concentrations.

Results: Although high in most patients, ARA did not correlate with disease activity or progression. Compared to healthy controls, most AIR patients (66%) had activated CD69+CD8+ cytotoxic T cells and 27% had natural killer cells that were at least one standard deviation (StDev) above normal. Regulatory CD24^{high}CD38^{high} B cells were lower in 45% of patients, while CD27+CD43+ B cells were elevated in 47% of patients compared to controls. The regulatory IL-10 response toward recoverin was low in 87% while proinflammatory Th1 cytokine IFNγ was elevated in 46% of patients. Inflammatory indexes IFNγ/IL-10 were >2 standard deviations above normal in 57% percent of AIR patients. Among a cohort of nine newly diagnosed and untreated AIR patients, the inflammatory index averaged 24.1±8.3 compared to 2.3±0.6 index for thirteen controls. After 5-10 months of immune suppression, IFNγ production decreased an average of 10.04±4.79 fold in patients (n=4) that were followed to date.

Conclusions: Our studies strongly suggest that IFNγ plays a major role in the pathogenesis of AIR, but the other cellular immunity abnormalities found suggest a complicated pathogenesis with variation of the disease stimulus in patients. With further development of these tests, we expect they can provide better diagnostic tools that detect active AIR, and allow improved monitoring of treatment.
North Carolina Macular Dystrophy (MCDR1): Mutations Found Affecting PRDM13

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Purpose: We originally reported four mutations affecting PRDM13 in eleven families causing North Carolina Macular Dystrophy. An international cohort of additional 20 families were sequenced and analyzed reporting mutations causing North Carolina macular dystrophy (NCMD, MCDR1).

Methods: We initially performed targeted Nex Gen sequencing of the MCDR1 region (870kb) in 8 affected individuals from 3 families representing 3 different haplotypes affected with chromosome 6 linked NCMD (MCDR1). In addition to our original 11 MCDR1 families recently published (141 total subjects), we now have an additional cohort of 10 families with the NCMD phenotype available for study. (total of 367 subjects, 21 families total).

Results: We initially found 14 rare variants spanning 870kb of the disease-causing allele. One of these variants (V1, ch6:1000400906) was absent from all published databases and all 261 controls, but was found in a total of 13 NCMD kindreds. This variant lies in a DNase 1 hypersensitivity site (DHS) upstream of both the PRDM13 and CCNC genes. Sanger sequencing of 1 kb centered on V1 was performed in the remaining NCMD probands, and 2 additional novel single nucleotide variants (V2, ch6:10000987, in 6 families and V3, ch6:100041040 in 1 family) were identified in the DHS within 134 bp of the location of V1. A complete duplication of the PRDM13 gene was also discovered in a single family (V4). The 4 mutations V1 to V4 segregated perfectly in the 118 affected and 33 unaffected members of the 21 NCMD families.

Conclusions: We identified 4 rare mutations in a non-coding region, each capable of arresting human macular development by causing over expression of PRDM13. Additional families with the NCMD phenotype continue to support that these mutations are causative of MCDR1 / NCMD.
ENDOPHTHALMITIS AFTER OPEN GLOBE INJURIES WITH AND WITHOUT RETAINED INTRAOCULAR FOREIGN BODIES

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PURPOSE: To report clinical and anatomic outcomes in the treatment of endophthalmitis associated with open globe injuries (OGI) with and without intraocular foreign bodies (IOFB).

METHODS: A retrospective, interventional case series of OGI (n=718) treated at a tertiary referral center between 2004 and 2015. Patients younger than 18 years old and patients undergoing primary enucleation were excluded. Patients underwent a standard management protocol for OGI including systemic broad spectrum antibiotics on presentation. All patients with IOFB received prophylactic intravitreal antibiotics (Vancomycin/Ceftazidime ± Amphotericin). Retinal surgeons performed globe repair with the use of pars plana vitrectomy for trauma involving zone three injuries and for IOFB removal.

RESULTS: The study included 718 patients, with a mean age of 51 years (range 18-98 years). The mean length of follow-up was 12.32 months. Anatomically, 33% (n=242) of eyes had zone 1 injuries, 19% (n=136) had zone 2 injuries and 10% (n=73) had zone 3 injuries. There was no significant relationship between the zone of injury and development of endophthalmitis (p>.05). For zone 2 and 3 injuries, the mean length of laceration was 7.96 mm. Increase in length of laceration was linearly related to worsening of presenting and final visual acuities (p<.01, p<.01). 6.8% (n=49/718) of eyes had an IOFB. VA improved from 1/200 (logMAR 2.12) at presentation to 20/800 (logMAR 1.55) postoperatively (p<.01).

The overall rate of endophthalmitis was 2.1% (n=15). The rates of endophthalmitis in eyes with IOFB were 8.1% (n=4/49) vs. 1.6% (n=11/669) in eyes without IOFB (p<.01). Two eyes (0.2%) had a clinical diagnosis of endophthalmitis on presentation. The mean time from injury to surgery was 28.4 hours for eyes that did not develop endophthalmitis vs. 28.0 hours for eyes that did develop culture positive endophthalmitis (p=.98). There was no significant relationship between time to surgery and final vision (r²=.01).

In eyes with IOFB (n=49), 24% (n=12) had retinal detachment (RD) or tears (RT); eyes with RD had a final VA of 20/1000 (logMAR 1.84) compared to 20/100 (logMAR .77) in eyes without RD/RT (p<.01). Of IOFB, 70% (n=35) were metallic and 22% (n=11) were glass. Of eyes with metallic IOFB, 11.4% (n=4) of eyes developed endophthalmitis vs. 7.1% (n=1) of eyes with non-metallic IOFB (p=1).

CONCLUSIONS: In the current study, the presence of an IOFB is a risk factor for endophthalmitis. In eyes with IOFB, intravitreal antibiotics may decrease rates of endophthalmitis. VA outcomes are variable depending on the extent and nature of the injury.
Post-injection Endophthalmitis Rates and Characteristics Following Intravitreal Bevacizumab, Ranibizumab and Aflibercept

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Purpose: To compare the incidence and clinical outcomes of endophthalmitis following intravitreal injections of bevacizumab, ranibizumab and aflibercept.

Methods: Multicenter, retrospective cohort study. All included patients had a diagnosis of neovascular age-related macular degeneration (AMD), diabetic eye disease or retinal vein occlusion (RVO) and received intravitreal injections of bevacizumab, ranibizumab or aflibercept between January 1, 2009 and September 30, 2013 at 5 retina practices. Billing records were used to identify the total number of anti-vascular endothelial growth factors (VEGF) injections administered during the time frame. Patients who developed endophthalmitis were ascertained from endophthalmitis logs and billing records. Chart review of these patients was performed to confirm that the endophthalmitis was related to the antecedent anti-VEGF injection. Visual outcomes, causative organisms and clinical course were also recorded.

Results: A total of 503,890 anti-VEGF injections were included, from which 183 cases of presumed endophthalmitis were identified. The rate of endophthalmitis for bevacizumab was 0.039% (60/153,812), which was similar to ranibizumab 0.035%; (109/309,722; \(P=0.522\)) and aflibercept 0.035% (14/40,356; \(P=0.693\)). Similarly, there was no difference in the rates between ranibizumab and aflibercept (\(P=0.960\)). The culture positive rate of the vitreous/aqueous tap was 38% for both bevacizumab and ranibizumab and was 43% for aflibercept. The most common organism was coagulase-negative *Staphylococcus* for bevacizumab and ranibizumab, while the culture positive cases after aflibercept injection were split between coagulase-negative *Staphylococcus* (50%) and *Streptococcus species* (50%). Furthermore, visual acuity remained decreased at 3 months follow-up for bevacizumab (\(P=0.005\)), ranibizumab (\(P<0.001\)) and aflibercept (\(P=0.07\)) compared to vision at causative injection.

Conclusions: Endophthalmitis following intravitreal bevacizumab, ranibizumab and aflibercept injection appears to occur at similar rates and have comparable visual outcomes. This study suggests that the choice of anti-VEGF agent should be primarily based on efficacy and patient response rather than concern for risk of infection.
Do Vancomycin and Amikacin Have Synergistic or Additive Effects Against MRSA Organisms at the Intravitreal Drug Concentrations Used for Endophthalmitis?

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Purpose: The Endophthalmitis Vitrectomy Study (EVS) chose vancomycin (V) and amikacin (A) as the drugs for intravitreal administration for acute post cataract surgery bacterial endophthalmitis for several reasons. One of the reasons was the possibility that synergy could exist between these two drugs to enhance the effect against Gram-positive organisms. When antibiotics are employed for systemic effect there is evidence of synergy when a cell wall acting drug (such as V) works with a ribosomal directed drug (such as A). The question as to whether synergy actually occurs between V and A at the high concentration of drugs employed intravitreally in endophthalmitis is unanswered. We tested the hypothesis that an additive effect exists between V+A but not between V+Ceftazidime (C) at the very high intravitreal drug concentrations achieved in clinical management of endophthalmitis.

Methods: In vitro time kill studies were performed on 5 isolates of MRSA isolated from endophthalmitis patients using antibiotics V, A, C, V+A, and V+C at 0,1,2,4,6,8 and 24h. The antibiotic concentrations were considered peak based on commonly employed clinical doses with an estimated 5ml vitreous volume to be V=200ug/ml, C=450ug/ml, A=80ug/ml, V+A -200/8ug/ml, and V+C=200/450ug/ml. A 2nd set of tests were performed at lower concentrations. Kill rates (log CFU/hr) were determined from the time-kill studies using regression, and analyzed non-parametrically with the Kruskal–Wallis test.

Results: Median time kill rates for peak concentration of antibiotics were V=-0.145, A=-0.075, C=-0.224, V+A= -0.095, V+C= -0.145. There was no significant difference in median time kill rates among the different drugs and combinations at full concentration (p=0.340) or at reduced concentration (p=0.462).

Median log reduction in CFU at 24hrs for peak antibiotic concentration was V=-3.14, A=-2.14, C=-3.2, V+A=-3.95, and V+C =-3.88, p=0.288. For reduced doses the median log reductions were V=-3.04, A=-2.14, C=-0.59, V+A=-2.08, and V+C=-2.73, p =0.155.

Conclusions: At peak calculated intravitreal drug concentration we could not demonstrate a significant in vitro difference in median kill rate between V+A over V alone, or between V+C over V alone against these MRSA organisms. While synergy was not demonstrated in vitro at these very high concentrations of antibiotic it is important to caution that this data does not mean the drug combinations (V+A versus V+C) have equal in-vivo efficacy, since other issues, such as the possibility of precipitation of C in the vitreous, inoculum effect, concentration dependent killing, and efflux of antibiotics out of the eye over time can also be at play in vivo, and were not tested.
Twenty-four Months Follow-up of Intravitreal Bevacizumab Injection versus Intravitreal Triamcinolone Acetonide Injection for the Management of Refractory Non-infectious Uveitic Cystoid Macular Edema

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PURPOSE: To report the efficacy of intravitreal bevacizumab (iVB) injection versus intravitreal triamcinolone acetonide (iVT) for the treatment of refractory non-infectious uveitic cystoid macular edema (CME).

METHODS: Interventional retrospective comparative case series. Forty eyes of 31 patients, aged 9-65 years (mean: 43.6 years), with uveitic CME as a consequence of intermediate uveitis, Vogt-Koyanagi-Harada syndrome, Birdshot chorioretinopathy, multifocal choroiditis, Behcet disease, Reiter’s syndrome, or panuveitis who were unresponsive to systemic medication were included. They were assigned to receive a single intravitreal injection of iVB (1.25mg/0.05ml) in 15 patients (19 eyes) and 4 mg/0.1ml of iVT in 16 patients (21 eyes).

RESULTS: The mean follow-up was 26 ± 8.8 months (range: 12 to 30) in the iVB group and 24 ± 7.5 (range: 18 to 26) months in the iVT group. In the iVB group mean baseline BCVA was logMAR = 1 ± 0.5 (range: 0.2 to 2) and final mean BCVA was logMAR = 0.7 ± 0.3 (range 0.3 to 1.3) (p = 0.096). In the iVT group mean baseline BCVA was logMAR = 1.1 ± 0.4 (range 0.5 to 2), and logMAR = 0.7 ± 0.3 (range: 0.7 to 0.3) after 24 months of follow up (p=0.025). CMT at baseline by OCT in the iVB group had a mean of 399.2 ± 150 µm (range: 145 to 817 µm), which was reduced to a mean of 321 ± 83 µm (range: 190 to 480 µm) at 24 months after initial treatment (p = 0.007). Mean of OCT CMT at baseline in the iVT group was 464.4 ± 226 µm (range: 244 to 1112 µm), which was significantly reduced to a mean of 267.1 ± 87.1 µm (range: 179 to 400 µm) at the end of follow up (p=0.0004).

CONCLUSIONS: IVT injection improves BCVA more effectively than IVB in the long-term management of uveitic CME refractory to systemic therapy. However, the risk of cataract progression and ocular hypertension was increased in the IVT group. Both therapies were associated with decrease of OCT CMT at the end of follow up.
Sarilumab for Non-infectious Uveitis (SARIL-NIU): Results at Sixteen Weeks from the Phase 2 SATURN Study

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PURPOSE: A phase 2 study evaluated the efficacy and safety of sarilumab, an investigational human anti-interleukin-6 (IL-6) receptor monoclonal antibody, for posterior segment non-infectious uveitis (NIU).

METHODS: SATURN, a 52-week, double-masked, phase 2 trial, randomized (2:1) 58 patients with posterior segment NIU to subcutaneous sarilumab (200 mg) q2 weeks or placebo. All patients had to receive a stable dose of systemic steroids ≥15 mg/day at baseline alone or in combination with methotrexate (≤25 mg/week). The primary endpoint, assessed at week 16, was the proportion of patients with a ≥2-step reduction in vitreous haze (Vh; per reading center using a 9-point scale) in the study eye or a dose of systemic corticosteroid <10 mg/day. Secondary endpoints assessed at week 16 included the change from baseline in VH and central retinal thickness (CRT) per reading centers and BCVA.

RESULTS: Overall, 94.7% (sarilumab) and 95.0% (placebo) of patients had active disease at baseline with 47% (sarilumab) and 55% (placebo) of patients having CRT >300 μm. At week 16, the proportion of patients with a ≥2-step reduction in Vh or steroid dose <10 mg/day was numerically higher in the sarilumab group vs placebo when Vh was measured by the reading center (46.1% vs 30.0%; p=0.2354) and significantly higher when Vh was assessed by the investigator (64.0% vs 35.0%; p=0.0372). Secondary outcomes at week 16 in the overall population included a greater mean change in Vh score (per reading center) in the sarilumab group vs placebo (LS mean difference: -0.74 [SE: 0.286]; 90%CI: -1.223 to -0.262; p=0.0127), improved BCVA (8.51 vs 3.87 ETDRS letters; LS mean difference: 4.65 [SE: 2.118]; 90%CI: 1.091 to 8.201; p=0.0333), and reduced CRT (LS mean difference: -26.55 [SE: 14.199]; 90%CI: -50.410 to -2.684; p=0.0683). Serious adverse events were reported in 2 sarilumab patients (neutropenia [n=1] and elective abortion [n=1]) and in 1 placebo patient (having both staphylococcal sepsis and deep vein thrombosis). The 52-week results of SATURN are expected by the time of presentation.

CONCLUSIONS: The SATURN Study has provided evidence at week 16 that inhibition of IL-6 with sarilumab may be efficacious in the management of posterior segment NIU.
Corticosteroid Tapering Success with Every-other-month Injections of Intravitreal Sirolimus in Subjects with Active Non-infectious Uveitis of the Posterior Segment (NIU-PS): SAKURA Study 1 Results

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**Purpose:** To report the degree of corticosteroid tapering success achieved in subjects with active NIU-PS treated with every-other-month injections of intravitreal sirolimus, a locally administered mTOR inhibitor, as part of the phase 3, multinational SAKURA Study 1.

**Methods:** 347 subjects with active NIU-PS and a vitreous haze [VH] score >1+ in the study eye were randomized 1:1:1 to double-masked intravitreal sirolimus injections of 440 µg, 880 µg, or 44 µg (active control). Injections were administered every 2 months. Non-corticosteroid systemic immunosuppressants and topical corticosteroids were discontinued prior to baseline, while subjects already receiving systemic corticosteroids at baseline with the overall prednisone-equivalent dose of >5 mg/d (the intent-to-taper population) were tapered off corticosteroids starting at baseline. Corticosteroid tapering success (the overall prednisone-equivalent dose tapered to ≤5 mg/d at Month 5) in the intent-to-taper population was a pre-specified key secondary endpoint. Additional analyses of this population were also performed.

**Results:** Sixty-nine subjects (44 µg, n=22; 440 µg, n=26; 880 µg, n=21) were receiving corticosteroids at baseline and comprised the intent-to-taper population. Tapering success was highest in the 440 µg group: 76.9% were tapered to ≤5 mg/d at Month 5, versus 63.6% in the 44 µg group and 66.7% in the 880 µg group. Tapering success plus a VH score of 0 or 0.5+ was achieved in 46.2%, 27.3%, and 33.3%, respectively. Differences among the 3 treatment groups did not reach statistical significance due to the small sample size. When results were stratified by the subjects’ baseline corticosteroid doses, the tapering success rate was 72.7% in subjects who started at a dose of 7.5-19 mg/d, 48% in subjects who started at 20-39 mg/d, and 45.5% in subjects who started at ≥40 mg/d.

**Conclusions:** In SAKURA Study 1, the majority of subjects who were on oral corticosteroids at baseline were successfully tapered to ≤5 mg/day with intravitreal sirolimus. Subjects starting at lower baseline corticosteroid doses (<20 mg/d) were more likely to achieve tapering success compared with those starting at higher doses (≥20 mg/d). These results support the potential use of intravitreal sirolimus to help patients taper corticosteroids to below recommended maintenance doses.
OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY OF PLACOID RELATED DISORDERS

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PURPOSE: To elucidate the origin of disease in acute posterior multifocal placoid pigment epitheliopathy (APMPPE) and related placoid disorders and to determine the principle tissue level of involvement using OCT angiography.

METHODS: Patients with clinical diagnosis of APMPPE or persistent placoid maculopathy (PPM) as determined by history, clinical exam and multimodal imaging underwent OCT angiography. Morphological evaluation of en face structural OCT and OCT angiography images with customized segmentation through the outer retina, retinal pigment epithelium, choriocapillaris and choroid was performed.

RESULTS: In this study, 23 eyes of 14 patients with APMPPE or PPM were recruited and 9 cases (64%) were bilateral. Of the 14 patients, 8 were male (57%) and mean age was 34.5 years (range 19-67). Of the 23 eyes, 96% (22/23) showed evidence of decreased flow within the choriocapillaris with OCT angiography. Areas of choriocapillaris ischemia closely co-localized with ischemic lesions identified with FA and ICG but were more extensive with OCT angiography and significantly improved with treatment or non-treatment follow-up. Corresponding zones of outer retinal disruption were also identified and closely co-localized with the areas of choriocapillaris ischemia identified with OCT angiography.

CONCLUSIONS: OCT angiography with its unique ability to measure flow at specific levels of the retina and choroid indicates that choriocapillaris ischemia is the primary site of disease pathogenesis in APMPPE and related placoid disorders with secondary photoreceptor disruption. OCT angiography may be used to enhance the diagnosis of placoid disease and to monitor the ischemic choriocapillaris response with follow up and after therapy.
Late Onset Severe Visual Field Loss in Patients with Retina Vasculitis

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**Purpose:** To study late onset severe visual field loss in patients with retinal vasculitis.

**Methods:** Retrospective review of the clinical records, images and fields of two patients with pars planitis and one patient with retina vasculitis.

**Results:** The visual fields showed marked constriction in one eye of two patients and both eyes of the third. The fields defects developed late (11,13,25) years after the patients were first treated. All of these patients were under treatment, had no signs of ocular inflammation but had minimal leakage on FFA. The field defects occurred relatively suddenly and were associated with worse leakage on FFA. OCT showed mainly outer retina damage in the areas corresponding to the field defects. The visual fields stabilized and the retina vascular leakage decreased after fluocinolone acetonide intravitreal implantation in three eyes (one also had a vitrectomy) and dexamethasone intravitreal implant injection every three months in the third patient. Central visual acuities remained 20/20, 20/25, 20/30 and 20/40 in the four affected eyes.

**Conclusions:** Photoreceptor damage on OCT corresponded to areas of visual field defects. Patients with vascular leakage require close follow-up including at least yearly FFA and visual fields. In our clinic there are other patients who appear stable with no sign of intraocular inflammation, but who still have mild vascular leakage on FFA. Eliminating all leakage often requires higher doses of, or additional immunomodulatory agents, either of which, increases the risk of treatment related side-effects. More information is needed to determine the best treatment paradigm in these patients.
Variables Related to the Ophthalmoscopic Findings Identified in Infants with Presumed Zika Virus Congenital Infection

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Purpose: To assess and identify possible risk factors for ophthalmoscopic findings in infants born with microcephaly and a presumed clinical diagnosis of Zika virus (ZIKV) intrauterine infection.

Methods: Cross-sectional study. The research included 40 infants (mean age, 2.2 ± 1.2 months; range, 0.1 – 7.3 months).

Ethical Issues: IRB was approved by Federal University Sao Paulo and Altino Ventura Foundation (FAV)

Inclusion criteria: Microcephalic newborns (anteroposterior diameter of head at birth < 33 cms) born in Pernambuco state, Brazil, between May and December 2015, around 9 to 15 months following a ZIKV outbreak. The infants and mothers underwent ocular and serologic examination that ruled out toxoplasmosis, rubella, cytomegalovirus, herpes, syphilis (TORCHS) and human immunodeficiency virus in infants and mothers.

Exclusion criteria: No possibilities to sign the consent form and to be submitted to eye and sorogical exams. Infants were divided into two groups for comparison: with and without ophthalmoscopic alterations.

Statistical analysis: The Mann-Whitney U-test was used to analyze differences between the groups. A P value < 0.05 was considered significant.

Results: The major symptoms reported by mothers in both groups were rash (65.0%), fever (22.5%), headache (22.5%), and arthralgia (20.0%). No mothers reported conjunctivitis or other ocular symptoms during pregnancy or presented signs of uveitis at the time of examination. Thirty-seven (46.3%) eyes of 22 (55.0%) infants had ophthalmoscopic alterations. Ten (71.4%) mothers of infants with ocular findings reported symptoms during the first trimester (P = 0.042). There was a significant difference between the group of infants with and without ocular findings regarding the cephalic perimeter (P = 0.004). Macular findings (chorioretinal atrophy and/or pigment mottling) were detected in 24 (30.0%) eyes of 17 (42.5%) infants and optic disc findings (hypoplasia with the double-ring sign, pallor, and increased cup-to-disc ratio) in 27 (33.8%) eyes of 16 (40.0%) infants.

Conclusions: Ocular involvement was identified in 55% of the infants with a presumed ZIKV infection and these findings were seen more often in infants with smaller cephalic diameter at birth and in infants whose mothers reported symptoms during the first trimester.
LATE BREAKING PRESENTATION

Panretinal Photocoagulation versus Intravitreous Ranibizumab for Proliferative Diabetic Retinopathy (PDR): Worsening of PDR

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for the Diabetic Retinopathy Clinical Research Network

PURPOSE: Compare rates and identify predictive factors for events that represent worsening of proliferative diabetic retinopathy (PDR) in eyes treated with ranibizumab or panretinal photocoagulation (PRP) for PDR.

METHODS: In a randomized clinical trial, 394 study eyes from 305 adults with PDR, visual acuity 20/320 or better, and no prior PRP were followed for 2 years. Participants were randomly assigned to intravitreous ranibizumab injections (0.5-mg/0.05-mL, N=191) or PRP (N=203). Main outcome measure was time from randomization to a PDR-worsening event defined as the first occurrence of vitreous hemorrhage (VH), retinal detachment (RD), vitrectomy, anterior segment neovascularization, or neovascular glaucoma.

RESULTS: Through 2 years, the cumulative probability of PDR-worsening was 42% (PRP) versus 34% (ranibizumab) (hazard ratio [HR]=1.30, 99% confidence interval=0.88 to 1.93; \( P=0.085 \)). Worse levels of baseline diabetic retinopathy severity (ETDRS) were associated with increased risk of PDR-worsening regardless of treatment (64% [high-risk PDR or worse] vs. 23% [moderate PDR or better], HR=4.04, 2.52 to 6.47; \( PP=0.008 \)), irrespective of the number of spots placed or number of sittings to complete PRP. Eyes in both groups with vision-impairing (visual acuity 20/32 or worse) center-involved diabetic macular edema (CI-DME) at baseline were required to receive ranibizumab to manage DME. Therefore an analysis was completed comparing eyes that did not have vision-impairing CI-DME at baseline. For these eyes, the cumulative probability of PDR-worsening rate was greater with PRP than ranibizumab (45% vs. 31%, HR=1.58, 0.99 to 2.52; \( P=0.012 \)).

CONCLUSIONS: In eyes with PDR, there was a trend suggesting ranibizumab reduces PDR-worsening compared with PRP. In the subgroup of eyes not requiring ranibizumab treatment for DME at randomization, ranibizumab for PDR reduced the rate of PDR-worsening more than PRP. While anti-vascular endothelial growth factor therapy requires compliance to a more frequent visit schedule than PRP, these findings provide additional evidence to support the use of ranibizumab as an alternative therapy to PRP for PDR, at least through 2 years of follow-up.
CONTINUED RANIBIZUMAB THERAPY FOR DIABETIC MACULAR EDEMA IN PATIENTS WITH LIMITED EARLY RESPONSE: A RETROSPECTIVE ANALYSIS OF RIDER/RISE TRIAL DATA

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PURPOSE: To assess the correlation between early response to ranibizumab therapy and long-term best-corrected visual acuity (BCVA) outcomes in patients with DME in the RiDe/RiSe trials.

METHODS: In this retrospective subanalysis, patients were categorized into 3 cohorts according to their BCVA change from baseline at month 3: initial ≥2-line gainers (gained ≥10 letters), initial 1-line gainers (gained 6-9 letters) or limited early responders (lost letters or gained ≤5 letters). The BCVA change from baseline in these patient subgroups was assessed at 6, 12, 24, and 36 months and patients were divided into 3 groups: improved to a better BCVA change category than that at month 3, remained stable in the same BCVA change category as at month 3, or worsened to a lower BCVA change category than that at month 3, for each time point.

RESULTS: At 3 months, 37.4% (88/235) of patients receiving ranibizumab 0.3 mg were initial ≥2-line gainers, 20.0% (47/235) were initial 1-line gainers, and 42.6% (100/235) were limited early responders. Among the initial ≥2-line gainers, vision gains remained stable at months 12, 24, and 36 in ~90% of patients. Among initial 1-line gainers, 58%, 71%, and 68% of patients improved to a better BCVA change category at months 12, 24, and 36, respectively. Among limited early responders, 52%, 71%, and 71% of patients improved to a better BCVA change category at months 12, 24, and 36, respectively.

CONCLUSIONS: In RiDe RiSe, the majority of the ranibizumab 0.3 mg treated limited early responders and 1-line gainers showed subsequent improvements in vision and continued to gain vision through month 36. The majority of patients who gained ≥2-lines of vision after 3 months of ranibizumab 0.3 mg maintained vision gains over the 36 months of the study. These results suggest that patients who do not seem to respond initially to ranibizumab therapy can achieve clinically meaningful improvements in vision with continued monthly treatment.
Intraocular Pressure Changes: Three-year findings of the Prospective Retinal and Optic Nerve Vitrectomy Evaluation (PROVe) Study

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Purpose: To report 3-year intraocular pressure (IOP) outcomes of the Prospective Retinal and Optic Nerve Vitrectomy Evaluation (PROVe) study.

Methods: Prospective, controlled, observational study of 80 eyes of 40 participants undergoing routine pars plana vitrectomy in 1 eye only for epiretinal membrane, macular hole, or vitreous opacities. Study patients underwent baseline evaluation of the study (surgical) and fellow (control) eyes by a masked fellowship-trained glaucoma specialist. Initial evaluation included visual acuity (VA) intraocular pressure (IOP: Goldmann applanation and Tono-Pen), central corneal thickness, gonioscopy, and cup-to-disc ratio measurement. Baseline testing included bilateral color fundus and optic disc photography, fundus autofluorescence, automatic perimetry, and spectral domain optic coherence tomography of the macula and optic nerve with central subfield thickness and peripapillary retinal nerve fiber layer thickness measurements. This testing was repeated at 3 months postoperatively and then annually for three years (5 total visits).

Results: Thirty-two of 40 patients (80%) completed three-year follow-up. At three years postoperatively, mean Logarithm of the Minimal Angle of Resolution (logMAR) visual acuity in the surgical eye was 0.10 ± 0.16 (Snellen acuity 20/25), which was significantly improved from baseline logMAR visual acuity 0.39 ± 0.37 (Snellen acuity 20/50, P=0.30). While there was no difference in IOP measurements in surgical eyes overall from baseline (P=0.36), analysis of pseudophakic eyes at baseline showed a significant elevation in IOP from 14.35 ± 2.90 at baseline to 16.83 ± 3.24 at 3-year follow-up (P=0.05). Fellow eyes did not experience a significant change from baseline. In contrast, eyes that were phakic at baseline demonstrated a steady decrease in IOP after vitrectomy, which corresponded to cataract surgery, reaching the level of statistical significance (P<0.05) at 2 years. However, at 3 years IOP trended upwards.

Conclusions: Our 3-year results show that IOP is consistently and significantly elevated in pseudophakic eyes compared to baseline after routine vitrectomy. In phakic eyes at baseline, IOP initially declines but then appears to increase after 2 years. To the authors’ knowledge, this is the first prospective, controlled trial to demonstrate these findings.
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SATURDAY
Spectral-domain Optical Coherence Tomography in Older Patients with History of Retinopathy of Prematurity

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Birmingham, MI

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PURPOSE: To characterize the in vivo microstructural features of patients with history of retinopathy of prematurity (ROP).

METHODS: A single center, retrospective chart review was performed of 226 consecutive patients with history of ROP who have undergone spectral domain optical coherence tomography (SD-OCT) with or without enhanced depth imaging. Eyes with time domain-OCT or uninterpretable SD-OCT images were excluded. The main outcome measures were best-corrected visual acuity (BCVA) and exploratory SD-OCT findings.

RESULTS: A total of 197 eyes of 113 patients (median age, 22 years; range, 8-69) were imaged. Median visual acuity was 20/80 (range, 20/20 – light perception). Central foveal thickness (CFT) and subfoveal choroidal thickness (SCT) measured 283.41 ± 55.62 uM SD and 240.52 ± 80.75 uM, respectively. There was a negative correlation between ROP stage and CFT (Rho = -0.19; P = 0.027), but not with SCT (Rho = -0.03; P = 0.748). There were negative correlations between BCVA and CFT (Rho = -0.23; P < 0.01) and SCT (Rho = -0.19; P = 0.04). Ellipsoid zone (EZ) abnormalities, inner retinal layer thickening and presence of chorioretinal atrophy were associated with higher ROP stage (P < 0.001) and poorer visual acuity (Rho = 0.59; P < 0.001). The presence of retinoschisis (n=36/197, 18%) was associated with poorer visual acuity (P<0.001), but did not correlate with higher ROP stage (P = 0.17). Epiretinal membrane-like dense hyaloidal organization and vitreoretinal traction were seen in 66% (130/197) and 32% (63/197) of eyes, respectively, but were not associated with ROP stage (P = 0.87) or visual acuity (P = 0.54). After controlling for EZ abnormalities, foveal hypoplasia, retinoschisis, inner retinal thickening, chorioretinal atrophy and ROP stage, the independent risk factors for poorer visual acuity were EZ abnormalities (Beta = 0.38; P < 0.001), chorioretinal atrophy (Beta = 0.18; P = 0.03), and ROP stage (Beta = 0.22; P < 0.01).

CONCLUSIONS: SD-OCT imaging identified a plethora of microstructural abnormalities present in patients with history of ROP. These findings may have important implications in the medical and/or surgical management of these patients.
ABNORMAL VESSELS IN THE FOVEAL CENTER IN PREMATURE EYES: AN OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY STUDY

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PURPOSE: The purpose of this study is to report foveal findings on a cohort of premature children previously treated for retinopathy of prematurity (ROP).

METHODS: Birth history, clinical examination, spectral-domain optical coherence tomography (SDOCT), and optical coherence tomography angiography (OCTA) were taken of children who had a history of laser therapy for ROP. Imaging findings were compared to age-matched healthy controls.

RESULTS: Ten eyes of 6 children treated with ROP laser were included. Average gestational age and birth weight were 24-5/7 weeks and 857 grams, respectively. Current age at time of retinal imaging ranged between 3-9 years old. Visual acuity ranged from 20/20 – 20/100. In ROP eyes, all SDOCT images showed lack of foveal depression development and presence of inner retinal layers in the central fovea all OCTA scans showed vascularization of the foveal avascular zone (FAZ). In six eyes of 3 non-ROP age-matched controls, the foveal pit was present on SDOCT and an FAZ was clearly visible on OCTA. Mean central subfield thickness, inner retinal thickness, and foveal vessel density in superficial and deep capillary networks were significantly higher in ROP eyes (p<0.01).

CONCLUSIONS: The FAZ of children treated with ROP laser was markedly abnormal with lack of foveal pit development, preserved inner retinal layers in the foveal center and abnormal foveal vasculature. These results lend insights into the arrest of foveal development associated with prematurity. It is unknown what effect, if any, laser itself had on foveal development.
Familial Exudative Vitreoretinopathy: Outcomes of 332 Eyes with Retinal Detachment

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PURPOSE: To report the outcomes of management of retinal detachment (RD) associated with familial exudative vitreoretinopathy (FEVR).

METHODS: Single center, interventional, retrospective, case-control study, of patients with FEVR-associated RD seen between 2009 and 2016. Eyes either underwent vitreoretinal surgery (surgery group) or elected to be managed with photocoagulation and/or observation (conservative treatment group).

RESULTS: A total of 332 eyes of 207 patients were included in the study. Mean presenting age was 7.6 ± 11.7 years. Macula-sparing RD (stage 3) was found in 17.4% of eyes, macula-involving subtotal RD (stage 4) in 40.0%, and complete RD (stage 5) in 42.6%. Median presenting visual acuity (VA) was hand motions (range: 20/20 to no light perception [NLP]). A total of 356 incisional surgeries in 223 eyes were performed (6.0% stage 3, 36.7% stage 4, 57.2% stage 5), and 109 eyes were treated conservatively (27.4% stage 3, 46.2% stage 4, 26.3% stage 5). Mean follow-up was 13.8 years.

Anatomic Outcomes: The posterior pole or peripheral retina was attached in 77.8% (97.4% of stage 3, 90.1% of stage 4, 57.3% of stage 5; P < 0.001) on the final visit. The anatomic outcomes were similar between the surgical and conservative treatment groups for all stages. Both groups resulted in downgrading of staging by the final visit (both P < 0.001). For stage 5 eyes that remained detached, surgical intervention resulted in more open funnels (P < 0.01).

Visual Outcomes: Presenting VA was similar in both groups. Overall, counting fingers or better was achieved in 41.0% of eyes (77.3% of stage 3, 65.8% stage 4, 15.5% stage 5). VA was stabilized in all stages for both groups, except for significant improvement in eyes with stage 4 in the conservative treatment group (P = 0.05). Of note, eyes with stage 5 achieved LP or better in 64.0% that underwent surgery, and 18.8% that were observed (P < 0.01). Final VA correlated with clinical staging (Rho = 0.61; P < 0.001) and initial VA (Rho = 1.00; P < 0.001).

CONCLUSIONS: Vitreoretinal surgical and nonsurgical intervention for RD associated with FEVR can yield favorable anatomic and visual outcomes.
Immediate Sequential Bilateral Pediatric Vitreoretinal Surgery: An International Multicenter Study

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PURPOSE: To determine the feasibility and safety of bilateral simultaneous vitreoretinal surgery in pediatric patients, to avoid multiple general anesthesia sessions and delayed treatment of bilateral progressive disease.


PARTICIPANTS: Patients 17 years of age or younger who underwent immediate sequential bilateral vitreoretinal surgery (iSBVS), defined as vitrectomy, scleral buckle, or lensectomy using the vitrectomy cutter (not injections, not lasers), performed in both eyes immediately one after another during the same anesthesia session.

METHODS: A total of 344 eyes from 172 iSBVSs in 166 patients were identified. Clinical history, surgical details and indications, time under anesthesia, and intra- and post-operative ophthalmic and systemic adverse events were recorded.

MAIN OUTCOME MEASURES: Ocular and systemic adverse events.

RESULTS: The mean age of the cohort was 1.3 ± 2.6 years. Nonexclusive indications for iSBVS were rapidly progressive disease (74.6%), systemic morbidity placing the child at higher general anesthesia risk (76.0%), residence remote from surgery location 30.2%, and limited finances (4.1%). Diagnoses included retinopathy of prematurity (72.7%; 4.8% stage 3, 44.4% stage 4A, 22.4% stage 4B, 26.4% stage 5, 2.0% stage 4 unspecified), familial exudative vitreoretinopathy (7.0%), abusive head trauma (4.1%), persistent fetal vasculature syndrome (3.5%), congenital cataract (1.7%), posterior capsular opacification (1.7%), rhegmatogenous retinal detachment (1.7%), congenital x-linked retinoschisis (1.2%), Norrie disease (2.3%), viral retinitis (1.2%), and other (2.9%). Mean surgical time was 148 ± 58 minutes. There were no intraoperative ocular complications (0.0%). During the immediate postoperative period, 2 eyes from different patients developed vitreous hemorrhage (0.6%). There were no cases of endophthalmitis (0.0%), choroidal hemorrhage (0.0%), or hypotony (0.0%). Mean total anesthesia time was 203 ± 87 minutes. Intraoperatively, there were: no cases of anesthesia-related deaths (0.0%), 1 case of reintubation (0.6%), and 1 case of prolonged oxygen desaturation (0.6%). During the immediate post-operative period, there were no cases of anesthesia-related deaths or complications (0.0%). Mean followup after surgery was 723 days, and anatomic success and globe salvage were achieved in 89.8% and 98.0%, respectively.

CONCLUSIONS: Our collective data shows that iSBVS is an option for pediatric patients with bilateral vitreoretinal pathology when repeated general anesthesia is undesirable.
Near-term Safety of Intravitreal Bevacizumab and Diode Laser Photocoagulation Treatments for Type 1 Retinopathy of Prematurity

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Purpose: This study aims to characterize the NICU course and near-term safety of Type 1 ROP infants receiving bevacizumab injections (iVB) as compared to diode laser photocoagulation (DLP) in the perinatal period.

Methods: A retrospective review of all infants with Type 1 ROP at Stanford Hospital and Clinics from January 1, 2013 and June 30, 2015 treated with either DLP or 0.625 mg IVB. Number and types of treatment for ROP were recorded. We assessed the total number of diagnoses, diagnoses pre- and post-treatment, oxygen requirements, intubations, cardiac procedures, the length of hospitalization, and the number of readmissions.

Results: A total of 61 eyes in 32 patients met Type 1 ROP criteria; 19 of the patients had complete medical records and are included in this study, with 13 being transferred in from other hospitals. Ten infants (20 eyes) were treated with IVB, and nine infants (18 eyes) were treated with DLP. Of note, 9 out of 10 IVB patients eventually required DLP for vascular arrest about 19 weeks after IVB. The two groups were similar in gestational age at the time of the primary treatment at approximately 25 weeks. All infants were extremely low birth weight, with the IVB infants on average 50g lighter and receiving primary treatment 2 weeks earlier than the DLP infants. The IVB infants also had significantly fewer total days of hospitalization and number of readmissions after initial hospital discharge than the laser infants (114.4 vs 122.8 days, p=0.037; 0.10 vs 1.39 readmissions, p=0.030). There was no significant difference in the number of diagnoses before and after primary treatment, oxygen requirement, days of intubation, or cardiac procedure requirement between the two groups.

Conclusions: IVB can slow the progression of ROP and delay the need for laser treatment by 4-5 months. Infants who received bevacizumab as their initial treatment had a significantly shorter hospital course and fewer readmissions after discharge than infants who had laser photocoagulation as their primary treatment, indicating excellent short-term safety when compared to diode laser photocoagulation.
National Trends in Retinopathy of Prematurity over Sixteen Years in the United States

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Purpose: To determine the change in incidence of Retinopathy of Prematurity over the last sixteen years and associated longitudinal trends in birth weight, gestational age, demographic, management and treating hospital characteristics.

Methods: A retrospective cohort study was undertaken using the National Inpatient Sample from 1998 through 2013. In total, 53,874 infants with an ICD-9 diagnosis of ROP from 1/1/1998 to 12/31/2013 were evaluated. Birth weight, gestational age, charges, length of stay, race and gender were assessed. Incidences of laser, vitrectomy, scleral buckle, diathermy, cryotherapy, and their relationship with birth weight, gestational age, age at the time of procedure were determined.

Results: In the US, ROP rates climbed linearly from 2.9% of premature babies in 1998 to 4.2% in 2013. Over these 16 years, incidence decreased in babies born between 500-1000g or 25-26w gestational age, whereas incidence increased in babies born between 1250-1999g or 27-30w gestation (P<0.0004 for all relationships). Incidence did not change at the extremes of birth weight and premature gestational age (≤24w, ≥33w, <500g, >2000g; P>0.05). Birth weight and gestational age were inversely related with ROP disease severity. Length of stay for ROP admissions increased by an estimated 0.56 days per year. Each additional day in the hospital cost an average of $11,227. The overwhelming majority of cases are treated in urban hospitals (98%) with large facilities (67%), and fewer rural hospitals treated ROP over time. ROP rates are greater in males. In 1998, 22% of ROP patients received any ophthalmic procedure, four times the 5% rate of procedures in 2013. A patient with a ROP diagnosis had a 4.27% chance of receiving laser, 1.14% of receiving vitrectomy, and <0.5% of any other therapy in 2013.

Conclusions: This study is the largest known survey of ROP infants. Disease incidence, distributions of birth weight and gestational age, treating hospital characteristics, charges and length of stay have all evolved with time. The last 16 years have heralded significant changes in surgical treatment of ROP. Declining overall surgical rates may reflect improved modern medical management of ROP and prematurity overall.
**577-nm Yellow Laser Photocoagulation for Coats’ Disease**

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**PURPOSE:** To describe the outcomes of children with Coats’ disease treated with 577-nm yellow laser indirect ophthalmoscopy (LIO)

**METHODS:** A retrospective consecutive case series of pediatric patients with Coats disease treated at a single institution between 2011 and 2014. LIO was performed under anesthesia. Full treatment was defined as complete ablation of all visible telangiectasias and resolution of subretinal fluid. No patients were treated with cryotherapy or bevacizumab.

**RESULTS:** Seventeen eyes of 16 patients were consecutively treated. At time of diagnosis, the eye was classified as Stage 1 (telangiectasias only) in 1 case, Stage 2A (extra-foveal exudation) in 2 cases, Stage 2B (fovea-involving exudation) in 6 cases, Stage 3A1 (extra-foveal exudative retinal detachment) in 2 cases, Stage 3A2 (subtotal foveal-involving detachment) in 1 case, and stage 3B (total exudative retinal detachment) in 5 cases. The mean age at initial treatment was 71.2 months. Mean length-of-follow-up was 20.8 months (median 18.5 months, range 3.7 – 37.3 months). Patients underwent an average of 2.5 laser treatments. Sixteen of 17 eyes achieved full treatment (94.1%) with a mean time-to-full-treatment of 11.2 months. One eye developed glaucoma and end-stage disease.

**CONCLUSIONS:** 577-nm yellow wavelength LIO is an effective treatment for Coats’ disease including cases of exudative retinal detachment.

B r a n d o n  B u s b e e ,  M D
N a s h v i l l e ,  T N

P U R P O S E :  T h i s  p r e s e n t a t i o n  w i l l  h i g h l i g h t  t h e  p o t e n t i a l  a d v a n t a g e s  o f  a  n o v e l  s u r g i c a l  i n s t r u m e n t  t h a t  c a n  b e  u t i l i z e d  i n  a l l  v i t r e c t o m y  s u r g e r y .  T h e  a u t o i n s e r t e r  h a s  n o w  b e e n  u s e d  i n  o v e r  f i f t y  s u r g i c a l  c a s e s  b y  t h e  a u t h o r .

M E T H O D S :  E v a l u a t i o n  o f  t h e  a u t o i n s e r t e r  i n  d i f f i c u l t  s u r g i c a l  s e t t i n g s  w i l l  b e  d e s c r i b e d .  I n s e r t i o n  o f  t r o c h a r  i n t r a o c u l a r  p r e s s u r e  ( I O P )  m e a s u r e m e n t  u s i n g  t h e  s t a n d a r d ,  m a n u a l  t e c h n i q u e  a n d  t h e  n o v e l ,  a u t o i n s e r t e r  t e c h n i q u e  w i l l  b e  r e p o r t e d .  T h i s  I O P  p r o b e  a l l o w s  f o r  r e a l - t i m e  I O P  m e a s u r e m e n t s  d u r i n g  t h e  2 5 - g a u g e  t r o c h a r / c a n n u l a  i n s e r t i o n .

R E S U LT S :  T h e  a u t o i n s e r t e r  d e m o n s t r a t e s  c l e a r  c l i n i c a l  a d v a n t a g e s  t o  m a n u a l  i n s e r t i o n  i n  d i f f i c u l t  e n t r y  c a s e s .  E n t r y  I O P  d a t a  i s  m a r k e d l y  d i f f e r e n t  a n d  a d v a n t a g e o u s  f o r  t h e  a u t o i n s e r t e r  i n  e v e r y  c a s e  t h a t  w i l l  b e  p r e s e n t e d .  T h e  I O P  r a n g e  f o r  m a n u a l  i n j e c t i o n  o f  t h e  2 5 - g a u g e  t r o c h a r / c a n n u l a  w a s  a n  e l e v a t i o n  b e t w e e n  1 5 0 - 3 0 0  m m H g  f o r  d u r a t i o n  o f  2 - 3  s e c o n d s  f o r  e a c h  i n s e r t i o n .  T h e  I O P  r a n g e  f o r  a u t o m a t i c  i n s e r t i o n  o f  t h e  2 5 - g a u g e  t r o c h a r / c a n n u l a  w a s  a n  e l e v a t i o n  b e t w e e n  7 5 - 1 2 5  m m H g  f o r  a p p r o x i m a t e l y  0 . 1  s e c o n d s  f o r  e a c h  i n s e r t i o n .

C O N C L U S I O N S :  T h e  a u t o i n s e r t e r  i s  a  n o v e l  e n t r y  s y s t e m  f o r  r e t i n a  s u r g e r y .  I t  h a s  c l i n i c a l  a n d  I O P - e n t r y  a d v a n t a g e s  c o m p a r e d  t o  s t a n d a r d ,  m a n u a l  i n s e r t i o n  o f  2 5 - g a u g e  t r o c h a r / c a n n u l a s  f o r  v i t r e c t o m y  s u r g e r y .
27-Gauge Vitrectomy for Vitreoretinal Disorders

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Purpose: To evaluate anatomic, functional and refractive outcomes after 27-gauge vitrectomy in a prospective study.

Methods: The study was designed to include patients presenting with vitreoretinal disorders (epiretinal membrane [ERM], macular holes, asteroid hyalosis and vitreomacular traction [VMT]) with or without coexisting significant cataract. Exclusion criteria were (a) patients with rhegmatogenous or tractional detachment, (b) previous vitreoretinal surgery, and (c) the need for silicone oil tamponade. Surgical conditions using a scaled questionnaire, complication rates, IOP, functional and refractive outcomes were evaluated.

Results: Up to now, 60 patients, 41 females and 19 males with a mean age of 72 years, have completed the 3 months follow-up. The vitreoretinal diagnosis was ERM in 36 eyes, macular holes in 9 eyes, VMT in 2 eyes, and asteroid hyalosis in 13 eyes. In 47 eyes cataract surgery was combined with vitrectomy. Intraoperative conditions were graded good to excellent. However, a slightly increased time needed for core vitrectomy was noted and particularly in hyperopic and left eyes the 27 gauge instruments were graded to be more flexible. No wound leakage was found and the IOP was stable in all eyes. Complication rates included a mild postoperative vitreous hemorrhage in one patient which spontaneously resolved during follow-up. Visual acuity improved in all patients and the refractive results in the combined cases were excellent.

Conclusions: These results suggest that 27 gauge vitrectomy with or without combined cataract surgery results in excellent wound architecture and offers promising functional and refractive results.
Modulation of Vitrectomy Console Parameters to Minimize Retinal Motion in Small-gauge Vitrectomy for Retinal Detachment

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PURPOSE: 3-port vitrectomy (PPV) results in a complex fluidic system with turbulent flow of intraocular fluid and resultant significant displacement of detached retina or other non-fixed intraocular tissues or fluids. Wide fluctuations in the amplitude and frequency of retinal displacement may be associated with intraoperative pathologic events, including retinal trauma from shear or inadvertent excision of retinal tissue. For this reason, a method to quantify the movement of retina in vivo during PPV is introduced.

METHODS: Surgical video recordings of PPV performed in a lapine model of rhegmatogenous retinal detachment with giant retinal tear were analyzed to quantify retinal motion. 25-gauge PPV was performed using a peristalsis-based vitrectomy unit. The displacement of detached retina at the margins of retinal breaks was analyzed using an image-processing algorithm created in our laboratory. Net displacement and velocity of retinal segments were obtained. Manual frame-by-frame analyses were performed to validate the method described herein. Retinal motion was assessed as a function of fluid flow and cut-rate during PPV.

RESULTS: Automated analyses of retinal displacement demonstrated that retinal motion was proportional to fluid flow and inversely proportional to the distance of the vitrectomy probe from the retinal tear. Cutting velocity (cuts-per-minute (CPM)) was compared under flow-limiting conditions appropriate to excising peripheral vitreous in the setting of giant retinal tear with mobile retina. Both 5000 CPM and 7500 CPM exhibited diminished retinal motion in comparison to 3000 CPM (p<0.01). Less retinal motion was assessed at 5000 CPM (31±2.3) than 7000 CPM (56±0.6 (pixels/sec) (mean±SD)) (p<0.01), though the clinical significance of this difference is unclear.

CONCLUSIONS: Retinal motion measured in situ during PPV is dependent on fluidic parameters, and the relation between cutting velocity and retinal motion may not be accurately predicted by ex vivo studies of particle flow or other surrogates.
Vitreous and Contrast Sensitivity

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Purpose: Contrast sensitivity (CS) diminishes with aging even in the absence of cataracts, but the mechanism is unknown. Decreased macular ganglion cell complex (GCC) thickness (Adam et al: JNO 2013;33:137-42) and increased vitreous echodensity (Sebag et al: Retina 2014;34:1062-8) are possible causes. This study evaluated the relationship between vitreous echodensity, posterior vitreous detachment (PVD), GCC thickness, and CS as related to age, both retrospectively and prospectively.

Methods: PVD was diagnosed by ultrasonography and OCT ruled out vitreoschisis. One eye of 24 subjects with PVD and 37 subjects without PVD had Freiburg Acuity Contrast Testing (Weber index: %W, where lower values mean better CS). Quantitative vitreous ultrasonography (QUS) was performed longitudinal to the macula, as previously described (Mamou et al: IOVS 2015;56:1611-7). GCC thickness was measured with SD-OCT at 5 loci 1.5mm nasal to the fovea. Prospective analyses were performed in 8 subjects with normal CS and no evidence of PVD, who subsequently developed PVD and underwent repeat testing.

Results: Mean CS was 53.9% worse (p<0.001) in eyes with PVD (2.97±0.26 %W) compared to those without PVD (1.93±0.13 %W). Subjects with PVD had worsening CS with increasing age (r=0.622, p=0.013), but not those without PVD (p=0.553). Increasing age also correlated with increasing vitreous echodensity in subjects with PVD (r=0.656, p=0.008), but not in those without PVD (p=0.387). Mean GCC thickness was not correlated with either CS (p=0.354) or age (p=0.832).

Prospectively, 8 adults (54.4 ± 10.1 years old) with normal CS and no PVD experienced unilateral PVD, confirmed by ultrasound. At study entry there was no difference in CS compared to fellow eye controls. Following PVD there was a 52.5% reduction in CS (1.81±0.61 %W to 2.76±0.30 %W; P=0.001). Following vitrectomy, CS improved an average of 43.2% and normalized in each case at 1, 3, and 12 months post-op (1.34±0.33 %W, P=0.0001), attaining the same CS as the control fellow eyes (1.34±0.20 %W).

Conclusions: PVD is associated with diminished CS, which further declines with age, seemingly due to progressive increase in vitreous echodensity. Thus, decreasing CS may be associated with progressive vitreous collagen aggregation after PVD, but not with GCC thinning in the papillo-macular bundle.
Multiple Intravitreal Methotrexate Injections for the Prevention of Proliferative Vitreoretinopathy

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Purpose: Methotrexate is an antiproliferative and anti-inflammatory agent with minimal ocular and systemic toxicity, and it is a good candidate to study for the prevention of proliferative vitreoretinopathy (PVR). The purpose of this study was to attempt to prevent recurrent retinal detachment (RD) due to PVR in a series of high risk eyes.

Methods: We conducted a prospective study of 10 eyes with RD due to PVR. Eight of this eyes had undergone multiple procedures for recurrent RD and two eyes had RD after primary repair of severe open globe injury. All 10 eyes underwent surgery which included retinectomy and silicone oil. A total of 10 intravitreal injections of methotrexate (400 mcg / 0.1 ml) were administered per patient: one at the conclusion of surgery, eight weekly injections from postoperative week 1 through week 8, and one additional injection at postoperative week 12. Outcomes included recurrent RD and PVR.

Fibrous proliferations excised at the time of PVR surgery in humans were grown in culture. The cells were exposed to varying concentrations of methotrexate.

Results: There was 99% compliance, as 99 out of a possible 100 total injections were given. All patients had 2-3 years of follow-up except for one patient who had only 4 months. One trauma patient developed severe PVR at month 4 (one month after the last injection), which is much later than expected. Three eyes developed retinal detachment without any observable evidence of PVR. Only one eye developed an observable epiretinal membrane, and it was clinically insignificant.

Cultured human PVR cells exhibited uncontrolled proliferation and extracellular band formation. Methotrexate exposure resulted in decreased cell proliferation and decreased band formation in a dose response manner.

Conclusions: The use of multiple intravitreal methotrexate injections is a reasonable approach for the prevention of PVR. This small prospective study with long term follow-up demonstrates safety and tolerability, and there is a suggestion of efficacy. In addition, there is some confirmatory laboratory evidence using cultured human PVR cells. There is enough favorable evidence that this approach warrants further study.
OM-101 Attenuates the Formation of Fibrotic Response Associated with Proliferative Vitreoretinopathy

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**PURPOSE:** This study aimed to investigate in animal model, the effect of OM-101 on the fibrotic response occurring in proliferative vitreoretinopathy (PVR).

**METHODS:** Seven weeks old c57black mice underwent intravitreal injection of dispase (0.3 units), to induce retinal detachment (RD) and PVR in vivo. Four days following dispase injection the mice were divided randomly to three groups, 25 mice in each group): Group A, the control group was treated with saline (5 µl) and group B with OM-101(5 µl). Group C, treated with the solvent of dispase only. After additional five days, mice were sacrificed, and the eyes were enucleated and processed for histological and immunohistochemical analysis. Blood and tissue samples were collected to evaluate the safety of OM-101. The severity of PVR was defined by infiltration of white blood cells such as macrophages or B cells (0- absence of cells, 1 low frequency, 2 - moderate frequency and 3- high frequency), edema and the appearance of pigment cells in the retina (cell migration). (N=25 for each group).

**RESULTS:** Intravitreal injection of dispase caused RD in 64% of the control group and 93% of those mice had PVR. In contrast, in mice that were treated with OM-101 after the dispase injection, only 32% of them developed RD and 25% of those developed PVR. The severity of the PVR measured in the control mice was significantly higher than in compare to mice treated with OM-101.

Safety and toxicity examinations including blood values of liver function, kidney and inflammatory markers were within normal ranges in OM-101 injected mice. Tissue morphology and histology of liver, brain, kidney and spleen were found normal in mice treated with OM-101.

**CONCLUSIONS:** In this study OM-101 was found effective in halting the progression of RD and preventing PVR. OM-101 reduced the number of proliferating RPE cells abolish the migratory capacity of RPE cells and prevent the chemotaxis of macrophages. Thus the outcome is attenuation of the fibrotic response underlying PVR and maintaining the anatomic structure for the retina. OM-101 was found safe with no side effects. This study suggests that OM-101 a potential effective and safe drug for treatment PVR patient.
Four-dimensional Optical Coherent Tomography-guided Vitreoretinal Surgery with Surgeon-controlled Heads Up Display

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**Purpose:** Intraoperative optical coherence tomography (OCT) has advanced vitreoretinal surgery, from initially handheld OCT during surgical pauses, microscope-mounted SDOCT, and more recently, the commercially available microscope-integrated SDOCT with monocular heads up display. Here we present a four-dimensional swept source microscope-integrated OCT (4D MiOCT) prototype with surgeon-controlled heads up display.

**Methods:** We first applied new technology in wet-lab studies with prototype systems followed by translation to first-in-human surgical application. Through these steps with system refinement and with Safety Committee review prior to IRB approval of the modified system, we progressed from high-speed near-real time imaging without surgeon view, to an integrated system with surgeon footstick control of binocular stereoscopic near-real-time volumetric display with adjacent B-scan display. We evaluated the findings from a consecutive series of 41 surgeries.

**Results:** Three-dimensional datasets were rebuilt, scaled, cut away, and processed in near-real-time (3.3 volumes per second in human surgery and over 10 volumes per second in a wet-lab in ex vivo porcine eyes) to augment the surgeon’s appreciation of the damaged or diseased tissue. Imaging data were lost during storage for 2 well-imaged surgeries. Images were acceptable for 36 of the 39 surgeries and showed the instrument position relative to the retinal surface for 31 of 35 surgeries: 78% of scraping (14 of 18) and peeling (25 of 32) maneuvers. In surgery, transient inner retinal deformation was visible after scraping maneuvers.

In the wet-lab, the surgeon and assistants could use heads up display alone (within the microscope heads up display, on a stereo screen or in a head-mounted virtual reality environment) without the conventional view for macular maneuvers. In the wet-lab, this eliminated the use of the endoilluminator during OCT-guided maneuvers. These included bimanual pre- and sub-retinal surgery.

Delivering information to the surgeon from real time data capture was a challenge. Selecting the visible output data for the surgeon must be at useful scaling and perspective, and may require further image processing. This varied depending on the surgical task such as external to the eye, pre- and sub-retinal.

**Conclusions:** We addressed the balance between methods for surgeon control, data capture, and communication of data to the surgeon during human vitreoretinal surgery and wet-lab experiments. Providing additional 3-dimensional information about the structures of and relationships between preretinal, retinal, subretinal tissue during vitreoretinal surgery is likely to enable new surgical techniques.
Fluid-air Exchange during Silicone Oil Removal is Not Effective, but Harmful for Reducing the Residual Silicone Oil

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PURPOSE: To determine the effect of fluid-air exchange during silicone oil removal procedure on reducing residual silicone oil droplets.

METHODS: This was a retrospective comparative study which involved 56 eyes of 56 patients that received silicone oil removal. Fluid air exchange was done during surgery in 30 eyes [Air Ex (+) group] and was not so in 26 eyes [Air Ex (-) group]. After surgery, every eye received B-scan ultrasonography on the largest plane. The image was converted to binarized image. The area of silicone oil droplets/ the area of vitreous cavity on that image was quantitated and expressed as, “silicone oil index (SOI)”. The correlation between SOI and clinical findings was evaluated.

RESULTS: The SOI of was significantly and positively correlated with the axial length (AL) and the preoperative intraocular pressure (IOP) (AL, R=0.444, P=0.023; preoperative IOP, R=0.5555, P=0.001). However, in Air Ex (+) group, SOI was not correlated with AL or preoperative IOP. The SOI of Air Ex (+) group was significantly higher than that of Air Ex (-) group (7.4 ± 2.6% vs 4.9 ± 3.4%, Air Ex (+) vs Air Ex (-) group, respectively, P=0.004). A multiple linear regression analysis revealed that SOI was independently significant with AL and Air Ex (+) group (P=0.003, P=0.006, respectively).

CONCLUSIONS: Fluid air exchange during silicone oil removal is not effective for reduction of residual silicone oil droplets. On the contrary, it may increase the risk of residual silicone oil droplets after surgery.
A Porcine Model for Venous Air Embolism from Fluid Air Exchange

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PURPOSE: Several case reports suggest venous air embolism (VAE) is a cause of acute circulatory collapse and possible mortality during fluid-air exchange (FAE) in pars plana vitrectomy (PPV) due to inadvertent infusion of air into the central circulation following displacement of a scleral trocar into the suprachoroidal space. A recent in vitro study confirmed that air could propagate from the choroid through the vortex veins during FAE. This in vivo porcine model demonstrates that infused air during PPV can egress from the suprachoroidal space into the central circulation, precipitating a fatal VAE.

METHODS: After approval from the Institutional Animal Care and Use Committee, two anesthetized pigs underwent vitrectomy and FAE with infusion cannulas intentionally directed into the suprachoroidal space. End-tidal CO₂, oxygen saturation, intra-arterial BP, EKG, and trans-esophageal echocardiography (TEE) were monitored in real time.

RESULTS: Air infusion at 30 mm Hg was used to create a pneumatic choroidal effusion by means of cannulation of the suprachoroidal space. Intracardiac air was detected on TEE less than 30 seconds after increasing pressure to 60 mm Hg. End-tidal CO₂ declined precipitously, followed by hypotension and EKG changes. Oxygen desaturation was a late phenomenon. Death occurred within 7 minutes. Profuse amounts of air effused from the ventricle post mortem.

CONCLUSIONS: This in vivo porcine model confirms that during the FAE in PPV, pressurized air from an infusion cannula in the suprachoroidal space, can transit through the eye to the central circulation, and result in fatal VAE.
ANALYSIS OF PARS PLANA VITRECTOMY INCISIONS USING LIVE BACTERIA

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PURPOSE: To analyze small gauge pars plana vitrectomy sclerotomies using live bacteria transformed with Green Fluorescent Protein (GFP).

METHODS: Twenty-eight human cadaver eyes were specially harvested for this study. Small gauge vitrectomy was performed on each eye and the wounds were closed with various techniques (sutured, sutureless, and cauterization). Live Staphylococcus epidermidis that has been transformed with a GFP was applied to the overlying conjunctival surface. Analysis of all vitreous samples was analyzed with confocal laser microscopy to identify the presence of bacteria. All wounds were analyzed histopathologically.

RESULTS: A high concentration of bacteria was noted in the sutureless, 23-G perpendicular incision group (positive control arm) post-inoculation. There were no bacteria detected in any post-vitrectomy sample that were closed with cautery or a beveled incision. No bacteria were found in post-vitrectomy samples of sutureless 27-G perpendicular incisions and sutureless 27-G beveled incisions. Finally, there were no bacteria detected in both eyes with 23-G perpendicular incisions that had a partial air-fill.

CONCLUSIONS: Live bacteria can be effectively used to analyze wound integrity. Closing sclerotomy sites with cautery proved effective in a model using fresh, human-cadaver eyes. The wound competency was similar in 27-G eyes with perpendicular incisions or beveled incisions.
A Single-center, Randomized, Prospective Study Evaluating the Safety and Efficacy of YAG Vitreolysis versus Sham for Symptomatic Weiss Ring Due to Posterior Vitreous Detachment

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Purpose: To determine the safety and efficacy of a single session of YAG vitreolysis for the treatment of symptomatic Weiss rings.

Methods: Randomized controlled clinical trial. Laser parameters were maximized for safety. Efficacy outcomes were then measured.

Results: Fifty-two eyes in 52 patients were randomized to YAG laser versus sham laser in a 2:1 ratio. Herein are the planned interim results of the first 21 patients completing the 6-month study. There were 13 laser and 8 sham patients. The self-rated 0-10 visual disturbance score significantly improved in the treatment group from 6.5 to 3.5 (p = 0.0015), and did not change in the sham group (6.25 to 6.25, p = 0.39). The YAG group was significantly better than the sham group at 6 months (p = 0.007). The YAG group reported a 50% improvement in symptoms (range 0-100%, median 50%), significantly better than the sham group (mean 5%, range 0-20%, median 0%, p = 0.0013). Objective grading of color fundus photos by a masked investigator revealed improved appearance of floaters after YAG compared to sham laser (mean 78.5% improvement after YAG, range 0-100%, median 100%; mean 0% improvement after sham, p < 0.0001). Many measures of visual quality on the VFQ-25 questionnaire improved after YAG vitreolysis, including quality of eyesight (question #2, 2.3 to 1.8, p = 0.027; 2.6 in sham, p = 0.025 compared to sham). There was no change in best-corrected visual acuity, nor were there any adverse effects.

Conclusions: A single session of YAG laser for symptomatic Weiss rings appears to be safe and well tolerated, with superior objective and subjective efficacy compared to sham laser. The entire dataset will be presented at Retina Society 2016.
Simultaneous Dexamethasone Intravitreal Implant and Anti-VEGF Therapy for Neovascular Age-related Macular Degeneration Resistant to Anti-VEGF Monotherapy

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Purpose: To evaluate efficacy of the dexamethasone intravitreal implant 0.7 mg in combination with anti-VEGF agents for treatment resistant neovascular age-related macular degeneration (nvAMD).

Methods: This study was designed as a single-center, retrospective interventional case series. Consecutive patients with treatment-resistant nvAMD underwent simultaneous combined injection of the same prior anti-VEGF agent and a sample of dexamethasone intravitreal implant (0.7 mg DEX off-label). The main outcome measures included change in best-corrected visual acuity, central foveal thickness (CFT), macular cube volume (MCV) and anti-VEGF injection-free interval post-dual therapy. Eighteen eyes of eighteen patients were included in the study. Mean age was 81.5 years. Patients received on average a total of 26.3 anti-VEGF injections before dual therapy. Mean follow up time was 8.2 months.

Results: Patients receiving dual therapy with intravitreal dexamethasone implant had a significant mean decrease in CFT of 126.3 µm, compared to a mean increase of 29.9 µm when treated with anti-VEGF monotherapy (p=0.0017). The patients also had a mean decrease in MCV of -0.85 mm³ with dual therapy compared with MCV +0.19 mm³ (p=0.0014). There was a moderate correlation between number of prior anti-VEGF injections and magnitude of anatomic response to dual therapy, suggesting that disease duration may influence response to combined treatment. Although there was a slight trend toward worsening mean visual acuity with anti-VEGF monotherapy and trend towards improvement in dual therapy, these differences did not reach statistical significance. Nevertheless, with combination treatment 33% of patients gained one or more lines of vision. The dual therapy resulted in a significantly increased anti-VEGF injection-free interval to 1.41 months from 1.12 months in this patient cohort (p=0.02). Dual therapy was well tolerated; two eyes developed mild IOP elevation effectively managed with topical therapy and one patient developed worsening cataract.

Conclusions: Simultaneous dexamethasone intravitreal implant in combination with anti-VEGF therapy represents a viable alternative for nvAMD patients with treatment resistance to anti-VEGF monotherapy, and may reduce treatment burden. Earlier treatment with dual therapy may be beneficial to maximize anatomic and visual outcomes in these patients.
Phase III Studies Comparing the Efficacy and Safety of Brolucizumab vs Aflibercept in Subjects with Neovascular Age-related Macular Degeneration: Testing an Alternative Treatment Regimen

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Purpose: Brolucizumab is a first-in-kind single-chain anti-vascular endothelial growth factor (VEGF) antibody fragment evaluated for the treatment of neovascular age-related macular degeneration (nAMD). Results from 2 previous Phase I/II studies support that brolucizumab has potentially greater duration of effect compared with existing anti-VEGF treatments. These studies provided the basis for the ongoing Phase III studies (HAWK and HARRIER).

Methods: HAWK and HARRIER (NCT02307682 and NCT02434328) are 2-year, randomized, double-masked, multicenter studies comparing the efficacy and safety of brolucizumab vs aflibercept in nAMD subjects. Based on results and additional analyses from the previous studies, HAWK and HARRIER assess an alternative treatment regimen, which utilizes the potential for longer duration of effect. As an alternative to ‘treat and extend’ regimen, subjects in the brolucizumab arm who meet prespecified criteria will be treated on a q12-week interval directly after the loading phase with the option for a q8-week interval in case of disease activity.

Results: Primary efficacy endpoint is change in best-corrected visual acuity (BCVA) from baseline to Week 48. Key secondary endpoints include average change in BCVA from baseline for Weeks 36-48 and q12-week treatment status at Week 48. Additional efficacy endpoints include change in central subfield thickness from baseline to each postbaseline visit, and absence of subretinal fluid and intraretinal fluid at each postbaseline visit. Following the loading phase of 3 4-week injections, brolucizumab subjects will be evaluated twice for disease activity in the first ‘learning’ q12-week cycle and once after at the end of each subsequent q12-week cycle. If disease activity is identified, subjects will be reassigned to receive q8-week injections thereafter, up to study exit. This regimen is based on the concept that the learning during the first q12 cycle will allow for an adequate allocation of subjects to q12 dosing, as historically no sound parameters could be identified to predict treatment need without direct exposure to a phase of less frequent treatment.

Conclusions: The alternative treatment regimen of HAWK and HARRIER allows evaluation of the potential of brolucizumab for q12-week dosing. Brolucizumab has the potential to address a significant unmet clinical need in the treatment of nAMD patients by reducing treatment burden.
Phase 1 Study of Combination Therapy with Nesvacumab, an Anti-Angiopoietin 2 Antibody, and Aflibercept, an Anti-Vascular Endothelial Growth Factor Agent, for Neovascular Age-related Macular Degeneration and Diabetic Macular Edema

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Purpose: There is opportunity to investigate the improvement of outcomes for patients with neovascular age-related macular degeneration (AMD) and diabetic macular edema (DME) by combining anti-vascular endothelial growth factor (VEGF) treatment with agents such as angiopoietin 2 (Ang2) that are involved in pathological ocular neovascularization but have potentially complementary mechanisms of action to anti-VEGF agents. A phase 1 study was conducted to investigate the safety and tolerability of combination therapy with nesvacumab, a fully human monoclonal antibody against Ang2 and aflibercept, an anti-VEGF agent.

Methods: Nesvacumab/aflibercept (REGN910-3) is a co-formulation of nesvacumab and aflibercept providing both agents in a single intravitreal injection. The first-in-human study of nesvacumab/aflibercept was an open-label, dose-escalation study of the safety and tolerability of intravitreal nesvacumab/aflibercept and nesvacumab alone in patients with neovascular AMD and clinically significant DME.

Results: A total of 20 patients (10 with neovascular AMD and 10 with DME) participated in the study. In the AMD cohort, the mean age was 76 years, 40% of patients were female, and the mean baseline best corrected visual acuity (BCVA) and central retinal thickness (CRT) were 61.7 letters and 414.7 µm, respectively. In the DME cohort, the mean age was 61 years, 70% of patients were female, and the mean baseline BCVA and CRT were 59.7 letters and 472.0 µm, respectively. The most common ocular adverse event was reduced visual acuity (2 patients [10%]). No adverse event considered dose-limiting toxicity (DLT), and no ocular serious adverse events were reported. Visual and anatomic improvements were seen with intravitreal nesvacumab/aflibercept at all dose levels.

Conclusions: Nesvacumab/aflibercept did not result in dose-limiting toxicity at all dose levels studied in both neovascular AMD and DME patients, and visual and anatomic improvements were seen at all dose levels in this phase 1 trial.
Choroidal Neovascularization Lesion Characteristics as a Predictor of Visual Outcome in Wet Age-related Macular Degeneration Patients Receiving Combination Therapy of Intravitreal Ranibizumab and Squalamine Lactate Ophthalmic Solution

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Purpose: To determine lesion characteristics that may impact outcomes with combination treatment in neovascular AMD.

Methods: This phase 2 double masked, placebo-controlled, randomized study enrolled subjects with a broad range of baseline lesion characteristics and visual acuity. Subjects received one intravitreal injection of ranibizumab at baseline, and were randomized 1:1 to receive Squalamine or placebo eye drops BID through the 9-month study duration. Subjects were seen monthly and received criteria-based PRN ranibizumab injections. Exploratory visual acuity analyses were performed including pre-specified analyses of ITT and mITT populations, as well as overall and classic-CNV containing lesions. Post-hoc analyses explored lesion characteristics as predictive factors for visual outcomes. These assessments were based on differences in the vascular biology of lesion types and potential differential responses to Squalamine when administered in a combination regimen.

Results: Visual acuity outcomes in the overall population at month 9 (mITT) showed mean gain in BCVA from baseline of 7.8 letters in the combination group (N=65), compared to 5.3 letters in the ranibizumab monotherapy group (N=63) (P=0.25). Subjects with classic CNV-containing lesions at baseline showed mean gain in BCVA of 11.0 for the combination group (N=36) and 5.0 for the monotherapy group (N=28) (P=0.086). Proportion of patients gaining 3 or more lines of BCVA trended similarly (44% vs 28%). Post-hoc analyses of lesion characteristics revealed the impact of occult CNV and occult CNV lesion size on treatment outcomes with combination therapy. Subjects in the combination therapy group with lesions whose occult component was < 10mm$^2$ (N=47) gained an average of 11 letters compared with 5.7 in the ranibizumab monotherapy group (N=46) at 9 months (P=.03). Similar benefits favoring combination therapy were seen in subjects gaining 3 or more lines of BCVA (40% vs 26%).

Conclusions: Clinical/anatomical responses to combination treatment of CNV due to AMD are dependent on baseline lesion characteristics. The post hoc analyses of lesion characteristics as predictive factors for visual outcomes in this phase 2 study revealed combination therapy with Squalamine was most effective in subjects whose occult component was smaller than 10 mm$^2$. This effect was not seen in the ranibizumab arm. This is the target population for the phase 3 program.
Is there a Role for Fluorescein Angiography in the Monitoring of Eyes with Neovascular Age-related Macular Degeneration Receiving Anti-VEGF Therapy?

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PURPOSE: Most retina specialists rely on OCT to guide treatment decisions in neovascular age-related macular degeneration (nAMD). However, OCT may not always detect exudative activity. Traditionally, FA was frequently performed in clinical practice, but its use has diminished due to reliance on OCT. The purpose of this analysis was to evaluate the agreement between detection of CNV activity by FA and OCT in the HARBOR study, to inform whether it is appropriate to reduce the use of FA in monitoring patients with nAMD.

METHODS: Baseline to Month 24 data from all randomized study eyes in HARBOR with both FA and OCT data were analyzed for 1) Evidence of CNV activity on OCT (e.g. presence of subretinal fluid, intraretinal fluid, or cystoid spaces); 2) Evidence of CNV activity on FA identified by the presence of leakage; 3) Cross tabulation of CNV activity identified by FA and OCT by office visit; and 4) Comparison of CNV activity by source of detection and predictor variables. If CNV activity was present in either OCT or FA then the case was considered to have CNV activity.

RESULTS: At baseline, 1094 cases (99.9%) had agreement between FA and OCT in detecting CNV activity. By Month 24, of the 779 total active cases the agreement was only 36% (277 cases). By month 24 most cases (n= 452, 58%) had evidence of CNV activity on OCT only, while 6% of cases (n=50) had CNV activity identified by FA only. At baseline and months 3, 6, 12, and 24, 92-100% of cases identified by FA only were occult CNV lesions. Agreement between FA and OCT at Month 24 (yes for both or no for both) was only 44%. Comparing against detection by FA, positive and negative predictive values for detection of CNV by OCT were 50% and 63%, respectively, with sensitivity and specificity of 92% and 13%.

CONCLUSIONS: OCT alone can be relied upon for detecting CNV activity while monitoring eyes with nAMD. However FA may be of value in those with occult lesions that appear quiescent on OCT, as these type of lesions may show leakage on FA.
Are Dilated Fundus Exams Needed for the Management of Neovascular Age-related Macular Degeneration (nAMD)?

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Purpose: Dilated fundus exams (DFEs) are performed to identify abnormalities undetected by OCT. In the HARBOR Study, retreatment decisions in the pro re nata (PRN) arms relied only on visual acuity and OCT. The objective of this analysis was to determine how often disease activity was detected on OCT imaging when a hemorrhage was present on red free (RF) or color fundus photography (CFP).

Methods: The HARBOR Study was a phase 3, multi-center, double-masked, randomized active-treatment-controlled clinical trial that evaluated intravitreal ranibizumab 0.5 mg or 2.0 mg administered monthly or PRN for nAMD. In this post hoc analysis, hemorrhage was considered present if extrafoveal or subfoveal hemorrhage was identified on either RF or CFP. OCT CNV activity included: 1) “presence of intraretinal fluid, subretinal fluid, or cystoid space”; or 2) the same definition plus “presence of pigment epithelial detachment (PED).”

Results: Hemorrhage was identified in 88.8% (973/1096) of eyes at screening, 30.6% (319/1042) at Month (M) 3, 11.2% (111/989) at M6, 11.7% (115/983) at M12, and 11.3% (106/935) at M24. With both definitions of CNV activity, agreement between RF/CFP and OCT was 100% at screening. With the definition excluding PED, agreement was 89.0%, 95.5%, 89.6%, and 90.5% at M3, M6, M12, and M24, respectively; when including PED, agreement was 90.9%, 95.5%, 95.7%, and 92.4%, respectively. At M3, 82 patients in the PRN arms had hemorrhages but did not meet PRN re-treatment criteria and therefore did not receive ranibizumab injections. Of those with data available, mean VA change was -0.06 letters from M3 to M4 and +9.36 letters from baseline to M24.

Conclusions: In the HARBOR study, OCT detected activity in ≥89% of eyes when hemorrhage was present on RF or CFP. When PED was included in the OCT parameters, agreement was even higher by -2%-6%. For patients who did not receive an injection when hemorrhage was present, significant vision improvement was still seen at M24. Overall, this analysis suggests that OCT may be sufficient for determining retreatment need in eyes with nAMD. The question then remains as to the necessity and optimal frequency of DFE in the routine management of nAMD.
Response of Eyes with Pigment Epithelial Detachments Treated with Ranibizumab, Including Those That Developed Retinal Pigment Epithelial Tears: Data from the HARBOR Study

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Purpose: To evaluate the visual/anatomic outcomes of ranibizumab-treated eyes with neovascular AMD and pigment epithelial detachment (PED), including those that developed retinal pigment epithelial (RPE) tears.

Methods: In HARBOR, 1097 study eyes were randomized to receive 3 monthly doses of 0.5 or 2.0 mg intravitreal ranibizumab and were then either continued on monthly therapy or treated PRN based on ≥5-letter decrease in BCVA or any evidence of disease activity on SD-OCT. In eyes with PED at baseline, outcomes were evaluated over 24 months (M), including change in BCVA from baseline, complete resolution of PED, number of ranibizumab injections, and development of RPE tear. All analyses used observed data.

Results: 598 eyes had PED at baseline with a height ranging from ~35-1400 µm. Eyes randomized to ranibizumab 0.5 mg and 2.0 mg PRN received 14.0 and 11.6 injections over 24M, respectively. At M24, mean change in BCVA from baseline was +9.0 letters (ranibizumab 0.5 mg monthly), +8.4 letters (ranibizumab 0.5 mg PRN), +7.1 letters (ranibizumab 2.0 mg monthly), and +7.2 letters (ranibizumab 2.0 mg PRN). PED resolution at M24 occurred most often in eyes randomized to ranibizumab 2.0 mg monthly (70.5%) compared with ranibizumab 0.5 mg monthly (53.2%), ranibizumab 0.5 mg PRN (44.5%), and ranibizumab 2.0 mg PRN (57.3%) (all doses P≤.03 vs 2.0 mg monthly). Eyes randomized to ranibizumab 0.5 mg PRN with or without complete resolution of PED received 12.7 or 16.3 injections over 24M, respectively (P=.0004). Twenty-eight (5%) eyes developed a new RPE tear, with 21 of these in eyes with the largest PEDs (≥352 µm) at baseline. Of eyes with new RPE tear, the median change in BCVA from baseline at M24 was +0.5 letters (n=24; eyes with non-foveal only tear, +3.5 letters [n=20], eyes with subfoveal/non-foveal tear, -24.5 letters [n=4]).

Conclusions: In the >50% of patients with PED at baseline in HARBOR, a mean of 8-9 letters was gained from baseline at M24 with ranibizumab 0.5 mg PRN or monthly. While more PED resolution was seen with a higher ranibizumab dose, there was no additional vision benefit. Generally, patients experiencing on-study non-foveal RPE tear avoided vision loss with continued ranibizumab.
Prospective, Multicenter Study of Aflibercept Treat and Extend for Neovascular Age-related Macular Degeneration (ATLAS): One and Two Year Results

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Purpose: To determine the visual outcomes, anatomic outcomes, and the number of injections required when using a treat and extend regimen with aflibercept for neovascular age-related macular degeneration (NVAMD).

Methods: Forty eyes of 40 participants met inclusion criteria for this multicenter, prospective, open label study. These eyes were treated every 4 weeks until no signs of macular exudation by clinical assessment including spectral domain optical coherence tomography. The treatment intervals were then extended by 2 weeks until either an exudative recurrence or a treatment interval of 16 weeks was achieved. Main outcome measures included change from baseline visual acuity, change in central retinal thickness (CRT), mean number of annual injections, treatment interval, and adverse events.

Results: Forty eyes of 40 patients were enrolled. An average of 8.0 treatments resulted in a median best corrected visual acuity (BCVA) improvement of 12 letters and CRT decrease of 163 micrometers during the first year. An average of 6.5 treatments resulted in a sustained median BCVA improvement of 8 letters and CRT decrease of 168 micrometers during the second year. A treatment interval of eight weeks or longer was obtained in 71% and 82% of patients at one and two years, respectively. A treatment interval of twelve weeks or longer was obtained in 35% and 40% of patients at one and two years, respectively. A single case of endophthalmitis occurred during the study. No related systemic adverse events were observed.

Conclusions: Aflibercept treat and extend therapy for NVAMD led to visual and anatomic improvement at year 1, and these gains were relatively well maintained at year 2 with a decreased treatment burden compared to year 1. A sustained treatment interval of 12 weeks or longer was obtained in 40% of patients.
A Meta-analysis of Anti-VEGF Treatment Regimens for Neovascular Age-Related Macular Degeneration: One Year Results Are Driven in Part by the Injection Frequency

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PURPOSE: Treatment of nAMD with anti-VEGF agents can be given monthly, as needed (PRN) based on findings of exudation, or on a “treat-and-extend” (T&E) regimen. We sought to better understand how frequency of antivascular endothelial growth factor (anti-VEGF) therapy impacts visual acuity in patients with neovascular age-related macular degeneration (nAMD).

METHODS: A meta-analysis of studies employing the treat-and-extend regimen for nAMD was performed by Pubmed search of “bevacizumab treat and extend” and “ranibizumab treat and extend”. Only studies that measured visual acuity with ETDRS letters were included. Four studies were analyzed (LUCAS, TREVAMID, Abedi et al, Oubrahim et al) to determine the relationship between number of injections and numbers of ETDRS letters gained. These results were compared to those from phase 3 trials employing monthly treatment (ANCHOR, MARINA, CATT, IVAN, VIEW), quarterly treatment (PIER and EXCITE), and PRN treatment (PRONTO, SAILOR, SUSTAIN, HARBOR, CATT, IVAN).

RESULTS: From the clinical trials above, 21 treatment arms were analyzed. When pooling these treatment arms encompassing monthly, quarterly, T&E, and PRN regimens of ranibizumab or bevacizumab, number of injections showed a linear correlation with number of letters gained at 12 months ($r = 0.65$, $R^2 = 0.331$). Studies were sorted by number of injections delivered in the first year; mean letters gained did not increase beyond a mean of 9 or more injections in the first 12 months, suggesting that visual outcome generally plateaus after approximately 9 injections during the first 12 months of treatment (8 of 21 treatment arms with 9 or more injections in the first year, mean number of injections 10.1, mean letters gained 8.9). Analysis of studies with fewer than 9 injections in 12 months revealed greater linear correlation ($r = 1.61$, $R^2 = 0.47$), suggesting that 47% of the variability in letters gained in the first 12 months is related to injection frequency. Trials of aflibercept were not analyzed.

CONCLUSIONS: Anti-VEGF injection frequency plays a substantial role in visual outcomes in nAMD, regardless of treatment regimen. There is a ceiling effect, highlighting a limitation of anti-VEGF therapy for nAMD. Fewer than 9 injections in the first year is associated with worse visual outcomes, highlighting treatment burden as a limitation of anti-VEGF therapy for nAMD.
FIVE-YEAR OUTCOMES WITH ANTI-VEGF TREATMENT OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION IN THE COMPARISON OF AGE-RELATED MACULAR DEGENERATION TREATMENTS TRIALS (CATT)

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PURPOSE: To describe outcomes 5 years after initiating treatment with bevacizumab or ranibizumab for neovascular age-related macular degeneration (AMD).

METHODS: Patients enrolled in the Comparison of AMD Treatments Trials (CATT) were assigned randomly to ranibizumab or bevacizumab and to 1 of 3 dosing regimens. After 2 years, patients were released from the clinical trial protocol. At 5 years, patients were recalled for examination. Best corrected ETDRS visual acuity, OCT, color photos, FA, and treatment history in the 3+ year interim were obtained.

RESULTS: Visual acuity was obtained for 647 of 914 (71%) living patients with average follow-up of 5.5 years. The mean number of examinations for AMD care after the clinical trial ended was 25.3, and the mean number of treatments was 15.4. Most patients (60%) were treated 1 time or more with a drug other than their assigned drug. At the 5-year visit, 50% of eyes had VA of 20/40 or better and 20% had VA of 20/200 or worse. Mean change in VA was -3 letters from baseline and -11 letters from 2 years. Among 467 eyes with fluorescein angiography, mean total lesion area was 12.9 mm², a mean of 4.8 mm² larger than at 2 years. Geographic atrophy was present in 213 of 515 (41%) gradable eyes and was subfoveal in 85 eyes (17%). Among 555 eyes with spectral-domain optical coherence tomography, 83% had fluid (61% intraretinal, 38% subretinal, and 36% sub-RPE). Mean foveal total thickness was 278 um, a decrease of 182 um from baseline and 20 um from 2 years. The retina was abnormally thin (<120 um) in 36% of eyes. Between 2 and 5 years, the group originally assigned to ranibizumab for 2 years lost more VA than the bevacizumab group (-4 letters; P=0.008). Otherwise, there were no statistically significant differences in VA or morphologic outcomes between drug or regimen groups.

CONCLUSIONS: Vision gains during the first 2 years were not maintained at 5 years. However, 50% of eyes had VA of 20/40 or better, confirming anti-VEGF therapy as a major long-term therapeutic advance for neovascular AMD.
Macular Morphology and Visual Acuity at Year 5 of the Comparison of Age-related Macular Degeneration Treatments Trials (CATT)

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Purpose: There are little data on the correlations of visual acuity and retinal morphology after long-term anti-VEGF therapy. Herein we describe the associations of morphologic features on OCT, fundus photography (FP), and fluorescein angiography (FA) with visual acuity (VA) in CATT at yr 5.

Methods: Design: A prospective cohort study within a randomized clinical trial (CATT), in eyes with active CNV secondary to AMD. From study yrs 2-5, CNV was managed per-investigator discretion according to a ‘real-world’ treatment approach.

Main Outcome Measures: fluid type, location and thickness, retina and subretinal tissue complex presence and thickness on OCT; size and lesion composition on FP and FA; and VA at yr 5.

Results: Among 523 patients with both OCT and FP data at 5 ys, residual intraretinal fluid (iRF) was present in 60%, subretinal fluid (SRF) in 38%, subretinal pigment epithelium fluid (SRPEF) in 36%, and subretinal hyper-reflective material (SRHM) in 66%. On FP/FA, subfoveal fibrotic scar was present in 17% and subfoveal GA in 16%. The unadjusted VA was significantly worse (feature present vs absent, respectively: p<0.0001) for foveal iRF (44 vs 68 ltrs), SRHM (41 vs 72 ltrs), ORT (52 vs. 63 ltrs); foveal GA and foveal fibrotic scar vs no pathology (46 vs. 70 ltrs), thick SR tissue, retinal thickness <120u (50 ltrs) or >212u (54 ltrs), large vs small lesions (49 ltrs vs. 72 ltrs). VA was better (p<0.02) for eyes with foveal SRF (68 vs 61 ltrs) and SRPEF (73 vs 60 ltrs). On multivariate analysis, the adjusted VA remained worse in eyes with foveal iRF, SHRM, GA, fibrotic scar, retinal thickness <120u or >212u, and large lesions.

Conclusions: There was residual subfoveal IRF, SRF, SRPEF, SHRM, GA, and subfoveal fibrosis in a sizeable proportion of eyes at CATT yr 5. Most associations between VA and morphologic features identified through year 2 were maintained or strengthened by yr 5. Eyes with foveal iRF, SHRM, GA, fibrosis, large lesions, and abnormally thin retina, had the worst VA, while, foveal SRF and SRPEF had the best VA. There is an unmet need for treatment that limits GA, fibrosis and lesion growth.
**THY-1 Induces Activation and Migration of Choroidal Endothelial Cells: Relevance to Neovascular Age-related Macular Degeneration**

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**PURPOSE:** Linking age-related changes in Bruch’s membrane to factors that activate choroidal endothelial cells (CECs) in choroidal neovascularization (CNV) is important in neovascular AMD. We assessed the role of the glycoprotein, Thy-1, found in ganglion cells and CECs and addressed the hypothesis that Thy-1 activated CECs and was necessary for CEC migration.

**METHODS:** Use of isolated human CECs and donor eyes obtained from the Eye Bank was exempt by the Human Subjects Committee of the University of Utah. Thy-1 mRNA expression (real-time PCR) and activation of Rac1 (pulldown assay) were determined following exposure to angiogenic factors (vascular endothelial growth factor [VEGF] or eotaxin) or 7-ketocholesterol, compared to controls. Thy-1 protein was measured by western blot in RPE/choroid lysates from old vs. young human donor eyes or murine eyes lasered to create CNV or left untreated. Human and murine ocular sections were co-labeled for Thy-1 and ve-cadherin to localize endothelial cells. Silencing of Thy-1 with siRNA vs. control was performed in CECs treated with VEGF, and phosphorylated VEGF receptor 2 (p-VEGFR2), activated Rac1 and CEC migration were determined.

**RESULTS:** Thy-1 mRNA was increased in CECs exposed to VEGF, CCL11 or 7-ketocholesterol compared to control (p<0.05) and was 30-fold increased in RPE/choroids from human old vs. young donor eyes (p<0.001) and significantly increased in lasered vs. untreated murine eyes (p<0.05). Thy-1 colocalized to CNV in human donor eyes and in murine laser-induced CNV. Thy-1 siRNA prevented VEGF induced p-VEGFR2, Rac1 activation and significantly reduced VEGF-induced CEC migration (p<0.001).

**CONCLUSIONS:** Thy-1, a glycoprotein that connects the extracellular matrix and cell membrane, was expressed in CECs after exposure to AMD-related angiogenic factors, VEGF or eotaxin, to 7-ketocholesterol, which accumulates in AMD, in human CNV in neovascular AMD and in laser-induced CNV in mice. Thy-1 mediated VEGF-induced CEC migration via Rac1 activation. Our findings suggest a mechanism that links age-related changes in Bruch’s membrane to activation of CECs that migrate to develop into CNV in neovascular AMD.
Semaphorins Inhibit Choroidal Neovascularization

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**Purpose:** Choroidal neovascularization (CNV) is a major blinding consequence of several retinal diseases including the exudative form of age-related macular degeneration (AMD). Anti-VEGF agents are widely used to treat AMD, however the high rate of non-responders calls for the exploration of anti-angiogenic agents that act independently from the VEGF pathway. This study was designed to investigate whether the anti-angiogenic molecules semaphorin-3C, and 3E may be used to effectively inhibit laser induced CNV formation in a mouse model.

**Methods:** CNV was induced in the eyes of C57B mice (n=15) by laser photocoagulation followed by an intravitreal injection of either 0.1µg FR-Sema3C, 5µg aflibercept or vehicle as a control. After a week flat whole mounts of retinas where used to determine CNV development and size. Results were assessed by the staining of blood vessels with dextran green and by calculation of the area of stained blood vessels using morphometric software. The effects of FR-sema3C, and sema 3E injection on the visual function of healthy mice were assessed using a non-invasive optokinetic testing system.

**Results:** FR-Sema3C (100 ng) injected into the vitreous cavity of mice reduced the area of laser induced CNV by 44% as compared to controls (121063±16957µm² for controls (n=48) vs 53383±5779µm² (n=40), P<0.001). This efficacy was similar to that of aflibercept (40%, 48713±7255µm² (n=40), P<0.0001). The optokinetic essays indicated that at this dose FR-sema3C does not compromise visual acuity. FR-Sema3C also inhibited significantly laser induced CNV using lower doses (10 and 50 ng per injection) although the inhibition was less effective than at 100 ng per injection (142578±23886µm² for controls (n=16) vs 0.1µg (53153±10094µm² (n=24), P<0.001), 0.05µg (93836±12890µm² (n=24), P<0.05) and 0.01µg (95042±16348µm² (n=24), P<0.05).

UNCL-Sema3E (50 µg) injected into the vitreous cavity of rats reduced the area of laser induced CNV by 50% (64040 ± 7321 µm² for controls (n=61) vs 32720 ± 2369 µm² (n=65), P<0.001) displaying efficacy similar to that of bevacizumab (32062±1806 µm² (n=54), P<0.001). UNCL-Sema3E (5µg) injected into the vitreous cavity of mice reduced the area of laser induced CNV by 35% (121063±16957µm² for controls (n=48) vs 78400±8802µm² (n=64), P<0.05) displaying somewhat lower efficacy than that of aflibercept (48713±7255 µm² (n=40), P<0.0001).

**Conclusions:** Both FR-Sema3C and UNCL-Sema3E inhibit laser induced CNV formation in the mouse model efficiently without toxic side effects. The semaphorins mechanism of action is unique because it is independent of VEGF. This suggests that semaphorins may be considered to be developed as possible novel therapeutic agents for the treatment of exudative AMD that is refractory to current VEGF targeting agents.
A Novel Subretinal Access Procedure Using a Suprachoroidal Approach

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for the Prelude Study Group

**PURPOSE:** Palucorcel (CNT02476; human umbilical tissue derived cells) is being evaluated for the treatment of geographic atrophy (GA). In a Phase 1 study, transvitreal delivery was associated with cell egress into the vitreous and membrane formation in 2 patients. A novel subretinal delivery procedure, without retinotomy, was developed along with an access kit and cannula. The suprachoroidal space is used as a pathway to the posterior globe, where a microneedle accesses the subretinal space by choroidotomy. We present preliminary results from a first-in-man safety study of this new subretinal delivery procedure.

**METHODS:** This ongoing open-label safety run-in of a Phase 2b study enrolled subjects 55-90 years old with advanced subfoveal GA to receive a single administration of palucorcel. Per protocol, 21 procedures conducted by ≥7 different surgeons were required prior to advancing to the masked-randomized phase. Concurrent anticoagulants were stopped prior to surgery. Local or general anesthesia was permitted. Ports were placed in the pars plana for chandelier illumination and fluid infusion, if needed. Surgery was standardized across sites and all procedures were videotaped. Prespecified events of interest included: endophthalmitis, significant hemorrhage, retinal detachment, egress of cells into the vitreous or need for vitrectomy, and failure to deliver cells to the subretinal space. The Data Safety Monitoring Board monitored study progress following each case.

**RESULTS:** Twenty-one procedures were performed by 8 surgeons. In 18/21 (86%) cases, cells were delivered to the subretinal space as intended. There was one case each in which the cannula tip could not be visualized; the microneedle did not engage the choroid; and cells were inadvertently delivered into the suprachoroidal space. There were no cases of infection, hemorrhage, or retinal detachment, and no detectable retinal perforations; no subject required vitrectomy.

**CONCLUSIONS:** Safe delivery of cells to the subretinal space without retinotomy was demonstrated across a group of 8 surgeons. Numerous minor improvements were made to the procedure during the course of the study, and further enhancements are possible. This procedure has the potential to improve subretinal delivery of cells, gene vectors, and other therapeutic agents. Clinician feedback from the ongoing clinical trial will inform further enhancement to the device and procedure.
Macular Holes in the Pediatric Population: A Retrospective Review

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**PURPOSE:** Retrospective review to look at macular holes in the pediatric population at a tertiary medical center.

**METHODS:** Retrospective chart review of macular hole cases in children.

**RESULTS:** Macular holes in children are not very common. They tend to be related to trauma. We have looked at the macular holes that presented to BPEI since the advent of MIVS.

**CONCLUSIONS:** Macular holes in children seem to close without intervention. The ones that persist seem to close easily with surgery despite intraocular agent placed in the vitreous.
High-dose Ranibizumab for Exudation and Hemorrhage in Polypoidal Choroidal Vasculopathy: PEARL 2 Trial (Polypoidal Choroidal Vasculopathy with IntravitREAl Ranibizumab (Lucentis))

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Purpose: To evaluate high dose ranibizumab in the treatment of Polypoidal Choroidal Vasculopathy (PCV) on stabilization of vision loss, anatomical changes within the macula, and its safety profile on continuous monthly treatments for 2 years.

Methods: A prospective open-label clinical trial of high dose ranibizumab was performed on patients diagnosed with PCV. Participants were examined and treated monthly with ranibizumab administered at each visit (2mg/0.5cc or 1mg/0.5cc). Dosing was dependent on drug availability, with discontinuation of the 2mg preparation during the study. The primary outcome was the mean change in visual acuity at 2 years. Secondary outcomes measured were the presence of subretinal hemorrhage, subretinal fluid, central foveal thickness (CFT), choroidal thickness, polypoidal complex morphology on indocyanine green angiography (ICGA), and incidence of adverse events.

Results: Twenty-four subjects entered the PeARl 2 clinical trial with 21 patients completing the study. Three subjects lost ≥ 15 ETDRS letters, 1 lost > 5 letters, 6 remained unchanged, 6 gained >5 letters, and 5 gained ≥ 15 ETDRS letters at 2 years. Mean ETDRS vision was 60.1 letters at baseline and 64.9 at 2 years (p=0.18). Subretinal fluid increased, decreased, and resolved in 1, 2, 1, 16 eyes respectively. Subretinal hemorrhage increased, decreased, and resolved in 1, 2, 1, 16 eyes respectively. Average CFT was 305 µm at baseline and 217 µm at 2 years (P<0.0001). Choroidal thickness measured at the fovea was on average 206 µm at baseline and 178 µm at 2 years (P=0.001). The branching vascular network (BVN) of the PCV complex increased, decreased, and remained stable in 1, 1, and 19 eyes respectively and the polyps decreased, remained stable, and resolved in 10, 9, and 2 eyes respectively. There were no ocular or systemic adverse effects. No increase in disease recurrence was noted with the switch from the 2mg to 1 mg preparation.

Conclusions: High dose ranibizumab is an effective treatment in hemorrhage and exudation in PCV. The morphology of the PCV complexes have varying response to high dose treatment, with the majority remaining stable. Additional prospective trials involving this therapy are needed to define its role in the current treatment paradigms.
**SUBMACULAR HEMORRHAGE IN PATIENTS ON NOVEL ORAL ANTICOAGULANTS (NOACs)**

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**PURPOSE:** To characterize the development and subsequent treatment of submacular hemorrhage in age-related macular degeneration (ARMD) patients on NOACs.

**METHODS:** Retrospective case series and comprehensive literature review.

**RESULTS:** Five patients on NOACs who developed submacular hemorrhage were identified. All patients had a history of atrial fibrillation, cardiac stent, or coronary artery bypass. Patients had a history of age-related macular degeneration (ARMD) that had been managed with intravitreal anti-vascular endothelial growth factor (anti-VegF) injections. Two of the patients were treated with subretinal tissue plasminogen activator, the other three were continued on intravitreal injections.

**CONCLUSIONS:** Vitamin K antagonists have been a mainstay of oral anticoagulation for decades. Recently, new oral anticoagulants have been released, these include direct thrombin inhibitors and direct factor Xa inhibitors. While these medications do not require pharmacologic monitoring, patients on NOACs can present with prominent submacular hemorrhage. This phenomenon appears even in stable ARMD patients on maintenance anti-VEGF injections. Given the vision threatening nature of these hemorrhages, retina physicians should be cognizant of which patients may be at risk for subretinal bleeding.
MANAGEMENT OF CHOROIDAL NEOVASCULARIZATION (CNV) THROUGH THE IMPLANTABLE MINIATURE TELESCOPE (IMT)

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PURPOSE: Eyes implanted with an IMT are at risk for developing new or recurrent choroidal neovascularization. The IMT poses unique challenges when examining or imaging the macula to diagnose and monitor the progression of CNV. Administering intravitreal injections can also be difficult in these eyes due to the large size and location of the IMT. We review these challenges as well as techniques for successfully managing exudative AMD in telescope-implanted eyes.

METHODS: This is a retrospective review of imaging and injection techniques based on management of patients implanted with an IMT. These patients were imaged through both the Zeiss Cirrus and Heidelberg Spectralis optical coherence tomography (OCT) modalities. Each OCT device has unique scanning capabilities which optimize detection of CNV. After reviewing the size, shape, and dimensions of the IMT, optimal safe and effective injection techniques in these eyes were established. A representative case will be reviewed.

RESULTS: Examining and imaging IMT eyes is difficult due to the minimized and distorted image through the telescope, and patients are unable to fixate due to central vision loss. The Cirrus HD-OCT offers two types of scans: a macular cube scan which allows scrolling through the entire macular image, and a 5 line raster scan that provides quicker and higher resolution scans. The Spectralis SD-OCT has a condensed volume scan and an automatic real tracking feature, both features increase scan resolution while decreasing capture time. Due to the IMT extending much more posteriorly than a standard intraocular lens, thereby stretching the posterior lens capsule, there is a significant risk of needle damage due to intravitreal injection. By directing the injection needle toward the optic nerve without applying globe pressure (there is a 12 mm sutured limbal wound following implantation), the injection can be performed safely. A single patient with recurrent CNV following IMT placement was successfully imaged and managed with a series of intravitreal anti-VEGF injections.

CONCLUSIONS: Using the imaging techniques described, it is possible to successfully image the macula in eyes with an IMT, allowing for detection and monitoring of CNV. With injection technique modification, these eyes can be easily treated with standard intravitreal anti-VEGF therapy.
**Reticular Pseudodrusen and Systemic Disease**

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**PURPOSE:** To investigate the relationship between systemic disease and the presence of reticular pseudodrusen.

**METHODS:** A retrospective review of multimodal imaging established that 198 of 1187 patients enrolled in the Unifying Genetic Epidemiology of Macular Degeneration Study had pseudodrusen in at least one eye. Patients completed documentation of their medical history including heart disease, elevated lipids/cholesterol, kidney disease, hypertension, stroke, and cigarette use. A chi-squared test was used to assess for an association between RPD and systemic disease variables.

**RESULTS:** No association was found between reticular pseudodrusen and these systemic conditions.

**CONCLUSIONS:** Further study is required to better characterize potential systemic associations with reticular pseudodrusen.
Systemic Beta-blockers in Neovascular Age-related Macular Degeneration

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Purpose: Anti-vascular endothelial growth factor has revolutionized the treatment of neovascular age-related macular degeneration (nAMD). However, the burden it poses on patients due to the need for frequent surveillance and treatment, has given rise to the exploration of other modalities that may extend or augment its efficacy. Beta-adrenergic blockade has been proposed as such a modality. The purpose of this study is to evaluate whether oral beta-blockers are associated with a decreased number of intravitreal injections in patients with incident nAMD.

Methods: A retrospective cohort study was conducted using a medical claims database from a large national US insurer of patients ≥60 years of age with a new diagnosis of nAMD after 2006 with at least one intravitreal injection and one year of follow up. Two cohorts were created for comparison consisting of patients with regular use of beta-blockers or calcium channel blockers, defined as >80% daily coverage for a prescription in the respective class of medication during the observation period. Additional exclusion criteria were a previous diagnosis of a disease that could lead to anti-VegF use, less than 2 years of data prior to initial diagnosis, or use of the other class of medication during the observation period. The main outcome measured was the difference in the mean number of intravitreal injections administered between the two cohorts. Covariates of interest included age, gender, race, diabetes, year of diagnosis, and the associated systemic diseases for which each class of medication is given.

Results: After inclusion and exclusion criteria, 239 beta-blocker and 155 calcium channel blocker subjects remained for analysis. Univariate analysis revealed that the mean number of injections in the beta-blocker group was 6.43 (95% CI 5.88-6.96) versus 6.55 (95% CI 5.88-7.21) in the calcium channel blocker group. After multivariate adjustment, the mean number of injections in the beta-blocker group was 6.32 (95% CI 5.88-7.21) versus 6.71 (95% CI 6.02-7.40) in the calcium channel blocker group. The overall difference between the two groups was -0.39 (95% CI difference -1.30-0.51).

Conclusions: The use of oral beta-blockers is not associated with a decreased number of injections in nAMD patients.
The Relationship between Non-steroidal Anti-inflammatory Drug Use and Age-related Macular Degeneration

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Purpose: To investigate the relationship between non-steroidal anti-inflammatory drug (NSAID) use and age-related macular degeneration (AMD).

Methods: Data from the California Men’s Health Study was analyzed. The cohort consisted of men between the ages of 45 and 69 years old with Kaiser Permanente insurance who completed self-administered questionnaires in 2002 and 2006. Subjects who completed both surveys were analyzed while those with a prior history of AMD were excluded. NSAID exposure was defined as self-reported use greater than three times per week. Subgroup analysis was done for aspirin and non-aspirin NSAIDs separately. Subjects were characterized as NSAID users if they self-reported use on the 2006 survey, non-users if they self-reported no NSAID use on both surveys, or former users if they reported use on the 2002 survey but not the 2006 survey. Age, race, smoking status, Charleston comorbidity index score, diabetes status, hypertension, hyperlipidemia, body mass index (BMI), and presence of peripheral vascular disease were included in the analysis. Incident AMD was identified using ICD-9 codes from electronic medical records. Multivariate analysis was performed.

Results: 51,371 subjects met inclusion criteria. Average follow up time was 7.4 years. There were 18,985 current NSAID users, 7,012 former NSAID users, and 25,374 non-users. Exudative and non-exudative AMD were diagnosed in 292 (0.6%) and 1,536 (3%) of responders, respectively. White race, advanced age, and smoking were statistically significantly associated with risk of AMD. There was no difference in the risk of AMD between non-users and former NSAID users for exudative or non-exudative AMD across all NSAID categories (all NSAIDs, aspirin, or non-aspirin NSAIDs). Current NSAID use was not associated with a difference in exudative AMD risk for any NSAID category; however, NSAID use was associated with a statistically significant reduction in non-exudative AMD risk [HR=0.89 (0.80-1.00), p=0.0425]. Among non-aspirin NSAID users, differences in non-exudative AMD incidence did not reach statistical significance [HR=1.04 (0.89-1.22), p=0.6122] while there was a statistically non-significant trend towards decreased non-exudative AMD incidence in current aspirin users [HR=0.90 (0.80-1.00), p=0.0576].

Conclusion: NSAID use is associated with a reduction in non-exudative AMD risk. Time of exposure is an important factor as this effect was seen in current, but not former, NSAID users.
INVESTIGATION OF RISK ALLELES FOR MACULAR DEGENERATION AMONG SEVERE DRUSEN PHENOTYPES AND RETINAL PIGMENTARY EPITHELIAL ALTERATIONS

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PURPOSE: To utilize commercially available genotype risk assessment testing for age-related macular degeneration (AMD) to segregate AMD from other drusen and retinal pigmentary epithelial (RPE) alterations, and to investigate for associations of specific single nucleotide polymorphisms (SNPs) with drusen phenotypes.

METHODS: Retrospective consecutive observational series of 82 patients, who underwent genetic evaluation between February 2013 and February 2015 for early-onset, severe, or atypical drusen phenotypes, or if RPE changes were suspicious for AMD. The test evaluated fifteen risk alleles among 12 genes for AMD and provides a comparative genetic risk subscore. Patients were clinically stratified based on drusen phenotypes into six categories. AREDS 4-step grading was performed by 3 independent retinal specialists. Genetic testing results were compared among the six disease categories to determine if genetic risk subscores could differentiate between AMD and non-AMD states. Specific SNPs were evaluated for associations with drusen phenotypes.

RESULTS: AREDS grading was similar among all groups. Dry AMD and drusen phenotype cohorts had higher genetic risk subscores (median 81) than other pigmentary alterations (median 40). In 18 patients (22%), AMD testing changed the clinical impression towards (13.4%) or against (8.5%) dry AMD. Additional genetic testing was performed in 14 patients, 2 of whom were positive for non-AMD diagnoses. Genetic risk was not statistically significant between six disease categories (one-way ANOVA F(5,76)=1.72,p=0.14). No risk alleles had statistically significant associations with specific drusen phenotypes (p>0.05 ANOVA, Tukey).

CONCLUSIONS: The utility of genetic testing for segregating AMD versus non-AMD states with drusen or RPE alterations was practically demonstrated but cannot be scientifically validated by the data presented. AMD remains a clinical diagnosis determined by the retina specialist without a definitive confirmatory test. No risk alleles studied were associated with specific drusen phenotypes, although subgroups were too small to evaluate for significance and would require validation with a second larger cohort.
RETeval and Age-related Macular Degeneration Patients with Good Visual Acuity

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Purpose: The RETeval is a small hand held device for clinical electoretinography (ERG). It uses a skin electrode that does not touch the eye or adnexa. Its ease of use and portability has changed how physicians perform ERG testing in patients.

Early age-related macular degeneration (AMD) is often seen in retina practices. Often, these patients have a family history of AMD and blindness. Currently 90% of all AMD is “dry” and it is unclear when this type of AMD might progress to “wet” AMD. Current methods of monitoring and documenting changes in AMD involve imaging with fundus photography, ocular coherence tomography, fluorescein angiography and/or indocyanine green angiography. However the retinal function of these patients has not been well studied.

We propose the use of RETeval to evaluate retinal function age related macular degeneration patients with good visual acuity.

Methods: RETeval using the ISCEV protocol, dilated pupils. All RETeval tests were performed between 6/1/2014 to 4/15/2016. Inclusion Criteria were: 20/20-20/50 vision, informed consent, pupil dilation. Exclusion criteria were patients with macular disease, macular laser. Controls were patients with non-retinal, non-macular disease diagnosis e.g. headaches, migraines. Eyes were randomized by coin toss.

Results: 12 Controls 4M/8F, Avg age=57.3±9.1yrs
14 AMD: 6M/8F, Avg age=71.1±16.3yrs

30 Hz Flicker (amp=amplitude, It=Implicit time)
Control(amp/It): 30.19±7.9uV/26.45±1.9ms
AMD(amp/It): 19.22±8.37uV/27.8±2.0ms
p values: 30Hz Amp: p≤0.00384; 30 Hz It: p≤0.0119

3ERG (photopic white): a-wave and b-wave
Control (amp/It) a-wave: 9.01±3.56uV/13.41±0.89ms; b-wave: 31.19±8.33uV/29.92±1.65ms
AMD (amp/It) a-wave: 5.51±3.89uV/14.09±2.52ms; b-wave: 20.01±9.35uV/31.62±2.56ms
p values: a-wave amp p=0.032/ It p=0.40; b-wave amp p=0.0054/ It p=0.069

Conclusions: In this small study, AMD patients had abnormal 30 Hz flicker amplitude and implicit times. This suggests that in AMD patients with good visual acuity, there is abnormal retinal function at the center of vision. Despite the RETeval’s slightly decreased waveform amplitudes vs. conventional ERG recordings, the reproducibility of the 30 Hz flicker waveforms in the study suggests that this may be a promising diagnostic modality in a retina practice.
Wet Age-related Macular Degeneration in Asian-Americans and Non-Asians: An Analysis of Comparative Outcomes

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Ferdinand Rodriguez

PURPOSE: To compare the presentation, clinical course, and outcomes of wet age-related macular degeneration (AMD) between Asian-Americans (AA) and non-Asians (NA) in a single retina practice.

METHODS: A retrospective comparative case series of consecutive patients seen by a single retina specialist at a tertiary retina practice between 1/1/2010 and 12/31/2014 with newly diagnosed wet AMD. Exclusion criteria included previous treatments for wet AMD, choroidal neovascularization secondary to non-AMD causes, and follow-up less than 12 months. Studied variables included baseline demographics, vision and anatomic features at presentation, treatments performed, and visual and anatomic outcomes at 3, 6, and 12 months.

RESULTS: 40 eyes from 32 AA patients and 218 eyes from 171 NA patients met the inclusion and exclusion criteria. The mean age at presentation for the AA and NA groups was 74.75 vs. 79.52 years respectively (p= 0.061, unpaired t-test). 21 were male and 11 female in AA vs. 56 males and 105 females in NA (P = 0.0015). 6 out of 32 (18.75%) were smokers in AA group vs. 40 out of 171 (23.4%) (p=1.00).

Mean visual acuity for AA eyes was 20/118 at the time of diagnosis, 20/91 at 3 months, 20/93 at 6 months, and 20/93 at 12 months. In contrast, the mean visual acuity for NA eyes was 20/89 at the time of diagnosis, 20/78 at 3 months, 20/74 at 6 months, and 20/58 at 12 months. AA patients experienced significantly less visual improvement from baseline to 12 months compared to NA patients (P<0.05, T-test).

70.8% of AA group had pigment epithelial detachment on presentation (PED) vs. 38% in the NA group (p<0.005, Fisher’s test). 37.5% (15/40) of AA had polypoidal features, vs. 12% (26/218) of NA (p<0.005, Fisher’s test). Other features such as subretinal fluid, intraretinal edema, and hemorrhage were not significantly different between the two groups.

On average, NA group required 5.8 injections during the 12 months, whereas the AA group required 5.3 injections during the same span (p=1.00).

CONCLUSIONS: Compared to non-Asian patients, Asian-American patients with wet AMD were more likely to be diagnosed at an earlier age with a higher male predominance. Further, Asian-Americans were more likely to have PED and polypoidal features at presentation. Finally, they presented with worse vision and were less likely to experience visual improvement in the first 12 months compared to non-Asian patients.
Intravitreal ICON-1 in Patients with Choroidal Neovascularization (CNV) Secondary to Age-related Macular Degeneration (AMD): A Phase 2 Study EMERGE

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Purpose: Examine the hypothesis that ICON-1, an immunoconjugate protein, binds to tissue factor (TF) overexpressed on choroidal neovascularization (CNV) in wet AMD and inhibits the CNV activity via a new mechanism of action, either alone or in combination with ranibizumab as compared to ranibizumab alone.

Methods: ICON-1 is composed at the targeting domain of a mutated factor VIIa protein and at the effector domain the Fc region from a human IgG1 immunoglobulin. In a phase 1 study, a single intravitreal dose of ICON-1 in patients with CNV was tolerated well and showed preliminary signs of biological activity. This phase 2, 6-month, randomized, masked, active control study EMERGE, will enroll approximately 90 treatment naïve eyes with CNV secondary to AMD. Patient inclusion criteria include: ≥ 50 years of age, active primary CNV, Best Corrected Visual Acuity (BCVA) of 70 to 24 letters (worse than 20/40 and up to 20/320 Snellen equivalent) in the study eye. Lesion characteristics include: a total lesion size <6 disc areas, CNV >50% of lesion, presence of retinal fluid on optical coherence tomography. Patients are randomized in a 1:1:1 ratio to receive intravitreal injections of ICON-1 0.3 mg as monotherapy or in combination with ranibizumab 0.5 mg or ranibizumab 0.5 mg monotherapy. The primary outcomes include the mean change from baseline in BCVA letter score and in central retinal thickness at 3 months, as well as ocular and non-ocular safety.

Results: The outcomes of the phase 1 study with a single dose of ICON-1 provided rationale for this phase 2 study with repeated doses of ICON-1, in which the safety and biological activity of intravitreal ICON-1 is evaluated. The baseline demographics, BCVA and CNV lesion characteristics of all enrolled patients will be presented.

Conclusions: The phase 2 study EMERGE will provide important insight into whether ICON-1 with its novel anti-TF mechanism of action, administered as monotherapy or in combination with ranibizumab, leads to a modification of the CNV lesion along with reduction of leakage, exudation and BCVA improvements, when compared to ranibizumab alone.
The Prevalence of Myopic Choroidal Neovascularization in the United States: Analysis of the IRIS Registry and National Health and Nutrition Examination Survey

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Purpose: To determine the prevalence of high myopia (HM), pathological myopia (PM), and myopic choroidal neovascularization (mCNV) in the United States (US).

Methods: Cross-Sectional Study, including individuals 18 years and older, participating in the National Health and Nutrition Examination Survey (NHANES) and patients 18 years and older seen in clinics participating in the American Academy of Ophthalmology’s IRIS® Registry (Intelligent Research in Sight). We analyzed NHANES data from 2005-2008 to determine the prevalence of HM in the US. HM was defined as myopic refractive error of ≥ -6.0 Diopeters in the right eye. This prevalence was then applied to estimates from the US Population Census (2014) to arrive at a population burden of HM at the diopter level in the US. Data from the IRIS Registry were used to calculate the real-world prevalence rates of PM and mCNV among patients with HM at the diopter level. PM was defined as HM with the ICD-9-CM code of “360.21: Progressive High (Degenerative) Myopia.” Myopic CNV was defined as HM with the ICD-9CM diagnosis of “362.16: Retinal Neovascularization NOS.” The rates of PM and mCNV from the IRIS® Registry were subsequently applied to the above reference population with HM to calculate the diopter-adjusted prevalence and population burden of PM and mCNV in the US in 2014.

Results: The estimated diopter-adjusted prevalence of HM, PM, and mCNV were 3.92% [95% Confidence Interval (CI), 2.82 – 5.60%], 0.33% (95% CI, 0.21-0.55%), and 0.017% (95% CI, 0.010-0.030%), respectively, among US adults aged 18 years and older in 2014. This translated into a population burden of approximately 9,614,719 adults with HM, 817,829 adults with PM, and 41,111 adults with mCNV in the US in 2014.

Conclusions: While HM and PM impose a relatively large burden among US adults, mCNV appears to be a rare disease. Relating data from the IRIS Registry and NHANES could be a novel method for assessing ophthalmic disease prevalence in the US. Given the potentially visually debilitating nature of mCNV, future studies should aim to better assess the risk factors, current treatment patterns, and optimal management strategies around this condition.
**Purpose:** To describe alternative uses of intravitreal anti-vascular endothelial growth factor (anti-VegF) drugs, bevacizumab, ranibizumab, and aflibercept from 2006-2014, i.e. use for ophthalmic diseases other than the following commonly accepted conditions: age related macular degeneration (AMD), diabetic macular edema, non-proliferative or proliferative diabetic retinopathy, and macular edema following central or branch retinal vein occlusions.

**Methods:** We utilized administrative claims data from a large U.S. commercial insurance database, Optum Labs Data Warehouse, to retrospectively identify patients receiving intravitreal injections of anti-VegF drugs based on Common Procedure Terminology code 67028. Medications and diagnoses were identified using Healthcare Common Procedure Coding System and International Classification of Disease (ICD-9) codes. Patients were categorized as being treated for any of the following indications: age-related macular degeneration (ICD-9 codes 362.50, 362.51, and 362.52), diabetic eye diseases (ICD-9 codes 250.50, 362.07, 362.02, 250.51, 250.52, 362.01, and 250.00), and retinal vein occlusions (ICD-9 codes 362.36 and 362.35). All other uses were considered alternative uses.

**Results:** Our study included 798,613 intravitreal anti-VegF injections among 109,504 patients between January 1, 2006 and December 31, 2014. 13.1% of those injections were used for alternative uses. The number of injections for alternative use increased each year from 1,335 in 2006 to 24,576 in 2014. Of all alternative use injections, 78.0% were bevacizumab, 16.6% were ranibizumab, and 5.4% were aflibercept. The following diagnoses accounted for the greatest proportion (n=67,531/104,585, 64.6%) of anti-VegF injections for alternative uses: retinal edema not otherwise specified (NOS) (n=27,476/104,585, 26.3%), retinal neovascularization NOS (n=21,135/104,585, 20.2%), cystoid macular edema (n=15,866/104,585, 15.2%), and vitreous hemorrhage (n=3,054/104,585, 2.9%).

**Conclusions:** Approximately 13% of anti-VegF injections were used for alternative uses, with the absolute number of injections for alternative uses increasing each year. Bevacizumab constituted the vast majority of alternative anti-VegF drug use in ophthalmology. Retinal edema NOS, retinal neovascularization NOS, cystoid macular edema, and vitreous hemorrhage are the leading alternative uses for anti-VegF drugs.
A Mouse Model of Chloroquine Retinal Toxicity

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Purpose: To develop and characterize a murine model of chloroquine-induced retinal toxicity.

Methods: A mouse model of chloroquine retinal toxicity was developed by intravitreal injection of chloroquine in physiological saline. Phenotypic changes were evaluated by multimodal imaging including fundus photography, optical coherence tomography (OCT), infrared reflectance, and autofluorescence. Functional assessment was performed using electroretinography (ERG). Histopathologic changes were examined by light microscopy.

Results: Fundus photography and infrared reflectance revealed areas of retinal atrophy and drusen-like deposits. OCT demonstrated disruption of the RPE and outer retina. In addition, there was pinpoint autofluorescence within affected areas of the retina. These findings mimicked the imaging changes seen in patients with chloroquine or hydroxychloroquine toxicity. ERG revealed a decreased scotopic response in both the A and B-waves. Histopathology revealed loss of the RPE and disruption of outer segments. Zona occludens staining by immunofluorescence of RPE flat mounts demonstrated RPE cell death, RPE cell enlargement, and loss of tight junctions.

Conclusions: Some of the phenotypic and functional changes of the retina observed in a mouse model of chloroquine toxicity are analogous to those observed in human subjects with chloroquine or hydroxychloroquine retinal toxicity. This mouse model may be used as a model of RPE toxicity to further understand the mechanisms of chloroquine-induced retinotoxicity.
Long-term Follow-up of Persistent Outer Retinal Defects (Micro Holes) Following Macular Hole Surgery

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Purpose: To describe a case series of persistent outer retinal defects following successful macular hole closure with vitrectomy, gas tamponade, and face down positioning.

Methods: Retrospective case series reviewing medical records of adults undergoing pars plana vitrectomy (PPV) for repair of stage 2 to 4 idiopathic macular holes from 2006 through 2009 at Casey Eye Institute and Devers Eye Institute. Spectral domain optical coherence tomography (OCT) in follow-up was reviewed.

Results: Of 43 eyes that had successful surgery with macular hole closure during the study period, 11 cases (25.5%) presented with persistent outer retinal defects on OCT at least three months after surgery. The group consisted of nine females and two males with mean age of 66.8 ± 8.2 years at the time of surgery. Mean follow up time was 60.5 ± 43.2 months, with a range of 3 to 118 months. Of these eleven cases, four had short follow up time (up to one year), during which the outer retinal defect persisted in three and macular hole re-opened in one. Seven eyes had longer follow-up with a minimum of 6 years (mean 89.8 ± 18.6 months, ranging 72 to 118). Of these eyes, three (42.8%) developed spontaneous late closure of the outer retinal defects. All three had improved visual acuity after the outer defect was closed (from average 20/50 to 20/25), although in two of these cases it is unclear if visual improvement was related to closing defect or the cataract surgery that was performed in the interval.

Conclusions: In this study, a quarter of patients recovering from macular hole surgery had persistent postoperative outer retinal defects at one year. Some of these defects improved spontaneously over time. Visual acuity may improve if the defect closes, although further studies are needed to investigate such changes.
Central Serous Chorioretinopathy Secondary to Cushing’s Disease

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Purpose: CSCR has been well described in the literature, but CSCR secondary to Cushing’s disease is rare and, if left undiagnosed, may have potentially devastating visual and systemic consequences. Here we describe a case chronic bilateral CSCR recalcitrant to multiple treatment modalities ultimately found to be secondary to Cushing’s disease.

Methods: Case report.

Results: A 49-year-old male presented with a fifteen year history of CSCR previously treated with focal laser. There was no history of steroid usage. Vision in the right eye was 20/20 and left eye was count fingers. Fundus examination of the right eye was notable for RPE atrophy, pigmentary hyperplasia, and subretinal fibrosis within the inferotemporal macula. The left eye had RPE changes on clinical exam and subretinal fluid (SRF) on OCT. Fluorescein angiography (FA) demonstrated diffuse staining and minimal leakage. Photodynamic therapy (PDT) was recommended, but the patient was lost to follow-up for eleven months. On follow-up, stable vision was noted with similar findings on FA. He again was lost to follow-up returning three years later with complaints of worsening vision of the right eye and with worsening SRF on OCT. FA showed multiple pinpoint areas of hyperfluorescence with minimal leakage and hotspots along the superior temporal arcade and within the temporal macula. Treatment with focal laser and bevacizumab resulted in no significant improvement. The patient underwent reduced fluence PDT with improvement of SRF and vision. Due to his recalcitrant disease and body habitus which were suspicious for Cushing’s disease, further work-up including urinary free cortisol, corticotropin-releasing hormone, and dexamethasone suppression test were performed and showed findings consistent with an ACTH secreting adenoma which was confirmed with magnetic resonance imaging. Transphenoidal resection was performed with confirmation of ACTH-secreting pituitary adenoma by histopathology. Follow-up demonstrated complete resolution of SRF and improvement in the patient’s symptoms.

Conclusions: Cushing’s disease is a rare and potentially treatable cause of CSCR. Given its rarity, a high index of suspicion must be present to make a timely diagnosis. If left untreated, significant loss of vision and potentially profound systemic consequences may occur.
**Scleral Fixation of an Akreos AO60 Intraocular Lens Using Gore-Tex® Suture: One Year Outcomes and Comparison to Anterior Chamber Intraocular Lens Placement**

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**PURPOSE:** To describe one-year clinical outcomes following combined pars plana vitrectomy (PPV) and scleral fixation of an Akreos AO60 intraocular lens (IOL) using Gore-Tex® suture and compare them to outcomes following PPV and anterior chamber IOL (ACIOL) placement.

**METHODS:** Retrospective, interventional case series of eyes undergoing pars plana vitrectomy and ab-externo scleral fixation of a IOL using Gore-Tex® suture. Primary outcome measures were change in visual acuity and occurrence of intraoperative and postoperative complications with minimum follow-up of one year. Outcomes were then compared to a contemporary cohort of eyes undergoing PPV and ACIOL placement.

**RESULTS:** Thirty eyes of 29 patients were identified. Mean patient age was 72±18 years, and 14 were female. Mean log-MAR visual acuity improved from 1.57±0.82 (20/740 Snellen equivalent) preoperatively to 0.51±0.56 (20/65 Snellen equivalent) postoperatively (p <0.001). Mean follow-up was 560±182 days. There were no intraoperative complications noted. Postoperative complications included vitreous hemorrhage in 4 eyes (13%), transient ocular hypertension in 3 eyes (10%), hyphema in 2 eyes (7%), cystoid macular edema in 3 eyes (10%), and corneal edema in 3 eyes (10%). All complications were managed non-operatively with topical drops or observation with resolution by post-operative day 30. There were no cases of endophthalmitis, suture erosion/breakage, retinal detachment, suprachoroidal hemorrhage, or uveitis-glaucoma-hyphema syndrome in the follow-up period. Compared to a contemporary cohort of 30 eyes of 27 patients similar in age (p=0.17) and baseline visual acuity (p=0.86) undergoing ACIOL placement, final logMAR visual acuity was similar between groups (p=0.86). In regards to post-operative complications, eyes undergoing ACIOL placement had higher rates of hyphema (17%, p=0.42), vitreous hemorrhage (23%, p=0.52), and corneal edema (40%, p=0.02). Two patients in the ACIOL group required subsequent surgery for hyphema (n=1) and vitreous hemorrhage (n=1).

**CONCLUSIONS:** Combined PPV and scleral fixation of an IOL with Gore-Tex® suture was well tolerated at one year. Visual acuity improved and no suture-related complications were encountered. Compared to PPV and ACIOL placement, this technique yielded similar visual acuity outcomes and lower rates of post-operative complications, particularly in regards to corneal edema.
How does Internal Limiting Membrane Peeling with Chromovitrectomy Augment Closure of Macular Holes and Resolution of Retinal Schisis?

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Purpose: The exact impact of internal limiting membrane (ILM) peeling on sensory retina has not been fully understood. Herein, we aimed to investigate the effects of ILM peeling with vitreoretinal dyes on retinal gliosis by studying gene and protein expression profiles associated with retinal glial activation.

Methods: Expression of glial activation genes and proteins (vimentin, glial fibrillary acidic protein (GFAP), SERPINA-3, endothelin receptor type B (ERB), bone morphogenetic protein 7 (BNP7), secreted phosphoprotein-1 (osteonectin, SPP1)) was studied in freshly enucleated (<24 hours) human eyes. ILM peeling with chromovitrectomy was simulated on full thickness human retina using four different intraoperative visualization agents (indocyanine green (ICG), brilliant blue G (BBG), trypan blue (TB) and triamcinolone). Tissue samples were kept in culture for 12 hours, and gene and protein expressions were studied with quantitative PCR and western blotting. Results were confirmed with immunohistochemistry.

Results: Independent of the dyes, ILM peeling itself lead to a significant up-regulation of glial activation genes (GFAP 6.93±0.20, SERPINA-3 3.42±0.26, ERB 5.84±0.27, BNP7 5.62±0.20, SPP1 3.65±0.28 folds compared to controls). Use of dyes augments this response even without ILM peeling. Highest amount of gliotic activity was noted with ICG (vimentin 1.53±0.29, GFAP 10.27±1.08, SERPINA-3 59.99±6.00, ERB 2.26±0.29, BNP7 4.63±0.52, SPP1 2.80±0.15 folds) and BBG (GFAP 6.84±1.28, SERPINA-3 33.82±5.85, BNP7 1.34±0.23 folds). Immunohistochemistry and protein expression profiles support the gene expression profiles.

Conclusions: Mechanical peeling of ILM and use of vitreoretinal dyes, both play role in retinal glial activation after vitrectomy. ILM peeling with chromovitrectomy can potentiate closure of macular holes as well as resolution of retinal schisis in high myopia and optic nerve pit by activating retinal gliotic response.
Open Angle Glaucoma Following Surgery for Primary Rhegmatogenous Retinal Detachment

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Purpose: To describe the incidence of open angle glaucoma (OAG) following surgery for primary rhegmatogenous retinal detachment (RRD).

Methods: Patients who underwent surgical repair of RRD were reviewed. The study included 110 eyes that underwent vitrectomy, of which 42 were combined scleral buckle/vitrectomy, and 85 eyes that had only scleral buckle. Controls were fellow uninvolved eyes. Eyes with pre-existing glaucoma, <6 months of follow-up, or confounding factors that could increase risk of glaucoma were excluded. Outcomes were diagnosis and suspicion of unilateral and bilateral OAG, determined at each providers’ discretion based on IOP, optic disc, retinal nerve fiber layer and Humphrey Visual Field assessments. Unilateral OAG was the primary outcome. Diagnosis of OAG required the long-term use of anti-hypertensive drops.

Results: Mean follow-up was 57.0 and 34.9 months in the scleral buckle and vitrectomy groups, respectively (p<0.0001, 2 tailed t test). Five vitrectomized patients developed unilateral OAG and 4 became unilateral OAG suspects. All of these occurred in the operative eye. No patients in the buckle group developed diagnosed or suspected unilateral OAG. Estimated five-year incidence of unilateral OAG in vitrectomized patients was 4.78%. Two vitrectomized and 2 non-vitrectomized patients developed bilateral OAG (p=1.0, Fischer’s exact test), while 3 vitrectomized and 2 non-vitrectomized patients became bilateral OAG suspects. Estimated five-year incidence of any OAG (one or both eyes) was 8.67% and 2.22% in vitrectomized and non-vitrectomized patients, respectively. There was a significant association between vitrectomy and incidences of unilateral OAG (p=0.02, log-rank test), of diagnosed and suspected unilateral OAG (p=0.005, Fischer’s exact test) and of any OAG (p=0.016, log rank test). IOP measurements of vitrectomized eyes were not significantly different from that of fellow or buckled eyes. There was a trend between pseudophakia and OAG in vitrectomized eyes. There were no significant differences in IOP or in incidence of OAG between vitrectomy and combined vitrectomy-buckling procedures.

Conclusions: Repairing primary RRD with vitrectomy may increase the risk of OAG when compared with scleral buckling. This should be given consideration when planning retinal reattachment surgery.
Silicone Oil Tamponade as a Pharmacological Modulator

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Purpose: Linear poly (dimethyl siloxane) (silicone oil) as intraocular tamponade has become an agent of choice for long-term tamponade. Anti-inflammatory, anti-vasogenic, and anti-metabolic agents are often instilled in eyes with silicone oil tamponade to modulate healing. The pharmacokinetics of silicone oil in combination with intravitreal medications are poorly understood. Oil-filled eyes have complex kinetics and dissolution, turbulence, altered permeability and surface chemistry may all play an important role in the eye. Methotrexate has, in addition to its role in treating intraocular malignancies, been investigated for the reduction of proliferative vitreoretinopathy. Improving the understanding of the pharmacodynamics of the oil-filled eye is important for developing new protocols.

In vitro experiments using silicone oil (5000 cs), solid poly (dimethyl siloxane) (PDMS) surfaces and methotrexate were performed to confirm the behavior of silicone oil and methotrexate in combination. UV-vis spectrophotometry was used to quantify methotrexate. 400 µg methotrexate in 0.1 mL was mixed with 4 mL 5000-cs silicone oil and with 4 mL PDMS surfaces. The supernatant aqueous solution of methotrexate was then removed and the remaining silicone material was subjected to quantitative analysis.

Commercial intramuscular formulations of methotrexate are sparingly soluble in silicone oil but demonstrate an affinity for the surface of both the oil bubble and the PDMS surfaces. Leaching of methotrexate from silicone oil and block-PDMS is observed, potentially altering in vivo pharmacokinetics. Rapid elimination of methotrexate from the oil followed by a slower leaching phase indicate biphasic kinetics and could signal the formation of a drug monolayer at the interface between silicone oil and aqueous.

Conclusions: The pharmacokinetics of small molecule drugs in the eye are significantly altered by the presence of vitreous or vitreous substitutes. Methotrexate cannot penetrate the blood-brain barrier and has been investigated in eyes without vitreous substitutes. Methotrexate-silicone oil interactions alter the tissue distribution and elimination of the target molecule. Leaching from silicone oil demonstrates that the kinetics and toxicity of methotrexate in combination with silicone oil are considerably altered. Much like a drug delivery device, the silicone oil serves to buffer the methotrexate in the eye. Animal studies are necessary to further quantify the in vivo tissue distribution of these metabolites.
23 AND 25 GAUGE PARS PLANAR VITRECTOMY HAVE SIMILAR RATES OF CLINICALLY SIGNIFICANT COMPLICATIONS

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PURPOSE: There are limited studies comparing surgical complication rates using 23 vs. 25 gauge Pars Plana Vitrectomy (PPV) instruments. This study seeks to determine any differences in clinically significant complications between the use of these instruments, which will influence and aid the vitreoretinal surgeon in the optimal instrument selection during future PPV surgeries. PPV is commonly performed during surgical repair of retinal detachments, non-resolving vitreous hemorrhage, endophthalmitis, epiretinal membranes, macular hole, intraocular foreign bodies, and many others. Major complications of PPV include hemorrhage, infection, retinal detachment, and development of visually significant cataract or epiretinal membrane.

METHODS: We completed an Institutional Review Board approved retrospective chart review of all patients (188) who underwent Pars Plana Vitrectomy (PPV) from 1/3/2013 to 1/30/2014 at the Casey Eye Institute/Oregon Health & Science University. Demographic data, indication for PPV, and surgical complications by standard clinical evaluation were reviewed. Patients were excluded if minimum follow up time was less than three months or if patients had undergone PPV in the past. Standard statistical analysis was used to evaluate the data.

RESULTS: A total of 188 patients were reviewed. 25 patients were excluded due to follow-up < 3 months or prior PPV in the past. Demographic data, indication for PPV, and past ocular history were similar in both groups (p-value > 0.05). 23 gauge PPV were performed more frequently than 25 gauge PPV (29 vs. 134 patients, respectively). Complications included cataracts requiring surgical intervention, visually significant epiretinal membranes, choroidal hemorrhages, tractional retinal detachment, retinal re-detachment, and secondary open-angle glaucoma. Complication rates were not statistically different between the groups (p-value = 0.3315) with chi-square test analysis.

CONCLUSIONS: This study suggests that there is no significant difference in the rate of clinically relevant complications between 23 and 25 gauge PPV instruments. Limitations of this study include a relatively small sample size and low rate of complications. 23 gauge PPV were also much more commonly performed at this institution. Further larger studies using prospective clinical trials are needed to better determine differences in complication rates.
The Retina Society

**IN-OFFICE VITRECTOMY FOR THE REMOVAL OF RETAINED LENS CORTEX**

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**PURPOSE:** To describe the use of a portable office-based vitrectomy system in the removal of retained cortical lens material after complicated phacoemulsification surgery.

**METHODS:** Retrospective non-comparative case series. Three cases that underwent an in-office procedure for removal of retained lens cortex using the Intreector portable vitrectomy unit were analyzed. Preoperative and postoperative factors were considered including visual and anatomic outcomes, ocular pathology, and complications during or after the procedure. The surgical technique is described.

**RESULTS:** None of the patients experienced significant postoperative complications. One patient developed transient exposure keratopathy as a result of previous neurologic disease. Anatomic and visual outcomes of office-based vitrectomy for removal of lens cortex were excellent.

**CONCLUSIONS:** Portable office-based vitrectomy can be utilized effectively to address visually significant retained cortical lens material after cataract surgery. Limitations to technique and patient selection should be noted. The minimally invasive in-office technique allows for rapid anatomic and visual recovery.
Is it Worth Operating Lamellar Macular Holes?

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PURPOSE: To investigate the visual and anatomic outcomes of visually symptomatic lamellar macular hole (LMH) repair with autologous platelets.

METHODS: Interventional prospective pilot study of visually symptomatic four patients that underwent LMH repair. Patients with clinical and spectral-domain optical coherence tomography (SD-OCT) findings of LMH that then proceeded to surgical repair were included. Subjective visual symptoms, preoperative and postoperative best correct visual acuity, preoperative and postoperative macular anatomy as examined by SD-OCT and postoperative complications were evaluated for each patient. LMH surgical repair consisted of 23-gauge vitrectomy, peeling of epiretinal membrane if present, administration of autologous platelets and gas tamponade. All surgeries were performed by the same vitreoretinal surgeon.

RESULTS: Results from this retrospective case series demonstrated functional visual improvement and anatomic closure in all patients. No other complications were observed. Reformation of foveal architecture was peculiar in all cases. Average time to visual recovery was 4-6 months.

CONCLUSIONS: Vision deteriorating LMH repair always pose a challenge with unpredictable results. Based on the results, LMH repair with autologous platelets improves functional vision and facilitates anatomic resolution of lamellar macular holes.
**Vitreoretinal Disorders in Patients with High Myopia and Pars Plana Vitrectomy**

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**Purpose:** To identify and characterize vitreoretinal pathology in a cohort of patients with degenerative myopia requiring pars plana vitrectomy. This study characterizes the wide range of spectral-domain optical coherence tomography (SD-OCT) findings in this specific patient subset.

**Methods:** With IRB approval, a list of ICD-9 codes was used in the Electronic Data Warehouse (EDW) of our electronic medical record to identify patients over the age of 18 years with high myopia (ICD-9: 360.21) and a history of pars plana vitrectomy who had undergone SD-OCT imaging between July 2009 to July 2015.

**Results:** 112 total patients were identified. The average age of this cohort was 57 years (range 19-78 years) with 53 males and 59 females. The specific vitreoretinal pathologies identified include: retinal detachment (71), retinal hole/tear without detachment (103), epiretinal membrane (56), macular hole (37), retinal/choroidal neovascularization (14), peripheral retinal degeneration (14), retinoschisis (10), posterior staphyloma (8), and vitreomacular adhesion/traction (5). Of the 71 retinal detachments: 65 were rhegmatogenous, 6 were tractional, 0 were serous. Of the 103 retinal defects without detachment, 65 had horseshoe tears, 27 had round holes, and 11 had multiple defects.

**Conclusions:** Patients with high myopia requiring pars plana vitrectomy often had multiple vitreoretinal pathologies that could be visualized using SD-OCT imaging. Retinal detachments occurred in 63% (71/112), epiretinal membranes 50% (56/112), macular holes 33% (37/112), choroidal neovascularization 13% (14/112). Average final visual acuity after pars plana vitrectomy in those with vitreoretinal pathology was better than 20/40.
INVESTIGATING THE POSTERIOR POLE: A TOOL AND TECHNIQUE FOR POST-MORTEM TISSUE RECOVERY IN ENUCLEATED HUMAN EYES

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PURPOSE: Retinal and choroidal histopathology is critical for disease diagnosis, treatment evaluation, and understanding anatomy and pathophysiology. Post-mortem histopathology is currently obtained through donation of whole eyes. However, patients are often resistant to donating their whole eyes to research for a variety of reasons, limiting the opportunity for advancement of histopathological study. Our goal was to create a tool and technique for obtaining localized, post-mortem, cosmetically unobtrusive, full thickness posterior segment specimens.

METHODS: A biopsy instrument was created using a 12mm ocular clamp welded to a 12mm cylinder. The device was tested on 12 de-identified human eyes provided by the New York Eye Bank. IRB approval was not required per the NYEMS IRB. Five samples were placed in formalin and four placed in glutaraldehyde and sent to pathology.

RESULTS: Twelve full-thickness eye wall specimens were harvested from 12 eyes. Samples were 15-20mm in diameter and 3mm in thickness. Photographs were taken before, during and following eye wall specimen removal. Histopathological examination on H & E stains revealed intact optic nerve and retina with minimal tissue distortion in the clamped sections.

CONCLUSIONS: Successful postmortem eye wall specimens can be harvested using this novel instrument. Donation of entire globes may not be necessary to obtain posterior segment pathology. The ability to remove sclera-choroidal-retinal specimens without enucleation should be more acceptable for patients. Greater access to histopathological samples may lead to better understanding of eye diseases and treatments.
Surgical Management and Outcomes of Pars Plana Vitrectomy for Late Sequelae of Infectious Endophthalmitis

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Purpose: To report the visual acuity (VA) outcomes after pars plana vitrectomy (PPV) for delayed vitreoretinal sequelae of infectious endophthalmitis in the small gauge vitrectomy era.

Methods: Multicenter, retrospective, consecutive case series.

Results: Forty-two eyes met study criteria. All eyes were initially treated with intravitreal antibiotics (Abx). Mean follow-up was 48 weeks (SD±31.8). Mean interval from Abx to PPV was 13 weeks (SD±14.3, range 2-70). Indications for PPV included vitreous opacity (VO) (n=22), epiretinal membrane (ERM) (n=9), and retinal detachment (RD) (n=11). LogMAR VA improved from 1.87 (Snellen equivalent 20/1482) preoperatively to 1.35 (Snellen equivalent 20/447) at final evaluation (p<0.001). LogMAR VA improved significantly for patients with vitreous opacities (P<0.01) and retinal detachment (P=0.02) but not for patients with epiretinal membranes (P=0.08). 

Conclusions: Patients with infectious endophthalmitis can gain vision after PPV for delayed sequelae such as vitreous opacities or retinal detachment. However, overall, patients requiring delayed PPV after endophthalmitis have a poor prognosis and final visual acuity results remain poor, with only about half achieving 20/400 and approximately a quarter achieving 20/40.
Optical Coherence Tomography Findings in Eyes with Unexpected Visual Loss after Vitrectomy

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Purpose: To explore the OCT findings in patients undergoing vitrectomy surgery that resulted in unexpected visual loss.

Methods: Retrospective chart review of five cases of unexpectedly poor visual results following vitreous surgery.

Results: Five eyes were reviewed, median age 32 years, all female. Two had macula-on retinal detachment, one had vitreomacular traction syndrome, one had an epiretinal membrane, and one underwent silicone oil removal. All underwent vitrectomy, one had vitreous disinsertion only and one had epiretinal membrane and internal limiting membrane removal.

Preoperative vision was 20/25, median; postoperative vision was 20/200, median. All patients experienced immediate loss of central vision. No patient had elevated intraocular pressure noted during or after surgery.

Anesthesia: Three patients received peribulbar block and two eyes had general anesthesia. All eyes developed an afferent pupillary defect.

Two eyes had an underlying diagnosis of Stickler’s syndrome. No eyes experienced elevated intraocular pressure in the postoperative period.

OCT Findings: One eye had a central retinal artery occlusion with a transient elevation of internal limiting membrane over a macular fold and three eyes developed internal nuclear layer schisis after surgery. Three eyes had ganglion cell and nerve fiber layer loss, and one eye had outer retinal damage in addition to the internal nuclear layer schisis.

Conclusions: We present a series of unexpected poor visual results following vitrectomy. OCT was helpful in making a diagnosis of central retinal artery occlusion in one eye, though the cause of the central retinal artery occlusion is unknown. Internal nuclear layer schisis was a finding in three eyes and ganglion cell/nerve fiber layer thinning was also seen in three eyes, raising the question of trauma during peeling procedures. However, one eye with ganglion cell and nerve fiber layer loss did not have any surgery done besides silicone oil removal and one had hyaloid removal only. The specific surgical maneuver responsible for the OCT findings was unclear.

OCT moves our understanding of retinal damage during vitrectomy forward, but does not show us exactly what surgical maneuver was responsible for the damage.
THE COMPARISON OF REGIONAL VERSUS GENERAL ANESTHESIA FOR SURGICAL REPAIR OF OPEN GLOBE INJURIES: A 20-YEAR EXPERIENCE

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PURPOSE: This study compares the features and outcomes of open globe injuries repaired under regional anesthesia (RA), using local block with monitored anesthesia care, compared with those repaired under general anesthesia (GA) in salvageable adult eyes.

METHODS: A consecutive case series of all adult repairable open globe injuries receiving primary repair at the Bascom Palmer Eye Institute between January 1st, 2004 and December 31st, 2014. Cases were identified by a postoperative diagnosis of open globe injury (ICD-9: 360.5, 360.6, 871, or 918.1). Exclusion criteria were patients less than 18 years of age and those treated with primary enucleation. Prior published data from our institution was added for historical comparison.

RESULTS: Inclusion criteria was met by 804 eyes. Overall, there was a high rate of RA use at 80%. This is significantly more frequent in the most recent cases (2004-2014) compared to the preceding 10 years: 64% from 1995 to 1999, and 41% from 2000 to 2003 [p<0.001). Patients repaired under RA/MAc had significantly shorter wound length (p>0.001), had more anterior wound location (p>0.001), and had shorter operative times (p>0.001). They also had a better presenting and final visual acuity (p>0.001 & p>0.001). Neither class of anesthesia conferred a greater visual acuity improvement (p=0.06). Also, the use of GA did not cause any delay in the time elapsed from injury till surgical repair (p=0.74).

CONCLUSIONS: Regional anesthesia is a suitable alternative to the risks of general anesthesia for the repair of open globe injuries in select adult patients. The type of anesthesia used conferred no benefit or detriment to postoperative visual acuity outcomes.
Diffuse Epiretinal Pigmentary Deposits after Retinectomy with Silicone Oil

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Purpose: Large relaxing retinectomies have become increasingly employed in the repair of retinal detachment related to proliferative vitreoretinopathy (PVR), and even higher rates of retinal reattachment have been reported when relaxing retinectomies are combined with silicone oil tamponade. Large retinectomies expose the retinal pigment epithelium (RPE) to the vitreous cavity; however, the direct effects of silicone oil on the RPE are still incompletely understood.

Methods: We conducted a case series of eyes that had undergone vitrectomy for repair of PVR-related retinal detachment involving retinectomy with silicone oil and observed the development of preretinal pigmentary deposits. We characterized these deposits clinically and via various imaging modalities. All eyes underwent peeling of these pigmented preretinal membranes during oil removal and the tissues were analyzed histologically and ultrastructurally using light microscopy, immunostaining, and electron microscopy.

Results: We describe here the development of diffuse preretinal pigmentary deposits in eleven eyes following surgery for complicated PVR detachments employing retinectomies with oil, with average onset of 3.2 months post-operatively. These pigment clumps produced a striking leopard-spot pattern on fundus autofluorescence imaging. Histological analysis of these epiretinal proliferations peeled at the time of silicone oil removal revealed RPE cells, silicone oil droplets, and glial tissue. Electron microscopy demonstrated RPE phagocytosis of silicone oil droplets.

Conclusions: This represents the first in vivo evidence that RPE cells can phagocytose emulsified silicone oil droplets. These findings underscore that direct contact with silicone oil may affect the behavior of the RPE, which may be clinically relevant in patients who have undergone large relaxing retinectomies with silicone oil tamponade for PVR-related retinal detachment.
Visual and Anatomical Outcomes of Diabetic Tractional Retinal Detachment Repair

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Purpose: To evaluate visual and anatomical outcomes of diabetic tractional retinal detachment repair.

Methods: In this interim analysis of an ongoing retrospective review, operative records were used to identify all patients with tractional retinal detachments secondary to proliferative diabetic retinopathy surgically repaired between November 1, 2009 and January 1, 2015 at the LAC + USC (Los Angeles County + University of Southern California) Medical Center. Primary outcomes were retinal attachment status and best corrected visual acuity (BCVA) at final follow-up.

Results: A total of 239 eyes with diabetic tractional retinal detachment in 218 patients were included. Average patient age at surgery was 50.0 years (range 26.8-67.9 years) and average peri-operative hemoglobin A1c was 8.5 (range 5.1-19.1). Pre-operative panretinal photocoagulation was performed in 199 eyes (83.3%), 164 of which received 3 or more photocoagulation treatments. At the time of surgery, the macula was detached in 149 eyes (62.3%). The surgeries were performed by 13 vitreoretinal fellows and 13 supervising attending surgeons. After an average of 18.2 months of follow-up, 211 eyes (87.9%) achieved successful retinal re-attachment. Average BCVA improved from $1.66 \pm 0.49$ logMAR pre-operatively to $1.39 \pm 0.77$ logMAR at final follow-up, a difference that was statistically significant ($p<0.0001$). Compared to pre-operative visual acuity, BCVA at final follow-up improved 2 or more lines in 51.5% of eyes, was stable in 24.7% of eyes, and decreased 2 or more lines in 24.3% of eyes. Pars plana vitrectomy was performed with 20-gauge, 23-gauge, and 25-gauge instrumentation in 31 eyes, 75 eyes, and 133 eyes, respectively, with no significant difference in anatomic ($p=0.84$) or visual outcomes ($p=0.67$). Overall post-operative complications included early vitreous hemorrhage (<3 months) in 33 eyes, late vitreous hemorrhage (>3 months) in 6 eyes, and neovascular glaucoma in 6 eyes.

Conclusions: While patients present with poorly controlled diabetes and advanced tractional retinal detachments at our medical center, patients undergoing pars plana vitrectomy achieve excellent anatomical outcomes with improvement or stabilization of visual acuity in approximately 75% of cases.
VISUAL AND ANATOMIC OUTCOMES OF PARS PLANA VITRECTOMY WITH MEMBRANE PEEL IN THE ELDERLY

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PURPOSE: Hitherto publications have reported on the visual and anatomic outcomes of pars plana vitrectomy with membrane peel (PPV/MP) in the general population. We sought to investigate visual and anatomic outcomes following PPV/MP in the elderly and compare to those in the general population.

METHODS: Retrospective chart review study of patients who underwent PPV/MP for visually significant epiretinal membrane by a single surgeon at a single institution between February 2010 and December 2015. The primary outcome measured was the comparison in the change in best-corrected visual acuity (BCVA) from the pre-operative visit to final follow up between older patients (above age 72, Group O) and the group of younger patients (Group Y). Secondary outcomes included comparisons between the change in central subfield macular thickness (CSMT).

RESULTS: There were 35 eyes in Group O (mean f/u 14.3 months) compared to 80 eyes in Group Y mean f/u 14.4 months). Even though at baseline Group O had worse mean BCVA compared to Group Y (logMAR 0.63 [20/86] vs. logMAR 0.49 [20/62], p=0.03), both groups showed similar visual gains at final follow-up (Group O: - 0.19 logMAR [+1.9 lines]; Group Y: -0.14 logMAR [+1.35 lines], p=0.54). Baseline CSMT was similar in both groups (Group O: 481um; Group Y: 502um, p=0.35) and mean CSMT at final follow-up improved similarly in both groups (Group O: 121um; Group Y: 137um in group Y, p=0.52).

CONCLUSIONS: Although older patients may have worse vision at baseline with similar retinal thickening, PPV/MP results in similar gains in vision and similar anatomic improvement as in the general population.
**Diurnal Variations in Luminal and Stromal Areas of Choroid in Normal Eyes**

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**Purpose:** There has not been a study to determine whether changes of the luminal or stromal area of the choroid were mainly responsible for the circadian changes in the choroidal thickness. Thus, the purpose of this study was to determine whether there are diurnal variations in the luminal and stromal areas of the choroid in normal eyes using binarization of the enhanced depth imaging optical coherence tomographic (EDI-OCT) images.

**Methods:** This was a prospective observational study of 42 eyes of 42 normal subjects. The blood pressure, heart rate, intraocular pressure, and EDI-OCT images were recorded every 3 hours between 6:00 to 21:00 hours. The horizontal EDI-OCT images were converted to binary images using ImageJ, a publicly accessible software. The central choroidal thickness (CCT), total cross sectional choroidal area, the luminal areas, stromal areas, and the ratio of luminal area to total choroidal area (L/C ratio) in the subfoveal choroid of 1,500-µm-width were determined.

**Results:** There were significant diurnal variations in the CCT, total choroidal area, luminal area, and L/C ratio with the maximum values at 6:00 h, and the minimum values at 15:00 h ($P < 0.001$ for the CCT, $P = 0.007$ for the total choroidal area, $P < 0.001$ for the luminal area, $P = 0.005$ for the L/C ratio). There was no significant variation in the stromal area ($P = 0.159$). The fluctuation range in the CCT was significantly correlated with the fluctuation range in the luminal area and the total choroidal area ($P < 0.001$). However, there was no correlation between the fluctuation range in the CCT and that in the stromal area ($P = 0.067$). There was no statistical relationship between the systemic parameters and the choroidal parameters.

**Conclusions:** There are significant diurnal variations in the total choroidal area, luminal area, and L/C ratio but not in the stromal area. These findings indicate that the changes in the luminal area is most likely responsible for the diurnal change in the CCT and subfoveal choroidal area. This information is useful in understanding the physiology in normal eyes and pathogenesis of chorioretinal diseases.
Optical Coherence Tomography (OCT) Angiography Findings in Acute Macular Neuroretinopathy

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Purpose: To report the OCT angiography findings in Acute Macular Neuroretinopathy.

Methods: Three eyes of two patients (one with unilateral involvement and one with bilateral involvement) who presented with acute macular neuroretinopathy were imaged using spectral domain optical coherence tomography, infrared reflectance, autofluorescence, fluorescein angiography, and OCT angiography.

Results: In addition to the classic imaging features seen on SD-OCT and infrared reflectance imaging, OCT angiography of Acute Macular Neuroretinopathy revealed ischemia in the deep capillary plexus, corresponding exactly to the abnormal areas seen on SD-OCT and infrared reflectance imaging. These previously unreported findings of OCT angiography in AMN provide an important insight into its pathophysiology.

Conclusions: This is the first case series demonstrating the OCT angiography findings of Acute Macular Neuroretinopathy and elucidating that its pathophysiology is related to deep capillary plexus ischemia.
Dexamethasone Implant with Rescue Ranibizumab for Treating Macular Edema Secondary to Retinal Vein Occlusion: DRIVEN Study

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PURPOSE: This study compares dexamethasone implant with rescue intravitreal ranibizumab to monthly intravitreal ranibizumab for the treatment of macular edema secondary to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

METHODS: The study was a randomized control trial of treatment-naïve patients with BRVO or CRVO and macular edema. Subjects were randomized 1:1 for treatment with dexamethasone implant with monthly rescue ranibizumab pro-re-nata and repeat dexamethasone implant at 4 months pro-re-nata vs. monthly ranibizumab alone. As a pilot study 10 subjects were included in each arm. Best corrected visual acuity (BCVA), intraocular pressure and spectral-domain optical coherence tomography measures of central macular thickness (CMT) were measured at baseline and monthly visits for 6 months.

RESULTS: Eight of 10 patients (5 BRVO, 5 CRVO) in the study arm and 8 of 10 patients (5 BRVO, 5 CRVO) in the control arm completed the study through all follow-up visits. Baseline BCVA and CMT were comparable between the two groups. At the 6-month final endpoint, there was no statistically significant difference in improvement of visual acuity between the two groups (12 letters vs. 16 letters; \( P = 0.608 \)). There was no statistically significant difference in improvement in central macular thickness between the two groups (386 vs. 370 microns; \( P = 0.866 \)). However, total number of injections was less in the treatment group (4.5 vs. 5.75 injections; \( P = 0.026 \)).

CONCLUSIONS: In this pilot study, intravitreal dexamethasone implant with rescue ranibizumab compared to monthly ranibizumab injections had comparable improvements in BCVA and CMT The mean number of injections was significantly lower in the dexamethasone arm. Larger scale trials are needed to determine which treatment methods provide optimal visual outcomes with the best safety profile and least burden on patients and providers.
SEQUENTIAL OPTICAL COHERENCE TOMOGRAPHY CHANGES OF MACULAR STAR IN CAT SCRATCH DISEASE

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PURPOSE: Cat scratch disease (CSD) is a relatively rare disease usually caused by *Bartonella henselae*. Ophthalmic manifestations of CSD include granulomatous conjunctivitis associated with preauricular lymphadenopathy, neuroretinitis, focal chorioretinitis, and uveitis. Macular star, either partial or complete, is often seen in CSD, thought to develop when lipid accumulates in Henle’s layer with decrease in macular edema. We have examined the macular star in three cases of CSD by spectral-domain optical coherence tomography (OCT).

METHODS: Six eyes of three women diagnosed with CSD on the basis of positive serum titer for antibodies to *B. henselae* and clinical finding of neuroretinitis with anterior uveitis were examined. All patients developed partial or complete macular star in the affected eye during the course of their disease. Spectral-domain OCT (2 patients by Cirrus OCT 5000 version 6.5 (Zeiss) and one by Spectralis SD-OCT (Heidelberg)) was carried out in all eyes. All three were treated with oral tetracycline, and one also received oral steroid. Clinical and OCT findings were noted.

RESULTS: All patients improved and recovered with a best corrected visual acuity of 20/20 or better in each eye. Presence of the macular star did not correlate with visual acuity or presence of serous retinal detachment. OCT revealed that the precipitates of macular star were located in the outer nuclear layer (Henle’s layer) and were matched in location to the intraretinal fluid seen earlier in the course in agreement with the mechanism that they represent lipid precipitation in the wake of resolution of macular edema. The location did not correspond to the area of serous retinal detachment. OCT findings of optic disc edema, serous retinal detachment, and intraretinal fluid were observed in 50% (3/6), 33% (2/6), and 66% (4/6) of eyes, respectively.

CONCLUSIONS: The intraretinal lipid precipitation of macular star is seen in the radial structure in the outer nuclear layer (Henle’s layer) and is related to the intraretinal fluid from inflammation in earlier stages of the disease.
Analysis of Predisposing Factors and Management Course of Endogenous Fungal Endophthalmitis: A Five-year Experience in a Tertiary Referral Center

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Purpose: To analyze risk factors, clinical features, treatments and outcomes in endogenous fungal endophthalmitis.

Methods: Medical records of all fungal endophthalmitis diagnosed from January 2010 through September 2015 at UPMC Eye Center were reviewed. The demographic data, medical and social history, fungus species, visual acuities, clinical findings, treatment modalities and treatment outcomes were analyzed.

Results: A total of 32 eyes from 28 patients were included, based on clinical disease and/or positive smears or cultures. Average age was 45.3 years. 16 patients were men. Thirteen patients (46.4%) had a history of intravenous drug abuse. Other risk factors included fungemia caused by indwelling lines (17.8%) and immunosuppression (28.6%). Treatment modalities included: 1) systemic antifungal agent alone (7 eyes), 2) primary vitrectomy with oral antifungal agent (10 eyes), 3) intravitreal (IVT) antifungal agent injection with oral antifungal agent (15 eyes) followed by vitrectomy (10 eyes). In the latter group, vitrectomy was performed in eyes without resolution, 2 to 56 days after IVT with antifungal medication. Only three of 23 eyes with noticeable vitritis were controlled without vitrectomy. Retinal detachment occurred in 8 eyes (25%). Inflammatory response noted in 2 eyes after treatment was initiated (Jarisch-Herxheimer type reaction). Presenting visual acuity ranged from 20/20 to light perception, with 62.5% having a visual acuity of 20/200 or less at presentation. 40.6% of subjects overall achieved a final visual acuity of 20/100 or better.

Conclusions: IV drug abuse was the leading risk factor for endogenous fungal endophthalmitis. Patients with chorioretinitis with or without minimal vitreous involvement were controlled with systemic or IVT antifungal therapy, alone. Two-thirds of eyes treated with initial antifungal IVT, later required a vitrectomy. Earlier vitrectomy, in conjunction with IVT or after IVT, may be a better choice for treatment in eyes with marked vitritis.
A Literature Review and Update on the Incidence and Microbiology Spectrum of Post-cataract Surgery Endophthalmitis Over Past Two Decades in India

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PURPOSE: To review the incidence and microbiology of acute post-cataract surgery endophthalmitis in India over the past 2 decades.

METHODS: A systematic review of English-language PubMed referenced articles published from January 1992 through December 2012 was done. The incidence data were collected from the articles describing endophthalmitis occurring within an institution’s own setting (in-house). The microbiology data was collected from all articles of acute post cataract surgery endophthalmitis. Additionally, medical records of two of India’s large eye care providers were reviewed for incidence and the microbiologic spectrum of endophthalmitis between January 2010 – December 2014.

RESULTS: There are 99 published articles. Six of them reported the incidence of in-house clinical acute post cataract surgery endophthalmitis; this was between 0.04% and 0.15%. From a cumulative half a million plus cataract surgery, between 2010-2014, the incidence of culture positive and clinical acute post cataract surgery in-house endophthalmitis in 2 large eye institutes from southern India was from 0.02% to 0.08% and from 0.05% to 0.16% respectively. The infection spectrum was different between South and North India. Bacteria (chiefly Staphylococcus species, and Pseudomonas species) were the common in south India and fungi were the commonly identified microorganisms in north India. Pseudomonas aeruginosa was the major organism in cluster infections.

CONCLUSIONS: The incidence of post-cataract surgery clinical endophthalmitis in India ranges from 0.04 to 0.15%. The microbiological spectrum differs in different regions. A national registry with detailed documentation of endophthalmitis is required for specific guidelines for post cataract surgery endophthalmitis management.
**Surgical Outcomes of Epiretinal Membranes in Patients with Uveitis**

**Lisa Faia, MD**  
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Prethy Rao, MD, Bozho Todorich, MD, PhD, Yoshihiro Yonekawa, MD, George Williams, MD

**Purpose:** To determine the surgical outcomes in patients with uveitis who underwent surgery for an epiretinal membrane (ERM).

**Methods:** This is a retrospective, interventional, consecutive case series of 16 eyes from 13 patients with a history of uveitis and ERM who underwent a pars plana vitrectomy (PPV) with membrane peeling between 2011-2015. All eyes were quiescent for at least 3 months before surgical intervention.

**Results:** The mean age was 65.4 years old (range 21-81 years old) and 8 of the 13 patients were male. The mean duration of follow up was 22.3 months. The underlying uveitic diagnoses included the following: tuberculous-associated uveitis (n=2), uveitis glaucoma hyphema (UGH) syndrome (n=1), toxoplasmosis panuveitis (n=1), acute retinal necrosis (n=1), presumed ocular histoplasmosis syndrome (n=1), treated infectious endophthalmitis (n=1), panuveitis or posterior uveitis associated with rheumatoid arthritis (n=3), and idiopathic uveitis (n=6). Five eyes required systemic medications for inflammatory control and two eyes had fluorocinolone acetonide intravitreal implants 0.59mg for control. All but one patient received intravenous methylprednisolone on the day of surgery. Intraoperative triamcinolone acetate was given in 10 eyes (62.5%).

Mean pre-operative best-corrected visual acuity (BCVA) was 0.78 (±0.56) LogMAR units (Snellen equivalent= 20/120) with mean central foveal thickness (CFT) of 542 microns and mean macular cube volume (MCV) of 12.3 mm³. Mean post-operative BCVA at 6 months was 0.70 (±0.65) LogMAR units (Snellen equivalent= 20/100) with mean CFT of 387 microns and mean MCV of 9.4 mm³. There was no statistically significant difference between mean pre-operative and post-operative visual acuity at 6 months (p = 0.62). However, there was a statistically significant improvement in CFT (p =0.01) and MCV (p = 0.02) at 6 months. There were no recurrences at 6 months. One eye required further systemic immunomodulatory therapy at 12 months due to persistent intraocular inflammation. One eye developed increased intraocular pressure that required topical therapy for control.

**Conclusions:** Eyes undergoing surgical intervention for ERMs with a history of uveitis can have good surgical outcomes with good inflammatory control. Most patients did not require escalation of immunomodulatory therapy.
Accumulation of Acrolein-Lys Adduct in the Vitreous Fluid of Proliferative Diabetic Retinopathy

Kousuke Noda, MD
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Susumu Ishida, MD, Miyuki Murata, PhD

Purpose: Acrolein (ACR) is a highly reactive unsaturated aldehyde and produced endogenously in the body as a result of polyamine metabolism mediated by amine oxidases. ACR reacts preferentially with Cys, Lys, and His residues on the protein with preserving the aldehyde functionality, and thereby ACR participates in cell toxicity and oxidative stress. Recently, we reported that ACR-Lys adduct is localized in glial cells and endothelial cells in fibrovascular tissues of proliferative diabetic retinopathy (PDR) [Dong Y, Noda K et al. Curr Eye Res 2016]. In this study, we measured the concentration of ACR-Lys adduct in the vitreous fluid samples of PDR.

Methods: Vitreous samples were collected from 12 eyes of 12 patients with PDR (7 males and 5 females; mean age, 58.2±14.2 y/o), who underwent pars plana vitrectomy for prolonged vitreous hemorrhage and tractional retinal detachment involving macular lesions. For a control, vitreous samples were obtained from 9 eyes of 9 patients with non-diabetic ocular diseases (non-PDR): epiretinal membrane and idiopathic macular hole (4 males and 5 females; mean age, 68.4±9.4 y/o). Vitreous levels of ACR-conjugated proteins, FDP-Lys, and semicarbazide-sensitive amine oxidase (SSAO) were measured by ELISA. This study was conducted in accordance with the tenets of the Declaration of Helsinki.

Results: The FDP-Lys was detectable in all the PDR and non-PDR vitreous samples and was significantly elevated in the vitreous fluids of PDR patients (11.2±2.6nmol/ml) compared with those of non-PDR patients (8.8±0.9ng/ml, P<0.05). In addition, protein levels of SSAO showed approximately 7.8-fold increase in the vitreous fluids of PDR patients when compared with those of non-PDR patients (9.4±4.9ng/ml vs. 1.2±0.6ng/ml, P<0.01). Furthermore, the level of FDP-Lys showed a moderate correlation with SSAO concentration in the vitreous samples of PDR patients (r=0.67, P<0.05).

Conclusions: The current data demonstrated that ACR-conjugated proteins were increased and correlated with SSAO in the vitreous fluid of patients with PDR, indicating that SSAO participates in the production of ACR.
Systemic Risks Associated with Treatments for Diabetic Macular Edema: A Cohort Study of 27,664 Patients

Andrew Barkmeier, MD
Rochester, MN

Purpose: Intravitreal anti-VEGF therapy has become the standard of care for management of diabetic macular edema (DME). Existing clinical trial data remains underpowered to evaluate relative rates of systemic adverse events (SAEs) following treatment. We use a large claims database to investigate rates of SAEs in patients receiving anti-VEGF therapy for DME compared to controls who were treated with macular photocoagulation or intravitreal corticosteroid.

Methods: Using a large U.S. insurance database we identified privately insured and Medicare Advantage patients treated with intravitreal anti-VEGF injections for DME along with control patients treated with either macular laser photocoagulation or intravitreal corticosteroid injections between 1/1/2006 and 12/31/2014. We included patients with 1 year of medical coverage prior to initial DME treatment. Pre-defined systemic outcomes occurring within 6 months of initial DME treatment were identified and patients receiving treatment within another therapeutic category prior to 6 months were censored at that time. We assessed associations between treatment modalities and risks of all-cause hospitalization, myocardial infarction (MI), stroke and major bleeding using Cox proportional hazards regression.

Results: A total of 27,664 adult patients received treatment for DME within the study period. 14,023 patients were initially treated with macular laser photocoagulation, 12517 patients received initial anti-VEGF therapy, and 1,124 patients received initial intravitreal corticosteroid. Baseline demographic and medical characteristics were similar between groups except laser-treated patients had a smaller proportion of patients aged 65+ compared to anti-VEGF and corticosteroid-treated patients (31.5% vs. 41.2% and 42.4% aged 65+, p<0.001). Anti-VEGF treated patients had an increased risk of hospital admission for MI compared to those receiving macular laser (adjusted hazard ratio (aHR) 1.45, p=0.01), but not in comparison to patients receiving intravitreal corticosteroid (aHR 2.44, p=0.08). No differences in the risk of stroke or major bleeding were identified between treatment groups.

Conclusions: Intravitreal anti-VEGF therapy for DME is associated with an increased risk of hospital admission for MI when compared to macular laser photocoagulation. No differences in the rate of stroke or major bleeding were identified between treatment groups.
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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The Retina Society

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FAIRMONT COLEY PLAZA HOTEL, BOSTON, MA

SPECIAL HISTORICAL SYMPOSIUM:
Retina and The Retina Society—
Where Have We Been
and Where Are We Going?

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