

# FRANCIS I. PROCTOR FOUNDATION

for Research in Ophthalmology



2012-2013 Annual Report



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The Francis I. Proctor Foundation for Research in Ophthalmology was established in 1947 in San Francisco through the joint action of Mrs. Francis I. Proctor of Sante Fe, New Mexico and the Regents of the University of California. Mrs. Proctor intended the Foundation to be a memorial to her husband, Francis I. Proctor, MD, who died in 1936. Dr. Proctor remained actively involved in eye disease research until his death.

# MISSION

The mission of the F. I. Proctor Foundation is the prevention of blindness worldwide through research and teaching focused on infectious and inflammatory eye disease.

## Executive Summary

I am pleased to report that we have had another terrific year at the Proctor Foundation. During the past year we have continued to expand our faculty, increase our extramural grant support, remodel space, and increase patient volumes all while maintaining excellence in our fellowship training program and staying true to our mission.

One of the major highlights of the past year was the \$14 million dollar grant from the Gates Foundation that Tom Lietman and colleagues received for studies aimed at further investigating the use of oral azithromycin in the prevention of early childhood mortality, a project that grew out of their observation that children in Ethiopia that received oral azithromycin for the treatment of trachoma had a lower mortality rate than untreated controls. In order to accommodate the growing Epidemiology/Clinical Trials group we also completed renovation of 2000 square feet of the third floor of the Medical Sciences building.

Additional highlights from the Epidemiology/Clinical Trials group include the awarding of a large NEI clinical trials grant to Nisha Acharya to compare the efficacy of methotrexate to mycophenolate mofetil as first line steroid sparing treatments for non-infectious uveitis, and ongoing ground breaking results in the use of topical steroids and both topical and systemic antifungals in treating infectious bacterial and fungal keratitis.

Our cornea and uveitis fellows continue to impress with their intelligence, imagination and hard work, and the cornea fellowship program continues to partner with Wilford Hall to give the cornea fellows an intense refractive surgery experience in San Antonio, Texas. Two of the recent graduates of our fellowship program have joined the faculty of the Proctor Foundation this past summer, John Gonzales (Uveitis) and Jennifer Rose-Nussbaumer. We are looking forward to great things from them in the coming years.

We have also continued to see faculty move on with their careers. Bennie Jeng left this past year summer to become Chairman of the Department of Ophthalmology at the University of Maryland. His expertise and ever-present smile will be missed.

In addition, after 14 years as Director of the Proctor Foundation I will be leaving to become Chairman of the Department of Ophthalmology and Visual Sciences at Washington University. As I have told many people over the years "I have the best job in the world", but it is time for new challenges. Thank you to everyone who has made my career at Proctor so wonderful.

Wishing you all the best for 2014.

Sincerely,



Todd P. Margolis, MD, PhD

# RESEARCH

For almost seven decades, Proctor Foundation faculty have been involved in internationally recognized research on blinding eye diseases caused by infection and inflammation.

The research interests of the Foundation focus on the prevention, pathogenesis and treatment of infectious and inflammatory eye disease. Specific research areas include:

- Epidemiology of corneal ulcers, trachoma, herpesvirus infections and uveitis
- Molecular mechanisms of chlamydial bacterial, and herpesvirus eye disease
- Molecular mechanisms of corneal wound healing
- Clinical microbiology of ocular disease
- Clinical trials (Trachoma, Sjögren's Syndrome, bacterial, fungal and parasitic corneal ulcers, corneal wound healing, and uveitis)
- Keratoconjunctivitis sicca
- Ocular complications of AIDS
- Prevention of blindness in developing countries
- Mathematical analysis of infectious disease transmission

Dr. Keenan meets with a female community health volunteer and her women's group to learn about the local community health infrastructure.





# TRAINING

A major goal of the Proctor Foundation has been to provide clinical and research training to the very best physician scientists from around the world.

**Medical students** – The faculty play a role in UCSF medical student education including teaching in the PISCES course, surgical subspecialty 110 course, and Epidemiology and Biostatistics course. Faculty also mentor medical students in research projects and/or in their clinics.

**Residents** – The faculty play a very active role in Ophthalmology resident education through their participation in lectures, grand rounds presentations, mentored research projects and as attending physicians. Faculty and fellows also serve as attending physicians at San Francisco General Hospital.

**Postdoctoral Fellows** – The faculty train two different types of postdoctoral fellows. In addition to the training of postdoctoral fellows in traditional bench and/or epidemiological research, the Foundation also prepares ophthalmologists for careers in academic medicine in infectious and inflammatory eye disease. The training includes research methodology, biostatistics, clinical epidemiology, laboratory science and clinical microbiology. The ophthalmologists also acquire extensive clinical expertise in the diagnosis and management of external and inflammatory eye diseases as well as concentrated surgical experience in corneal and anterior segment surgery. Training support is provided from the Proctor Endowment, the Heintz Endowment and extramural fellowships. Generous gifts from alumni have also helped to support these programs.



Faculty, fellows, and residents discuss cases during Proctor conference in the Hind Library.



Cornea fellow, Joseph Sheehan, MD doing research.

### **Educational activities associated with fellowship training include:**

- Uveitis and Cornea Clinics with weekly Uveitis and Cornea Conferences.
- A weekly “Kodachrome” conference (replaced by digital images) at which unknowns are discussed. Over a year's time, there is comprehensive coverage of all of the basic areas of cornea and external disease pathology.
- Seminars and case presentations prepared by the fellows
- A weekly one-hour seminar on corneal diseases, which includes detailed discussion of degenerations, dystrophies, and infectious and inflammatory diseases.
- Time with Laboratory Specialist Vicky Cevallos in the Ocular Microbiology Laboratory.
- Clinical rotations with Drs. Margolis, Lietman, Acharya, Keenan, Gaynor, Gonzales, and Wong at the Proctor Foundation Clinical Unit as well as rotations with Drs. Abbott, Hwang, McLeod, and Jeng at the Beckman Vision Center, Dr. Holsclaw at the Northern California Kaiser Foundation Hospitals, and a two week refractive surgery rotation at the Airforce's Willford Hall hospital in San Antonio, Texas. The clinical and surgical experience in these rotations covers broad areas from the diagnosis and treatment of severe posterior uveitis, endophthalmitis, and corneal ulceration to participation in complicated keratoplasty, deep lamellar procedures and the latest refractive surgery techniques.



# PROCTOR MEDICAL GROUP

The faculty of the Proctor Foundation provide state-of-the-art medical and surgical care of patients with infectious and inflammatory diseases of the eye.

For over 50 years the Proctor Medical Group has been a leader in the medical and surgical management of red eyes (external diseases), corneal diseases and uveitis (inflammation inside the eye). PMG providers are particularly well known for the diagnosis and management of inflammatory eye problems that occur in association with diseases affecting other organ systems. Specific interests of the Medical Group physicians are dry eye, diseases caused by herpes simplex, herpes zoster and Chlamydia, corneal ulcers, allergic eye disease, mucous membrane pemphigoid, scleritis, all forms of uveitis including iritis and retinitis and AIDS-related eye diseases.

PMG is also one of 11 PROSE, prosthetic replacement of the ocular surface ecosystem, providers in the United States. Developed by the Boston Foundation for Sight, PROSE is a pioneering treatment for patients with complex corneal disease that restores vision, supports healing, reduces symptoms and improves quality of life. The PROSE Clinic at UCSF is only one of two providers in the western United States.



## Proctor Medical Group Providers:

Nisha Acharya, MD, MS  
Matilda F. Chan, MD, PhD  
John A. Gonzales, MD  
Jeremy Keenan, MD, MPH  
Nancy Lee, OD  
Thomas M. Lietman, MD  
Todd P. Margolis, MD, PhD  
Nancy McNamara, OD, PhD  
Ira G. Wong, MD

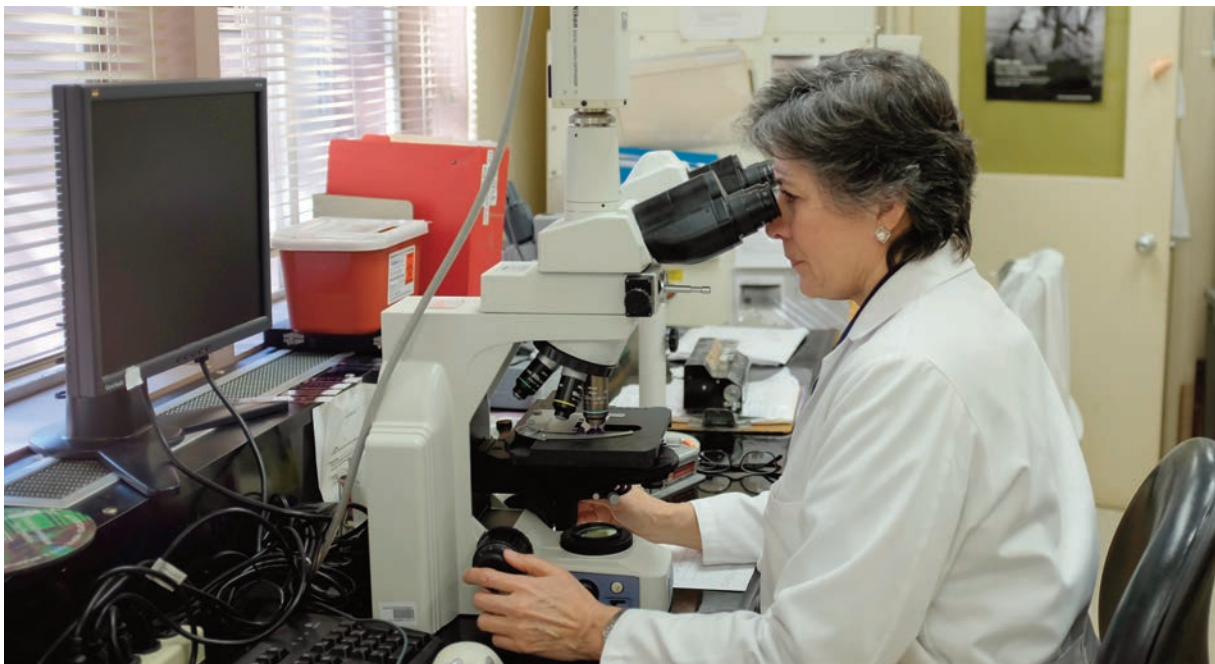


# CLINICAL LABORATORY

In addition to diagnostic testing of patient specimens, the laboratory supports faculty on research studies in clinical ocular microbiology.

The Proctor Clinical Diagnostic Laboratory is certified by the State of California and CLIA in microbiology, mycology, mycobacteriology, acanthamoeba, and molecular diagnostic tests. Dr. Todd Margolis is Medical Director of the laboratory, Vicky Cevallos is the Senior Clinical Laboratory Technical Specialist, and Cathy Donnellan is a Technical Specialist.

In addition to diagnostic testing of patient specimens, the laboratory supports faculty on research studies in clinical ocular microbiology. In keeping with the Proctor Foundation's goal to constantly upgrade the laboratory services available to the community, the clinical laboratory offers PCR for ocular VZV, HSV-1, HSV-2, CMV and T. gondii.



# RESOURCES

## Space

The Foundation occupies 12,296 square feet of assignable space. This space is located in the Medical Sciences Building and at 95 Kirkham Street and includes several special laboratories and conference rooms.

### **Ralph and Sophie Heintz Laboratory**

Room S-310, Medical Sciences Building

Dr. Margolis is the director of the Heintz Laboratory. Research in this laboratory focuses on cellular and molecular mechanisms of herpesvirus pathogenesis.

### **Pearl and Samuel J. Kimura Ocular Immunology Laboratory**

Room PF-101, 95 Kirkham Street

Research in this laboratory focuses on basic research in the immune mechanisms responsible for severe ocular inflammation.

### **Harry William Hind Library**, Room PF-314, 95 Kirkham Street

The Hind Library serves as a library, conference room, and seminar room.

### **Elizabeth C. Proctor Library**, Room S318, Medical Sciences Building

The Proctor Library serves as a library, conference room, and seminar room.

## Endowment

The F.I. Proctor Foundation endowment provides base support for the Foundation. As of June 30, 2013 the endowment had a market value of \$37,905,994 which represents a 7% increase over the prior year. Two new endowment funds have been established to support foundation activities, the Pearl & Samuel Kimura Ocular Immunology Laboratory and the Ruth Lee & Phillips Thygeson distinguished Professorship. Other endowment funds include:

**Rose Graciano Library Fund**

**Ralph and Sophie Heintz Lecture and Laboratory Fund**

**Harry Hind Library Fund**

**E.C. Proctor Research Professorship Fund**

**E.C. Proctor Fellowship Fund**

**Cecilia Vaughan Fellowship Fund/Heintz Endowment**

## Contracts and Grants

Grants and contracts are the major source of funds supporting expenses and personnel costs associated with research projects. In 2012-2013, \$7,119,144 was available in direct costs to the Foundation from grants and contracts. This represents an increase of 123% from the prior year. The increase was due mainly to a grant from the Bill & Melinda Gates Foundation. Federal awards increased by 33% and represents 40% of our total grant research budget. Other sources of research income included The Peierls Foundation, the Bill and Melinda Gates Foundation, Alta California Eye Research, the Harper-Inglis Fund Memorial Fund for Eye Research, the American Cancer Society, Research to Prevent Blindness, That Man May See, the Bruce J. and Gladys Ostler Fund, the Deloris Lange Research Fund, the Genevieve Langdon Trust, the Littlefield Trust, Brooks Family Foundation, the IBM International Foundation, Pearl Kimura Trust, Laurence Spitters and individual donors.

## Fundraising

That Man May See, a 501©(3) organization dedicated to fundraising for vision research at UCSF, is continuing to take an active role in fundraising for the Foundation. Priorities for fundraising include Endowed Chairs, Capital improvements, Endowed Research Programs and support for the Fellowship Training Programs. TMMS is also working with the UCSF Foundation, in support of efforts to increase planned giving on behalf of the Proctor Foundation.

## Board of Governors

**Chancellor, University of California,  
San Francisco**

**Susan Desmond-Hellmann, MD, MPH**

(Represented by Executive Vice Chancellor  
and Provost, Jeffrey Bluestone, PhD)

**Chair, Department of Ophthalmology,  
University of California, San Francisco**

**Stephen D. McLeod, MD**

**Independent Governor**

**John P. Whitcher, MD, MPH**

Children wait to be examined  
for trachoma in Niger.



# FACULTY

## Faculty with Primary Appointments in the F.I. Proctor Foundation



**Nisha Acharya, MD, MS**  
Associate Professor,  
Departments of Ophthalmology  
and Epidemiology, Director,  
Uveitis Service, Francis I. Proctor  
Foundation



**Bruce Gaynor, MD**  
Assistant Professor,  
Department of Ophthalmology and  
the Francis I. Proctor Foundation



**John A. Gonzales, MD**  
Clinical Instructor  
Francis I. Proctor Foundation



**Jeremy Keenan, MD, MPH**  
Associate Professor,  
Department of Ophthalmology  
and the Francis I. Proctor  
Foundation



**Associate Director**  
**Thomas M. Lietman, MD**  
Professor, Departments  
of Ophthalmology, Epidemiology  
and Biostatistics, and the  
Francis I. Proctor Foundation,  
Pearl and Samuel Kimura  
Professor of Ophthalmology



**Director**  
**Todd P. Margolis, MD, PhD**  
Professor, Department of  
Ophthalmology and Francis I.  
Proctor Foundation, Rose B.  
Williams Chair in Corneal  
Research

## PROCTOR FACULTY



**Nancy McNamara, OD, PhD**  
Associate Adjunct Professor,  
Departments of Anatomy,  
Ophthalmology, and the  
Francis I. Proctor Foundation



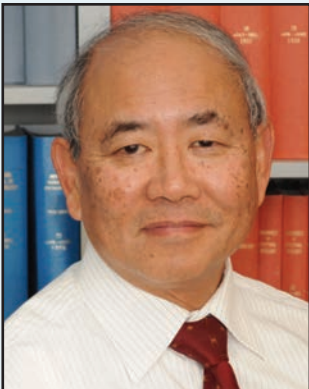
**Travis Porco, MPH, PhD**  
Professor, Departments of  
Epidemiology and Biostatistics,  
Ophthalmology, and the Francis  
I. Proctor Foundation



**Jennifer Rose-Nussbuamer, MD**  
Assistant Adjunct Professor,  
Department of Ophthalmology  
and the Francis I. Proctor Foundation



**John P. Whitcher, MD, MPH,**  
Professor Emeritus of Clinical  
Ophthalmology, Departments of  
Ophthalmology and  
Epidemiology and Biostatistics,  
and the Francis I. Proctor  
Foundation



**Ira Wong, MD, MS**  
Clinical Professor, Department of  
Ophthalmology and the  
Francis I. Proctor Foundation

## Faculty with Primary Appointments in Other Departments



**Richard Abbott, MD**  
Clinical Professor, Department of Ophthalmology, Thomas W. Boyden Endowed Chair



**Matilda Chan, MD, PhD**  
Assistant Professor, Department of Ophthalmology and the Francis I. Proctor Foundation



**David Hwang, MD, FACS,**  
Professor of Clinical Ophthalmology; Co-Director, Cornea Service, Director, Refractive Surgery Service; Department of Ophthalmology



**Bennie Jeng, MD**  
Associate Professor and Co-Director of Cornea Service, Department of Ophthalmology, and Chief of Ophthalmology San Francisco General Hospital



**Stephen D. McLeod, MD**  
Chairman, Department of Ophthalmology, Theresa M. Caygill, Wayne M. Caygill Endowed Chair and Professor of Ophthalmology



**Ayman Naseri, MD**  
Associate Professor of Ophthalmology, and Chief of Ophthalmology, San Francisco V.A. Medical Center



**Julius Schachter, PhD**  
Professor, Departments of Laboratory Medicine, Epidemiology & International Health

## Clinical Faculty WOS Appointments



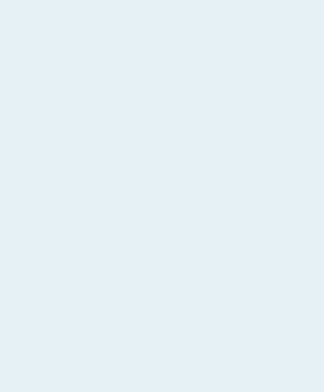
**Kenneth Chern, MD, MBA**  
Assistant Clinical Professor, Department of Ophthalmology



**Douglas Holsclaw, MD**  
Assistant Clinical Professor, Department of Ophthalmology



**Robert Nasser, MD**  
Assistant Clinical Professor, Department of Ophthalmology



**Robert Kim, MD, MBA**  
Associate Clinical Professor, Department of Ophthalmology

## Faculty with Primary Appointments at Other U.C. Campuses



**Lu Chen, MD, PhD**  
Associate Professor, Morton D. Sarver Endowed Chair, Program in Vision Science and School of Optometry, University of California, Berkeley



**Suzanne M.J. Fleiszig, OD, PhD, FAAO, FARVO**  
Professor of Optometry and Vision Science, Infectious Diseases & Immunity, and Microbiology, University of California, Berkeley

## Other Affiliated Faculty

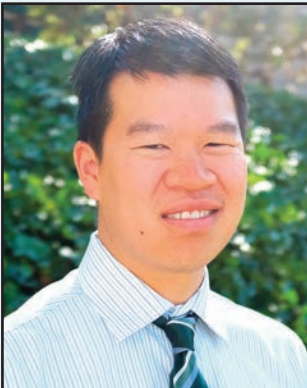
**James Chodosh, MD, MPH**  
Professor, Harvard Medical School, Massachusetts Eye and Ear Infirmary

**Muthiah Srinivasan, MBBS, OD, MS**  
Chief Medical Officer, Aravind Eye Hospital, Madurai, India

**Russell Van Gelder, MD, PhD**  
Professor and Chairman, Department of Ophthalmology University of Washington

**Michael Zegans, MD**  
Associate Professor, Department of Ophthalmology Dartmouth-Hitchcock Medical Center

## OUR FELLOWS



**Neil Chungfat, MD**  
Cornea Fellow



**Julie Schallhorn, MD**  
Uveitis Fellow



**Joseph Sheehan, MD**  
Cornea Fellow



**Nutto Somkijrongroj, MD**  
Cecilia Vaughan Research Fellow

Dr. Todd Margolis with PMG providers and fellows during Proctor afternoon conference.



# STAFF

## Administrative Staff



**Leslie Aguayo**  
Administrative Director  
(Retired September, 2013)



**Joey Bernal, MEd**  
Fellows Affairs and  
Communications Manager



**Pauline Chin, MBA**  
Financial Manager



**Connie Chong**  
Financial Analyst and  
Facilities Manager



**Susan Ford, MBA**  
Assistant, International Programs



**Liz Obana**  
Financial Assistant

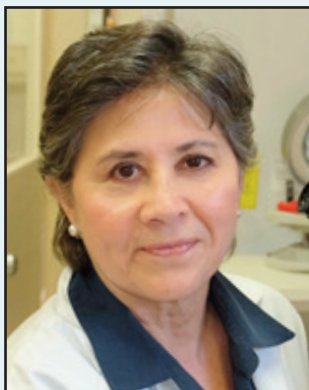


**Sally Tsang, MHA**  
Administrative Director



**Jassel Vanegas**  
Research Financial Analyst

## Microbiology Laboratory



**Vicky Cevallos, MT (ASCP)**  
Sr. Clinical Laboratory Technical  
Specialist



**Cathy Donnellan**  
Clinical Laboratory Technical  
Specialist



**Josephine Gesulga**  
Lab Assistant

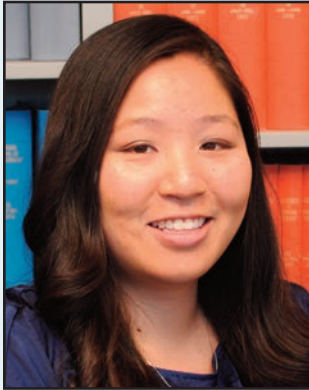


**Maya Talbott**  
Staff Resource Associate



# PROCTOR STAFF AND PERSONNEL

## International Programs



**Stephanie Chin**  
Staff Research Associate



**Puja Cuddapah, MPH**  
Study Coordinator



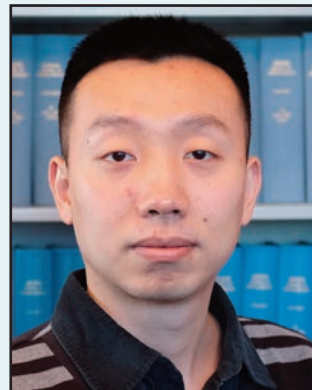
**Kieran O'Brien, MPH**  
Study Coordinator



**Kathryn Ray, MA**  
Statistician



**Nicole Stoller, MPH**  
Program Manager



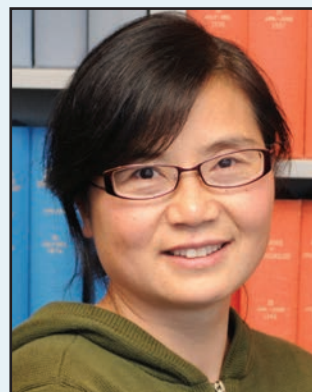
**Yunming Xu**  
Administrative Assistant



**Sun Yu, MPH**  
Study Coordinator



**Lina Zhong**  
Staff Resource Associate



**Zhaoxia Zhou**  
Analyst II

## Heintz Lab



**Nicole Giordani, PhD**  
Postdoctoral Scholar



**Aye Aye Ma**  
Staff Research Associate

## Uveitis Service

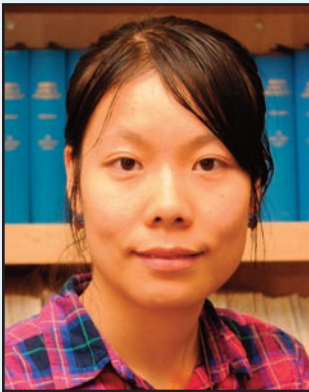


**Erica Browne, MS**  
Research Analyst



**Rachel Weinrib, MPH**  
Research Coordinator

## McNamara Lab



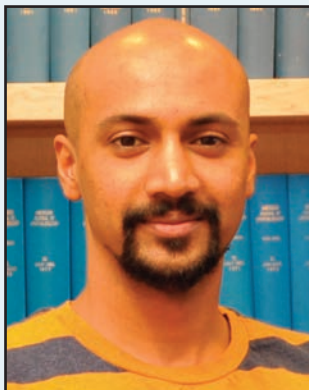
**Feeling Chen**  
Research Associate



**Marianne Gallup**  
Research Associate



**Denise Stephens, PhD**  
Postdoctoral Scholar



**Trinka Vijmasi**  
Assistant Specialist



**Lili Zhang, PhD**  
Postdoctoral Scholar

## Porco Personnel



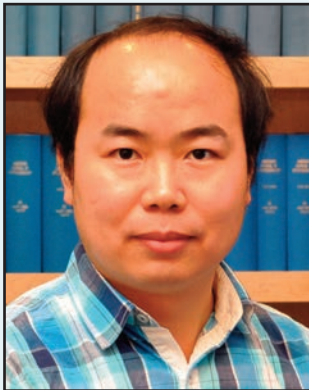
**Sarah Ackley**  
Assistant Study Coordinator



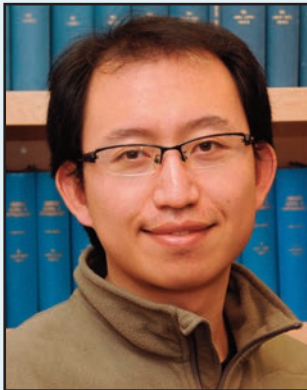
**Seth Blumberg, MD, PhD**  
Associate Specialist



**Wayne Enanoria, PhD**  
Research Epidemiologist



**Daozhou Gao, PhD**  
Postdoctoral Fellow



**Fengchen Liu, MS**  
Associate Specialist



**Nick Sippl-Swezey**  
Associate Specialist

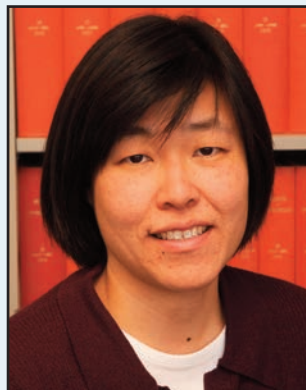
## Proctor Medical Group



**Veronica Alvarez**  
Patient Care and Insurance  
Claims Specialist



**Nancy Lee, OD**  
PROSE Senior Optometrist



**Salena Lee, OD**  
Senior Optometrist



**Delilah Trail**  
Medical Record Assistant

# RESEARCH OVERVIEW

## Richard L. Abbott, MD

Dr. Richard Abbott has focused his research efforts in the area of clinical practice guidelines, the development of cognitive knowledge modules, and medical ethics. He serves as Secretary for Global Alliances for the American Academy of Ophthalmology, and directs the Academy's educational and teaching efforts for its international members. In addition, Dr. Abbott is a member of the International Council of Ophthalmology and serves as Chair of their Guidelines Development Committee to create evidence-based guidelines for eye care on an international basis.

## Nisha Acharya, MD, MS

Dr. Acharya's research focuses on the design and implementation of epidemiological studies to determine risk factors impacting clinical outcome in ocular inflammatory disease as well as clinical trials to determine the optimal treatment for these conditions. Current projects include epidemiological studies on immunosuppressive therapies, juvenile idiopathic arthritis-associated uveitis, sarcoidosis, clinical trials on corneal ulcers and uveitis, and case-control studies looking at the association between various medical conditions or exposures and uveitis.

## Matilda Chan, MD, PhD

Dr. Chan's research focuses on understanding the role of extracellular matrix proteolysis in normal and pathological corneal repair. Dr. Chan's research addresses the importance of proteolysis by matrix metalloproteinases (MMPs) in modulating various aspects of the repair process following corneal injury including inflammation, neovascularization, and fibrosis. Mouse models of corneal injury and real-time imaging of cells in corneas in live mice are used. These studies will hopefully lead to the identification of novel therapeutic targets.

## Lu Chen, MD, PhD

Dr. Chen's research mainly focuses on defining the molecular and cellular mechanisms of corneal inflammation and immunity, particularly those related to lymphatic and blood vessel formation and regulation. Lymphatic and blood vessels are induced into the cornea after an inflammatory, infectious, immunogenic, traumatic, or chemical insult. These vessels enhance delivery of antigens and inflammatory cells, and are associated with many pathologic conditions such as inflammation and transplant rejection. Our long-term goal is to elucidate the basic mechanisms underlying the pathologic vascular events and to identify new therapeutic targets for vascular-associated ocular diseases.

## **Suzanne M.J. Fleiszig, OD, PhD, FAAO, FARVO**

Research in Dr. Fleiszig's laboratory focuses on the pathogenesis of bacterial infection of the cornea. The long-term goals are to determine why patients who wear contact lenses are prone to infection and to develop novel preventative/therapeutic strategies. The approach being utilized is to work towards developing an understanding of how bacteria interact with the epithelial cells that line the surface of the cornea.

## **Bruce D. Gaynor, MD**

Dr. Gaynor is currently conducting clinical research on trachoma under the mentorship of Dr. Tom Lietman. He is particularly interested in the effects of mass treatments with Azithromycin on trachoma but also secondary effects of these mass treatments on nutrition and growth, and malaria. He is also interested in emerging antimicrobial resistance particularly macrolide resistance in nasopharyngeal pneumococcus.

## **Douglas Holsclaw, MD**

Dr. Holsclaw is interested in defining the clinical parameters of ocular pemphigoid and other cicatrizing conjunctivitis.

## **David G. Hwang, MD, FACS**

Dr. Hwang participates in clinical research focused on ocular infectious disease and the development of new surgical techniques in corneal and refractive surgery.

## **Bennie H. Jeng, MD**

Dr. Jeng's primary research focus for that last year has been a clinical trial investigating a novel compound for the treatment of persistent epithelial defects in diabetic patients. Persistent epithelial defects (PED) of the cornea are uncommon, but can have serious consequences for the health of the eye including infection, scarring, melting, and even perforation. Treatments for PED include tear supplements, punctal plugging, therapeutic contact lenses, autologous serum, and surgery. Other treatments that are used to try to promote re-epithelialization are corticosteroids, collagenase inhibitors, ascorbate, or epidermal growth factors. However, there is no treatment that can be relied upon to consistently improve outcomes in PED. The purpose of this study is to evaluate the safety and efficacy of NEXAGON, a novel therapeutic agent, in the healing of PED. This compound qualifies in the orphan drug category as PED resulting from these indications has an estimated prevalence of less than 200,000 persons in the United States. However, having this compound available commercially to these individuals would potentially add a powerful non-surgical treatment option for a condition that is difficult to treat and that often times results in poor visual outcomes.

## Research Overview (cont'd)

### Jeremy Keenan, MD, MPH

Dr. Jeremy Keenan conducts clinical research on ocular infectious diseases. He is currently funded through a career development award through the National Institutes of Health, with primary mentorship from Dr. Tom Lietman. Dr. Keenan's research involves (1) ancillary analyses of clinical trials for trachoma that are currently being carried out by the Proctor trachoma team in Ethiopia and Niger; (2) epidemiological studies of cytomegalovirus retinitis in Thailand; and (3) diagnosis and treatment of acanthamoeba keratitis.

### Thomas M. Lietman, MD

Dr. Thomas Lietman, in collaboration with the Proctor team, is investigating whether blinding trachoma can be eliminated, or whether the chlamydial infection which causes the disease could possibly be eradicated. He and Dr. Porco are constructing mathematical models to determine who within communities needs to be targeted, how often communities need to be treated, and whether the World Health Organization's antibiotic treatment program is in danger of generating significant drug resistance. He, Dr. Keenan, and Dr. Gaynor are conducting clinical trials that evaluate the long term effect of mass antibiotic treatment of trachoma to determine if infectious trachoma can, indeed, be eliminated with repeat community antibiotic treatment. The team is also assessing whether these antibiotic distributions may decrease childhood mortality. Dr. Lietman and Dr. Nisha Acharya are running a fungal ulcer trial in collaboration with the Aravind Eye Care System in South India. The corneal ulcer team is also conducting a community-randomized trial in Nepal to see whether village eye care workers who prophylax corneal abrasions with antimicrobial ointment, can have a large impact on the incidence of corneal ulcers.

### Todd P. Margolis, MD, PhD

The primary focus of the Margolis laboratory is research on the cellular and molecular mechanisms that regulate the establishment and maintenance of latent neuronal infection with herpes simplex virus (HSV). Ongoing research is aimed at documenting the role of both neuronal and viral gene expression in the establishment and maintenance of HSV latency. The ultimate goal of this work is to gain enough of an understanding about the regulation of HSV latent infection that therapeutic interventions can be devised to eliminate latent infection or prevent viral reactivation. A second line of investigation focuses on the use of telemedicine to screen AIDS patients for CMV retinitis in developing countries.

### Stephen D. McLeod, MD

Dr. McLeod's major areas of work include the development of implanted accommodating devices for the treatment of presbyopia and the development of new devices for cataract removal. In the area of refractive surgery, he studies methods for improving the outcome of LASIK and PRK. He collaborates with colleagues in the Proctor Foundation in studies of improved methods for the treatment of infectious keratitis worldwide.

## Nancy A. McNamara, OD, PhD

Dr. McNamara's research centers on understanding the pathological effects of damaging extrinsic stimuli on mucosal epithelia. Her laboratory is working to understand the pathogenesis of ocular surface damage in patients with autoimmune disease, as well as the molecular mechanisms that promote the transformation of airway mucosal epithelial cells to tumor cells in response to cigarette smoke. Although seemingly different, these studies share in common the need for a better understanding of the molecular events that contribute to pathological alteration of mucosal epithelia, and their potentially devastating consequences. Dr. McNamara's research program involves both clinically based, human studies to characterize key components of mucosal defense, as well as studies to decipher the mechanisms whereby they modulate disease.

## Travis C. Porco, PhD, MPH

Dr. Travis Porco is an ophthalmological biostatistician and researcher working on the mathematical analysis of disease transmission. He has consulted on projects involving trachoma elimination in Ethiopia, seasonality of keratitis in South India, treatment of fungal ulcers with voriconazole, treatment of retinal degenerative diseases using ciliary neurotrophic growth factor, pediatric enucleation, and the cost-effectiveness of endophthalmitis prevention using fourth generation fluoroquinolones.

## Ira Wong, MD

During the past year Dr. Wong's research focused on population-based studies of the epidemiology of uveitis and other ocular inflammatory diseases, clinical trials, and developing better diagnostic instrumentation for clinical practice and uveitis trials.



# DR. NISHA ACHARYA'S RESEARCH

## First-line Antimetabolites for Steroid-sparing Treatment (FAST) Trial

**N. Acharya, T. Porco, T. Lietman, W. Enanoria, S. Lee, R. Weinrib, E. Browne, J. Gonzales, T.P. Margolis**

Treatment of uveitis is currently not evidenced-based. Patients often are treated with multiple immunosuppressive agents until one is found which successfully controls their inflammation. The antimetabolites methotrexate and mycophenolate mofetil are the two most commonly used immunosuppressive agents used to treat chronic non-infectious uveitis in the US. After conducting a pilot clinical trial to gather preliminary data, we are conducting an NIH sponsored multicenter clinical trial to definitively compare these therapies. The Proctor Foundation is the clinical and data coordinating center, and we will be enrolling patients at the Proctor Foundation, Oregon Health and Sciences University, and Northwestern University, in addition to international sites including Asociacion Para Evitar la Ceguera en Mexico, I.A.P. (APEC), Hospital in Mexico City (collaborator Dr. Lourdes Arellanes Garcia) and the Centre for Eye Research Australia (CERA) at Royal Victorian Eye and Ear Hospital in Melbourne, Australia (collaborator Dr. Lyndell Lim and Dr. Anthony Hall).

## Multi-Center Uveitis Steroid Treatment Trial (MUST)

**N. Acharya, I.G. Wong, J. Gonzales, T.P. Margolis**

Dr. Acharya is site PI of the Multicenter Uveitis Steroid Treatment Trial (MUST), which is comparing the Retisert fluocinolone acetonide steroid implant to systemic immunosuppressive therapy for the treatment of chronic intermediate, posterior or panuveitis. This study has completed enrollment, and patients are now being followed for long-term outcomes. Dr. Acharya is serving as a protocol chair to help design future clinical trials on uveitic macular edema to be conducted with the MUST network.

## Epidemiologic Studies on Uveitis

**N. Acharya, R. Weinrib, E. Browne, J. Gonzales, W. Enanoria, T. Porco**

Dr. Acharya's research group is studying the predictors of clinical outcomes such as visual acuity and ocular complications in subtypes of uveitis, as well as assessing clinical outcomes in patients treated with various immunomodulatory treatments, including biologic therapies. The research group is also investigating risk factors for developing ocular inflammation, including exposure to various medications and having other concurrent medical conditions. The latter studies are being conducted in conjunction with Dr. Vivien Tham (Proctor alumna) and Kaiser Permanente Hawaii. We are also the coordinating center for a multicenter international study to validate diagnostic criteria for ocular sarcoidosis. Dr. John Gonzales from Proctor is a co-investigator for the sarcoidosis study.



## Mycotic Ulcer Treatment Trials

**N. Acharya, T. Lietman, S. McLeod, T. Porco, K. O'Brien, K. Ray, N.V. Prajna and other collaborators at Aravind Eye Hospital in South India**

Fungal corneal ulcers tend to have poor outcomes with the commonly used treatments, natamycin and amphotericin B. Recently, voriconazole has been used to treat fungal corneal ulcers with anecdotal reports of success reported in the literature. However, there has been no systematic attempt to determine whether it is more effective clinically than the commercially available natamycin. Although there are suggestions that particular fungi respond better to one agent or another, there is little data available for physicians to make an evidence-based decision on choice of antifungal. The Mycotic Ulcer Treatment Trial (MUTT) 1 studied which topical antifungal treatment, voriconazole or natamycin, resulted in better visual acuity in patients with fungal corneal ulcers. This trial found that natamycin was associated with better visual outcomes compared with topical voriconazole. MUTT 2 is studying whether adding oral voriconazole to topical voriconazole improves clinical outcomes in severe fungal ulcers.

UCSF Medical Student, Cathy Sun, at the slit lamp examining a patient at the Cornea clinic in Madurai.



## DR. MATILDA CHAN'S RESEARCH

### Confocal Intravital Imaging of the Cornea Following Injury

**M. Chan, J. Li, A. Bertrand, Z. Werb**

After tissue injury, there are many dynamic cellular changes within the extracellular matrix. We are interested in the studying the behavior of cells within their microenvironment following injury. The recent development of time-lapse video microscopy has allowed for the direct visualization of these cellular dynamics in vivo and in real time. We have developed an imaging platform that has combined long-term mouse anesthesia with fluorescent, real-time microscopy so that we are able to visualize inflammatory cell dynamics in the wounded cornea of a living mouse.

## The Role of Extracellular Enzymes in Regulating Corneal Repair

**M. Chan, J. Li, A. Bertrand, J. Lin, A. Casbon, I. Maltseva, S. Rosen, Z. Werb**

Corneal opacification affects millions of people and is the second leading cause of blindness in the world. Corneal injury is a major cause and can occur by a variety of mechanisms including infectious and noninfectious ulcers, incisional and laser surgery, and trauma. Regardless of the type of injury, a common set of cell-extracellular matrix (ECM) interactions mediated by growth factors, cytokines, and angiogenic factors become activated in the repair process. This normal response to injury can lead to pathologic results when corneal fibrosis and angiogenesis occur. Clinically, this can result in severe corneal opacification with vision loss and corneal transplantation may be the only option to restore functional vision.

Matrix metalloproteinases are a family of extracellular proteinases and represent the most prominent group of proteinases associated with tissue repair. These enzymes become activated upon tissue injury and affect various aspects of the repair process including turnover of the ECM, angiogenesis, signaling events, and immune cell infiltration. Previous studies have shown that the expression of several matrix metalloproteinases (MMPs), including MMP-8 and MMP-12, are up-regulated in the cornea after injury implicating their roles in corneal repair. These enzymes are produced by epithelial, stromal and inflammatory cells and their roles in corneal repair have not been well-studied. Using a genetic approach, we are examining how the extracellular degradative enzymes, MMP-8 and MMP-12, contribute to the corneal epithelial and stromal repair processes. Our results suggest that these enzymes regulate the inflammatory and angiogenic responses to corneal injury (Figure 1). These findings are significant because corneal inflammation and angiogenesis are key determinants of the amount of scarring that will occur after injury. Therefore, these results improve our understanding of the role of extracellular enzymes in regulating molecular processes that may affect corneal fibrosis and suggest them as potential therapeutic targets for modulating corneal repair.

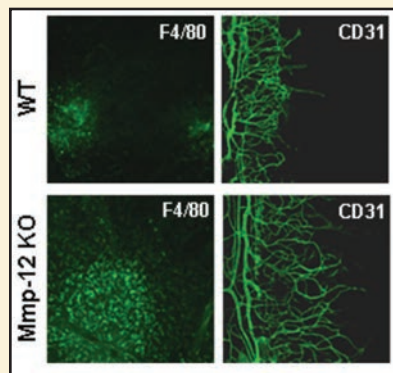


Figure 1: Immunofluorescent staining of wounded corneas from wild-type (WT) and MMP-12 deficient mice (Mmp-12 KO) showing differences in macrophage (F4/80) infiltration and angiogenesis (CD31).

## DNA Methylation in Corneal Disease

**M. Chan, J. Lin, B. Jeng, D. Hwang**

Corneal disease can result from abnormal gene regulation and expression which has led to several genetic studies to help clarify the underlying molecular processes involved in the pathophysiology of corneal disease. While corneal genetics has given some insight into corneal disease processes, the role of epigenetic modifications in corneal disease not been

characterized. Epigenetic modifications are heritable changes in gene expression that are not accompanied by changes in DNA sequence and result in alterations in gene expression. The goal of the project is to use a global DNA methylation assay to identify candidate genes that become abnormally methylated in corneal diseases and to assess the effects of reversing DNA methylation.

## **Trials of a HSV mutant strain as a live vaccine**

**M. Chan, J. Lin, J. Draper, J. LaVail**

Herpes simplex virus (HSV) infection is one of the most common viral infections acquired by humans. Corneal infection and inflammation leads to corneal scarring, ulcers, thinning, and neovascularization which eventually leads to blindness. A major obstacle in HSV research on the recurrent disease has been the lack of a mouse model of recurrent HSV infection. Our studies will use a model of recurrent HSV infection to test the efficacy of a mutant HSV strain to reduce the severity or incidence of recurrent infection and to study the corneal immune response following HSV-reactivation.

## **DR. LU CHEN'S RESEARCH**

### **Mechanisms of pathologic lymphangiogenesis, angiogenesis, and transplant rejection**

Multiple projects are aimed to define the molecular and cellular mechanisms underlying pathologic lymphangiogenesis, angiogenesis, and transplant rejection using an assortment of in vitro and in vivo models. We have shown that corneal lymphangiogenesis and angiogenesis are complex processes orchestrated by a number of factors and have identified several new potential targets for therapeutic development.

### **Mechanisms of corneal lymphatic plasticity**

We recently reported that the cornea is not devoid of lymphatic vessels during embryogenesis. Spontaneous lymphatic formation and regression occurs in this tissue before it matures. Thus, the cornea is the first tissue identified to possess a full range of lymphatic plasticity. Further investigation is being undertaken to reveal basic mechanisms underlying this novel phenomenon and to provide critical information regarding lymphatic formation as well as regression.

### **Mechanisms of corneal lymphatic valve formation**

We recently reported a novel finding that newly formed lymphatic vessels in the cornea develop luminal valves during lymphangiogenesis. These valves may serve as a maturation marker for corneal lymphatic vessels. Further investigation is being undertaken to study their anatomical features as well as functional roles in directing lymph flow and mediating immune responses.

## DR. LU CHEN'S RESEARCH (cont'd)

### Live imaging of lymphangiogenesis and angiogenesis in the cornea

We recently reported a new and highly advanced technology for live imaging of lymphatic vessels in the cornea. The system allows for longitudinal study of the same cornea over time. Both time-lapse images and real time videos can be taken from low to high magnification and along various axes for data analysis. This system is being used in multiple projects to study dynamic events of lymphangiogenesis together with angiogenesis in various pathologic settings.

## DR. SUZANNE FLEISZIG'S RESEARCH

Research in Dr. Fleiszig's laboratory focuses on the pathogenesis of bacterial infection of the cornea. The long-term goals are to determine why patients who wear contact lenses are prone to infection, and to develop novel preventative/therapeutic strategies based on the knowledge acquired. The approach being utilized is to work towards developing an understanding of how *P. aeruginosa*, the bacterium most commonly isolated from contact lens related infections, interacts with the epithelial cells that line the surface of the cornea on which contact lenses are placed.

*P. aeruginosa* causes sight threatening pathology in the eye and life threatening infections at other sites, including serious lung disease in people with cystic fibrosis or HIV, and serious skin infections in burns victims. Thus, this line of research could ultimately lead to new means to prevent or treat several types of disease.

Specific projects include:

### 1. Determining how the healthy corneal surface resists infection and how contact lens wear then compromises those defenses.

The aims of this effort include determining the molecular factors and events that normally prevent bacteria from penetrating into the corneal epithelium when the eye is healthy, how the functionality of that defense system is modulated, and the bacterial factors that enable penetration when this system is compromised. In recent years, the Fleiszig lab has developed a number of in vivo and in vitro models that are now allowing the lab to study factors that modulate bacterial interactions with the eye when its defenses are not compromised, and a suite of imaging technologies that allow infected corneal epithelium to be studied in the live intact eye.

Utilizing these new techniques, graduate student Aaron Sullivan is working towards determining the virulence factors that bacteria use to traffic through the epithelium. His data show that the type III secretion system, used by bacterial to deliver toxins into host cells, can mediate bacterial penetration, but that proteases can instead be utilized when bacterial exposure is prolonged.

## DR. SUZANNE FLEISZIG'S RESEARCH (cont'd)

In the past year, the laboratory has continued its efforts to develop novel therapies for preventing infection. This has led to the discovery of a previously unknown class of antimicrobial peptides within corneal epithelial cells derived from keratins. These keratin derived antimicrobial peptides (KDAMPs), are small and stable, and show great potential for the eventual development of new anti-infective medicines. Laboratory members who have contributed to this research include Drs. Connie Tam and James Mun, and UC Berkeley undergraduate student volunteers Gary Chan and Jong Hun Kim.

In a separate project Susan Heimer, a Specialist in the laboratory, with the assistance of undergraduate volunteer Kelsey Li-Chinn Liu, has been working towards understanding the relationship between dry eye and susceptibility to infection. New data show that in an otherwise healthy mouse, dry eye does not predispose the eye to infection, due to the upregulation of specific known defense factors. Their results have furthered our understanding of how the eye normally defends itself against infection, while informing us about how dry eye impacts ocular surface biology.

### **2. Fundamental studies of bacterial/epithelial cell interactions using *P. aeruginosa* as a model organism.**

A second major line of research in the Fleiszig laboratory involves studying how bacteria survive inside corneal epithelial cells, and the relevance of that intracellular survival to ocular disease. Previously, the laboratory had found that ExoS, a protein encoded only by invasive *P. aeruginosa* strains, is critical for intracellular survival and replication involving its ADP-r activity. New data show that the translocon, thought to be required for injecting ExoS across host cell membranes into the cytoplasm, is not needed to allow ExoS to exert these effects. Since known targets of ExoS are all in the cytoplasm, this result suggests that ExoS utilizes different targets to enable intracellular survival, or that ExoS can use other strategies to cross host membranes. Other new data reveal new insights into how the host responds to internalization by bacteria; for example that bacteria lacking the capacity to secrete ExoS are targeted to acidic compartments, wherein they are killed. Laboratory members who contributed to this research include postdoctoral fellows Amber Jolly, Victoria Hritenenko, and Desire Takawira.

### **3. Classification of *P. aeruginosa* strains and relationship to therapeutic response.**

A project completed and published in the past year is an offshoot of the SCUT (Steroids in Corneal Ulcer Therapy) study being conducted by other investigators at the Proctor Foundation in collaboration with a number of other international organizations. The role of the Fleiszig Laboratory was to classify *P. aeruginosa* strains isolated from infections to determine if they are invasive or cytotoxic. The results show that invasive and cytotoxic strains, which differ in how they interact with cells, are associated with different treatment outcomes in patients. Lab members who were involved in this project include UC Berkeley School of Optometry students Chelsia Leong and Avanti Ghanekar, lab manager Arjay Clemente and Drs. Connie Tam and James Mun.

# DR. BRUCE GAYNORS'S RESEARCH

## Do Mass Antibiotic Treatments Result in a Morbidity & Mortality Reduction?

**T. Lietman, T. Porco, J. Keenan and B. Gaynor**

Data from Ethiopia suggest mortality reductions in children following azithromycin treatments, but it is unclear which specific diseases contribute to this overall reduction. Periodic distributions of azithromycin could also improve childhood nutritional status and growth indices, perhaps by treating gastrointestinal or other diseases that affect nutrient absorption and metabolism. We performed a pilot study of anthropometric indices, anemia and malaria parasitemia in 2011 in Niger. We will continue to measure these indices as part of a larger randomized clinical trial with azithromycin for trachoma over the next 3 years. Assessments of cause-specific mortality and growth parameters in azithromycin-treated children allow us to measure the positive secondary effects of mass antibiotic treatments.

## What are community risk factors for ocular chlamydia infection in Niger: results from a cluster –randomized trachoma trial.

**T. Lietman, J. Keenan, T. Porco and B. Gaynor**

Trachoma control programs utilize mass azithromycin distributions to treat ocular Chlamydia trachomatis as part of an effort to eliminate this disease world-wide. But it remains unclear what the community-level risk factors are for infection.

We are performing a cluster-randomized, controlled trial entering 48 randomly selected communities. A pretreatment census and examination established the prevalence of risk factors for clinical trachoma and ocular chlamydia infection including years of education of household head, distance to primary water source, presence of household latrine, and facial cleanliness (ocular discharge, nasal discharge, and presence of facial flies). Before treatment in May to July 2010, the community-level prevalence of active trachoma (TF or TI utilizing the World Health Organization [WHO] grading system) was 26.0% and the mean community-level prevalence of chlamydia infection by Amplicor PCR was 20.7% in children aged 0-5 years. In multivariate analysis, facial flies ( $P=0.03$ ) and years of formal education completed by the head of household ( $P=0.02$ ) were associated risk factors for ocular chlamydial infection. We have found that the presence of facial flies and years of education of the head of the household are risk factors for chlamydia infection when the analysis is done at the community level. This will help guide programs on how limited resources should be used. This study was done in partnership with The Carter Center and PNLCC (Programme National de Lutte Contra la Cecite.) of Niger.

## Do mass antibiotic treatments affect malaria in endemic areas?

**T. Lietman, T. Porco, J. Keenan and B. Gaynor**

Mass azithromycin distributions are used to control the ocular strains of Chlamydia trachomatis that cause trachoma, but may also affect other infectious diseases, including malaria. We are

conducting a cluster-randomized trial in 24 communities in Niger to determine whether mass azithromycin treatments reduce malarial asexual parasitemia, gametocytemia, and anemia, when an additional treatment is given during the dry, low-transmission season.

We found significantly higher malarial parasitemia in 12 once-treated communities (29.8%) than 12 twice-treated communities (19.5%,  $P=0.03$ ). Parasite density was higher in once-treated communities (354 parasites/ $\mu\text{l}$ ), than twice-treated communities (74 parasites/ $\mu\text{l}$ ,  $P=0.03$ ). Mass distribution of azithromycin reduced malarial parasitemia 4-5 months after the intervention. Gametocytemia prevalence was not significantly higher in once-treated communities (1.5%) than twice-treated communities (0%,  $P=0.29$ ), nor was hemoglobin concentration significantly lower in once-treated communities (10.0 gm/dl) than twice-treated communities (10.2 gm/dl,  $P=0.20$ ). The results suggest that drugs with antimalarial activity can have long-lasting impacts on malaria during periods of low transmission.

## Do mass antibiotic distributions affect growth and nutrition?

**J Keenan, T. Lietman, T. Porco, and B. Gaynor**

Antimicrobials are used primarily to treat infectious disease, but they have other effects. We assessed anthropometry measurements in children 6 to 60 months in 24 communities randomized to one versus two mass azithromycin distributions over a one year period in Niger. We compared the prevalence of wasting, low mid-upper arm circumference, stunting, and underweight in communities in the two treatment arms. We were unable to prove there was a difference in the prevalence of wasting in the 12 communities which received one mass azithromycin distribution versus the communities which received two mass azithromycin distributions (odd ratio 0.75, 95% CI = 0.46 to 1.23). Likewise, we were unable to detect a difference in the two treatment arms for low mid-upper arm circumference, stunting, and underweight. There may not be an association between antibiotic use and improved growth in humans, or this trial was not powerful enough to detect an association if it exists. We plan to return to the same communities in Niger to measure anthropometry following repeated antibiotic administrations over a period of 3 years.

Dr. Gaynor trains ophthalmic nurses on trachoma grading.



## DR. DAVID HWANG'S RESEARCH

Dr. Hwang has a longstanding and continuing interest in ocular infectious diseases and pharmacotherapy, and in particular the mechanisms and epidemiology of antimicrobial resistance. He recently served as the Principal Investigator for a multi-center prospective randomized study of treatments for blepharitis and helped develop a standardized photography evaluation tool for blepharitis grading in collaboration with colleagues at the University of Pennsylvania.

Dr. Hwang is also active in the development, introduction, and clinical research evaluation of innovative surgical techniques and instruments for use in keratoplasty, refractive surgery, and other types of anterior segment surgery. These include endokeratoplasty, complex descemetopexy, deep anterior lamellar keratoplasty, femtosecond laser-assisted lamellar and penetrating keratoplasty, permanent keratoprosthesis implantation, and intracorneal ring segment surgery. He is collaborating in the development of nanoknife instrumentation for novel anterior segment surgical applications. Dr. Hwang has also developed a “no ultrasound” technique for phacoemulsification that may reduce the risk of ultrasound-related surgical complications, such as corneal burns and other forms of anterior segment tissue damage.

Dr. Hwang has a longstanding interest in corneal endothelial cell transplantation and participated in the development of the bioengineered corneal allograft using in vitro-grown corneal endothelial cells. He has built on this interest by launching an active clinical endokeratoplasty program at UCSF, in order to refine and advance current endokeratoplasty techniques and to lay the surgical technique groundwork for potential future clinical application of bioengineered corneal endothelial allografts. An ongoing prospective evaluation of patients undergoing endokeratoplasty allows analysis of clinical outcomes, facilitates development of new surgical methods, and provides opportunities for data-driven refinement of perioperative management protocols. Of particular interest is the development of techniques for using selective keratoplasty techniques in high-risk eyes, including those heretofore judged as relatively poor candidates for a selective approach due to their anatomic complexity or disease severity.

Dr. Keenan and local team members walk to the examination station in the Amhara region, Ethiopia.







Elephant blessing a girl in response to an offering at a temple in Pondicherry, India.

Ms. Kieran O'Brien reviews health records with Nepal Program Director, Ram Prasad Kandel in the Nawalparasi District in Nepal.



## DR. TRAVIS PORCO'S RESEARCH

During the past year Fengchen Liu and Dr. Porco worked with the Lietman group here at Proctor as well as the Partnership for Rapid Elimination of Trachoma (PI: Sheila West, Johns Hopkins) continuing our work in estimating the efficacy of mass azithromycin distribution in eliminating trachoma infection in Tanzania. This work includes an analysis of transmission dynamics in Tanzania over several years, showing that transmission did not seem to intensify over time and helping to allay fears that loss of immunity due to successful control would undermine our efforts in the future.

Daozhou Gao, who began with our group in June 2012, analyzed a game theoretic model of drug resistance in the two-infection setting, extending earlier work begun by Tom Lietman and Travis Porco. This model was designed to provide insight into macrolide resistant pneumococcus resulting from trachoma elimination programs. He also analyzed a model of malaria amelioration through mass azithromycin distribution, in collaboration with Tom Lietman and the other members of the group.

Nick Sippl-Swezey, who began in July 2012, developed a game theoretic model of cooperation during contact investigations, and is also funded to work with the Office of Science Education and the MIDAS program (Modeling Infectious Disease Agent Study) to develop educational modules for teaching epidemiology.

Sarah Ackley, who began in September 2012, is developing a transmission model of tuberculosis, in collaboration with our colleagues Jim Scott and Caitlin Pepperell.

Wayne Enanoria and Fengchen Liu developed a simulation model for measles contact investigation, to determine which intervention components are most cost-effective under different vaccine coverage levels.

Seth Blumberg developed estimates of measles transmission in California, and contributed to analysis of measles contact investigation.

# DR. JEREMY KEENAN'S RESEARCH

## Optimal trachoma control after mass antibiotic distributions

**J. Keenan, T. Lietman, T.P. Margolis, G. Rutherford, D. Jamison, T. Porco, Z. Zhou, N. Stoller, S. Yu**

Trachoma, caused by repeated ocular chlamydial infection, is the leading cause of infectious blindness worldwide. Led by Dr. Tom Lietman, we are currently studying several ancillary questions from clinical trials. For example, we found that children in Ethiopia can be infected with the same type of chlamydia for many months in a row, suggesting either a long duration of infection or poor immunity. In the upcoming year, we will assess the cost effectiveness of various treatment strategies for trachoma, and assess the role of a smartphone camera for the diagnosis of trachoma.

## Diagnosis and treatment of cytomegalovirus retinitis

**J. Keenan, T.P. Margolis, G. Holland, D. Heiden**

Cytomegalovirus (CMV) retinitis is a retinal infection commonly seen in HIV patients with severe disease. CMV retinitis is still a major cause of blindness in southeast Asia. Since many patients do not have visual symptoms early in the disease, regular eye exams of at-risk patients are necessary. However, there are not enough ophthalmologists in many countries to screen for CMV retinitis. Telemedicine diagnosis is a potential alternative. We started a study in Thailand comparing a traditional retinal camera with a novel iPhone retinal camera for the diagnosis of CMV retinitis. If the smartphone camera performs well, this may reduce the potential costs of screening examinations and therefore make screening more available.

## Diagnosis and treatment of acanthamoeba keratitis

**J. Keenan, T. Lietman, T.P. Margolis, N. Acharya, K. O'Brien**

Acanthamoeba keratitis is a corneal infection that primarily affects contact lens wearers in the United States, and agricultural workers in developing countries. This infection can be difficult to diagnose and treat. We currently have a planning grant from the National Eye Institute to design a clinical trial. The proposed trial will (1) assess the value of newer diagnostic modalities for acanthamoeba keratitis, including confocal microscopy and polymerase chain reaction, (2) compare treatment with a single anti-amoebic agent versus multiple agents, and (3) assess the value of adjunctive topical corticosteroid therapy. We are currently performing several preliminary studies, including studies of the risk factors and outcomes of acanthamoeba keratitis, and microbiological studies of the susceptibility of recent acanthamoeba isolates to a variety of anti-amoebic agents.

## Screening Tests for Glaucoma

**J. Keenan, R. Stamper, K. O'Brien**

Glaucoma is the second leading cause of blindness in the world. Affected persons often are unaware that they have glaucoma until they have lost vision. Screening is not typically performed for glaucoma, especially in resource-poor settings. Moreover, it is unclear that screening should be performed, since this may not be a cost-effective utilization of resources. Together with collaborators in India, we have started a study to assess different screening tests for glaucoma in a resource-limited setting. The results of this study will allow us to investigate which tests would be the best candidates for a community-based screening program.



Ms. Vicky Cevallos, Dr. Bruce Gaynor, Dr. Tom Lietman, Ms. Nicole Stoller, Ms. Sun Yu, and Dr. Jeremy Keenan in the Amhara region, Ethiopia.

## DR. THOMAS LIETMAN'S RESEARCH

### Mathematical Modeling of Infectious Diseases

#### T. Lietman and T. Porco

The World Health Organization (WHO) recommends mass administration of single-dose oral antibiotics in trachoma endemic areas. However it is not clear how often mass treatment should be administered. Clinical trial results, including those being performed by the Proctor Foundation, are providing useful information, but will take years to complete and may be prohibitively expensive. Mathematical models can help assess whether infectious trachoma can be eliminated, not just controlled, as is the current WHO goal. Our studies suggest infection can be eliminated if mass antibiotic treatments are given repeatedly (annually in areas of moderate disease, and perhaps even biannually in hyperendemic areas). Further operations research is being done to determine if these estimates are indeed accurate, and tailoring treatment frequencies to countries of different endemicity. We have also shown with mathematical models that if infection is eliminated from a core group of children, then it should disappear from the rest of the community as well. We are now developing strategies from these models to bring about elimination using the fewest possible antibiotic treatments.

A single dose of azithromycin is extremely effective in eliminating the causative agent of trachoma, *Chlamydia trachomatis*, from an individual. In addition to chlamydia, azithromycin

## DR. THOMAS LIETMAN'S RESEARCH (cont'd)

has antibacterial activity against many bacterial species including pathogenic bacteria that are routinely found in trachoma endemic communities. While chlamydia has remained sensitive to macrolides and azalides including azithromycin, other bacteria may develop resistance, and there is some concern that large-scale trachoma programs may interfere with bacterial flora. Drs. Porco and Lietman are using mathematical models of chlamydia and streptococcus transmission to estimate the amount of drug resistance caused by trachoma programs.

### Trachoma Community Treatment Strategies

**N. Stoller, Z. Zhou, J. Keenan, J. Whitcher, S. Yu, B. Gaynor, T. Porco, and T. Lietman**

It is uncertain if annual repeat treatment of trachoma with mass azithromycin distribution will eliminate ocular Chlamydia from a community, particularly in hyperendemic areas. We have recently completed the NIH-funded TANA-TIRET study, in collaboration with the Carter Center and the Ethiopian Ministry of Health. We were able to demonstrate that children form a core group for trachoma—that is, if you eliminate infection in children, then it should disappear in the rest of the community. We have also found that biannual treatments are more likely to completely eliminate infection than annual treatments. Future studies will determine if infection will return after treatments are discontinued.

We are soon completing a research program funded by the Gates Foundation through Johns Hopkins University (PI Dr. Sheila West) that determines whether complete elimination in the entire community is possible by only treating a core group of children. This study is taking place in Matamaye District, Niger, in collaboration with the Programme National de Lutte Contre la Cécité.

### Mortality Reduction with Oral Azithromycin administration

**N. Stoller, S. Yu, Z. Zhou, J. Keenan, J. Whitcher, B. Gaynor, T. Porco, and T. Lietman**

In our Ethiopian trachoma studies, we also monitor mortality with antibiotic administrations, as diarrhea, respiratory infection, and malaria are all major causes of infant mortality and all may be affected by azithromycin. We found that in pre-school children, mortality was reduced with the mass antibiotic treatments, even though the target disease trachoma is not itself a lethal disease. We are in the process of setting up a large, 3-country (Niger, Tanzania, and Malawi), community-randomized clinical trial to confirm this reduction in mortality, funded by the Bill and Melinda Gates Foundation. This trial will need to be far larger than the previous study—it will be performed in an area totaling 1,500,000 individuals.

### Fungal ulcer treatment: the Mycotic Ulcer Treatment Trials

**T. Lietman, N. Acharya, K. O'Brien, K. Ray, J. Whitcher, M. Zegans, S. McLeod, P. Lalitha, and N. Prajna**

With Dr. Nisha Acharya at UCSF, and our Indian colleagues at the Aravind Eye Hospital, we are evaluating which topical agent, voriconazole or natamycin, is the superior treatment for

fungal keratitis in a randomized, masked, controlled trial. Historically, fungal ulcers are relatively uncommon in the United States. They make up only about 8% of infectious ulcers seen at the Proctor Foundation at UCSF prior to 2005. However, in the past year, there has been an epidemic of keratitis due to *Fusarium* species in the U.S., and caring for these patients has become a particular concern for corneal specialists. In warmer, tropical climates, fungal ulcers have always been endemic. In settings such as South India, as many as one half of infectious ulcers are fungal. We recently completed a pilot study, and are in now the midst of a second, 240-patient trial. The Aravind Eye Hospital in Tamil Nadu is the ideal partner for this project.

## Corneal ulcer prevention: the Village Integrated-Eye Worker study

**T. Lietman, J. Keenan, K. O'Brien, J. Whitcher, M. Srinivasan, N. Acharya, and M. Srinivasan**

When infectious corneal ulcers present to health care facilities, the infection can typically be eliminated, although there is often little that can be done to prevent corneal scarring and subsequent blindness. With the corneal ulcer team at Proctor and our colleagues at SEVA and the Aravind Eye Hospital, we are evaluating whether corneal ulcers can be prevented. RPB and the NIH-NEI have funded a community-randomized trial in which ½ the communities are randomized to have a village eye care worker treat all corneal abrasions within 24 hours. The other ½ of communities will receive diabetes screening. We will monitor incident corneal ulcers over 24 months.



Dr. Lietman teaching Ethiopia team members how to grade trachoma for the TIRET study.

# DR. TODD MARGOLIS'S RESEARCH

## Establishment of Latent Infection with Herpes Simplex Virus.

**T.P. Margolis, N. Giordani, A. Bertke, A. Ma, M. Margolis, A. Zhadmehr**

The primary focus of this laboratory is to carry out research on the viral and cellular mechanisms that regulate the establishment and maintenance of latent neuronal infection with herpes simplex virus (HSV-1). Previous work suggests that establishment and maintenance of HSV latent infection is heavily dependent on the genetic expression of the host neuron. Ongoing research is aimed at documenting the role of both viral and neuronal gene expression in the establishment and maintenance of HSV latency. This is being accomplished through a number of different basic strategies. The first strategy is to test the effect of host candidate genes on the outcome of infection with HSV. A second strategy has been to develop an in vitro system for studying both productive and quiescent (latent) infection of neurons.. Through this system we have also discovered that two key viral regulatory genes, ICP27 and ICP22, which are required for productive HSV-1 infection of replicating cells, do just the opposite in neurons. They appear to promote the establishment of a latent infection. This is a key finding which suggest that expression of these two genes plays a key role in regulating HSV latent infection and reactivation. A third strategy has been to examine why HSV-1 and HSV-2 preferentially establish latent infection in different subsets of ganglionic neurons. This is being accomplished through a set of HSV-1/HSV-2 intertypic recombinant viruses. The ultimate goal of our work on HSV is to gain enough of an understanding about the regulation of latent infection that therapeutic interventions can be devised to eliminate latent infection or prevent viral reactivation.

## Telemedicine for CMV Retinitis

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Cytomegalovirus (CMV) retinitis is a treatable infection of the retina affecting AIDS patients, and is a leading cause of blindness in many developing countries. There are currently 33.2 million people living with HIV worldwide, with the most severely affected regions being Sub-Saharan Africa, Southeast Asia and India. In many of these countries, intensive national and international efforts have led to the development of programs for HIV diagnosis and treatment. However, most of these programs have no systems in place for screening patients for CMV disease. In collaboration with investigators at Chiang Mai University Medical Center in Thailand we have begun investigating the feasibility of using telemedicine as a means of diagnosing CMV retinitis. At a tertiary care center we found that remote readers had about 90% sensitivity and 88% specificity in diagnosing CMV retinitis as compared to examining retinal specialists. We have just completed studies looking at the prevalence of CMV retinitis in a primary care HIV clinic at Nakornping Hospital as well as the efficacy of using telemedicine to screen for CMV retinitis in this primary care setting. This data is currently being analyzed. Finally, we have completed constructing and initial testing of a very low cost cellphone based camera to be used by non-Ophthalmologist to photograph the retina to screen for CMV retinitis. This camera is also being evaluated for its ability to screen patients for diabetic retinopathy, glaucoma, macular degeneration, emergency room care and retinopathy of prematurity.

Our long-term goals at this point include the further development and testing of 1) lower cost devices for imaging the retina and 2) artificial intelligence systems for screening these images for CMV retinitis, diabetic retinopathy and glaucoma without the need of a highly trained ophthalmologist.

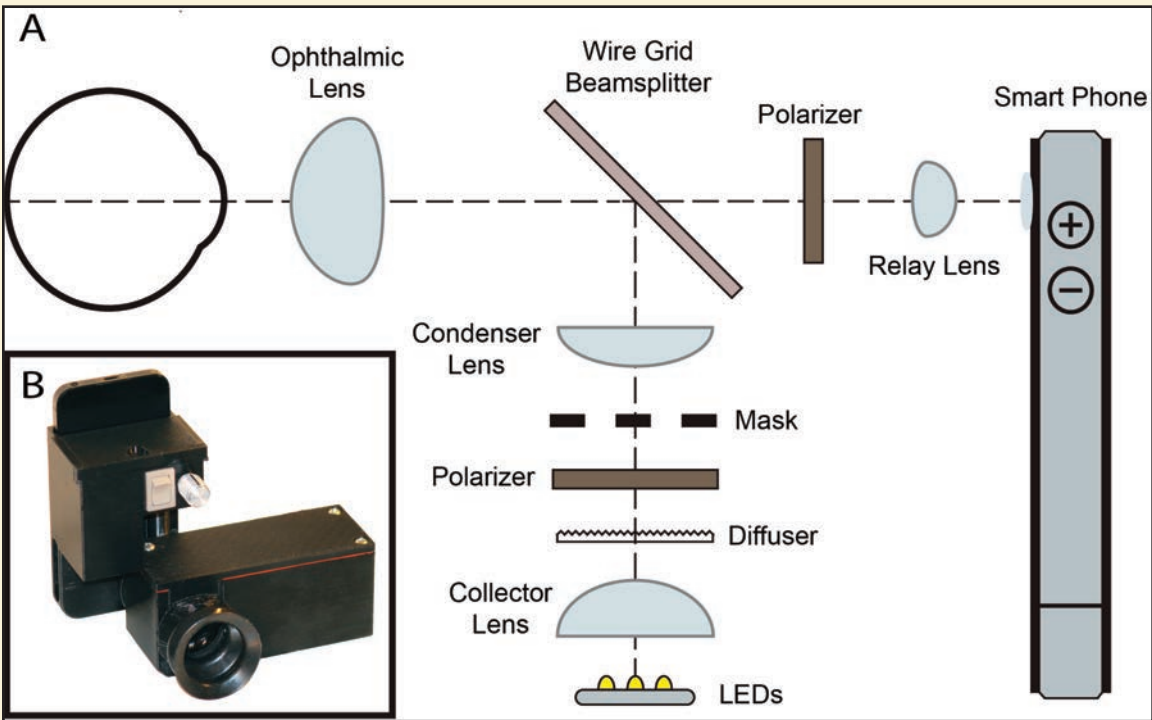


Figure 1. Mobile phone-based retinal camera schematic and prototype. (A) A schematic demonstrating the optical layout that couples the mobile phone camera to the off-the-shelf optical components. Not to scale. (B) A current prototype with the optical components housed in the ABS plastic encasing and the mobile phone inserted into the holder. Device dimensions are 14cm x 15.25cm x 9cm. To use, the device is held up to the eye of the patient so that the rubber cup shown in the figure is positioned at the orbit of the eye.

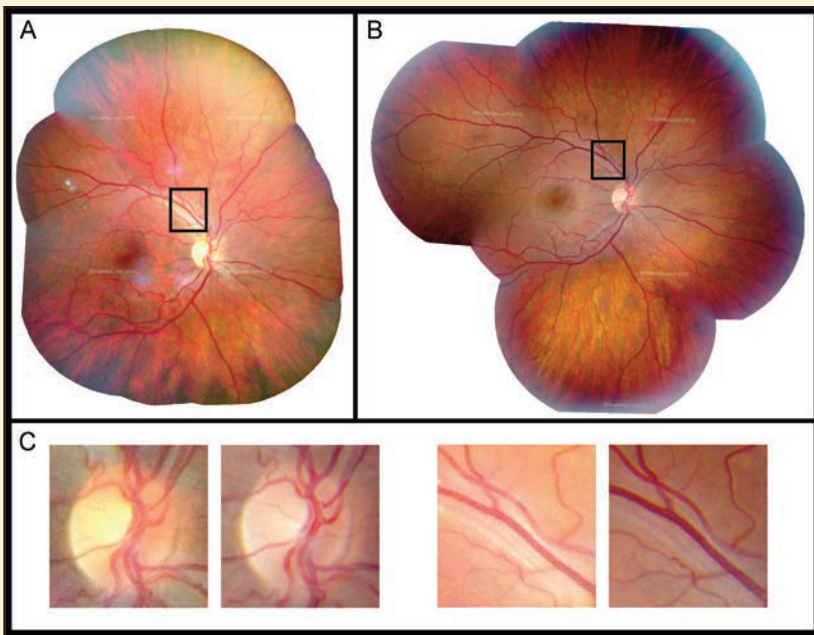


Figure 2. Comparative images of a healthy retina. (A) A wide field retinal map of a healthy retina was created from 6 fundus images taken by the Ocular CellScope using the DualAlign i2k Retina software. (B) A comparative wide field retinal map of the same healthy retina using 6 fundus images taken with the Topcon TRC-50EX retinal camera. (C) Magnified view of the optic disc and the boxed region in A & B (Ocular CellScope – OC; Topcon retinal camera – TRC)

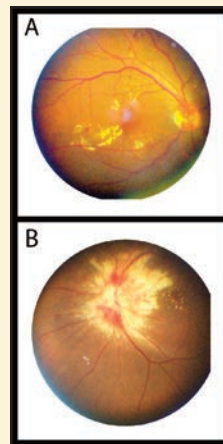


Figure 3. Retinal pathology images taken with Ocular CellScope. (A) A fundus photograph demonstrating diabetic retinopathy with exudate and dot blot hemorrhage. (B) A fundus photograph demonstrating an active CMV retinitis infection.

# DR. NANCY MCNAMARA'S RESEARCH

The prevalence of Dry Eye Disease in the United States ranges from 6 to 43.2 million people. Among these about 4 million people suffer from a true aqueous-deficient dry eye, known clinically as keratoconjunctivitis sicca (KCS). While it is well established that chronic inflammation represents the predominant driving force in KCS, the precise mechanism is unclear. To date, there is only one FDA-approved treatment of dry eye that is effective in less than 30% of patients.

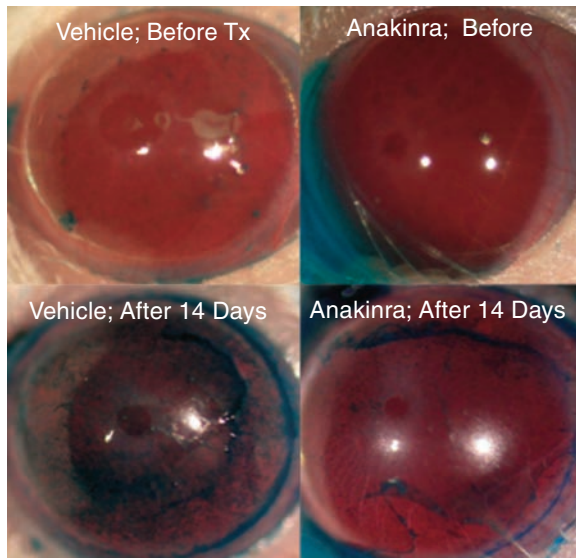


Figure 1. A 14-day course of topical Anakinra significantly decreased progression of lissamine green staining in Aire KO mice with aqueous-deficient dry eye. Top: lissamine green staining of Aire KO mice before (upper panels) and after (lower panels) treatment (Tx) with Anakinra or CMC vehicle control.

The focus of Dr. McNamara's work is to identify alternative approaches to relieve the signs and symptoms of dry eye. Using tear proteomics they identified pro-inflammatory cytokines were upregulated in the tears of patients with Sjogren's syndrome where increased protein levels of interleukin 1 alpha (IL1) and IL1 were correlated with dry eye symptoms.<sup>1</sup> Dr. McNamara's group also used the autoimmune regulator knockout mouse model (Aire KO) to test the therapeutic potential of topical IL-1R1 antagonist in restoring a healthy ocular surface. Mice treated with IL-1R1 antagonist had less ocular surface damage, increased tear secretion and reduced presence of acidic mucins in the conjunctival goblet cells (Figure 1).<sup>2</sup>

Dr. McNamara's group also identified a pathological role for macrophages in aqueous-deficient dry eye. In mice with aqueous tear deficiency, depletion of macrophages restored ocular surface integrity and normalized tear secretion<sup>3</sup> (Figure 2). In future studies, Dr. McNamara's group will explore the mechanism whereby macrophages contribute to autoimmune-mediated ocular surface disease.

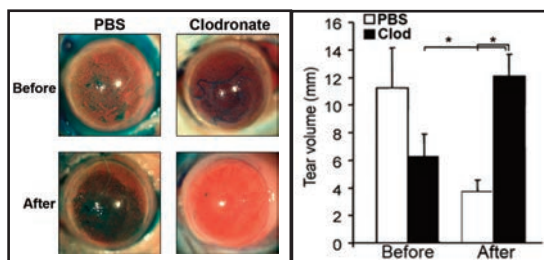


Figure 2. Depletion of macrophages with clodronate liposome (Clod) reduced corneal damage assessed by Lissamine green staining (left panels) and tear secretion by cotton thread test (right panel).



Most recently, Dr. McNamara's group identified a role for stem cells in dry eye pathogenesis. They discovered that corneal stem cells become activated in KCS and this activation drives the aberrant program of cellular differentiation that leads to ocular surface disease. They are now testing the hypothesis that ocular stem cells and Pax6 are the cellular and molecular links between chronic inflammation and pathological keratinization of the ocular surface in patients with KCS. Forced expression of Pax6 in diseased eyes normalized stem cell activity and restored the tissue phenotype (Figure 3).<sup>4</sup>

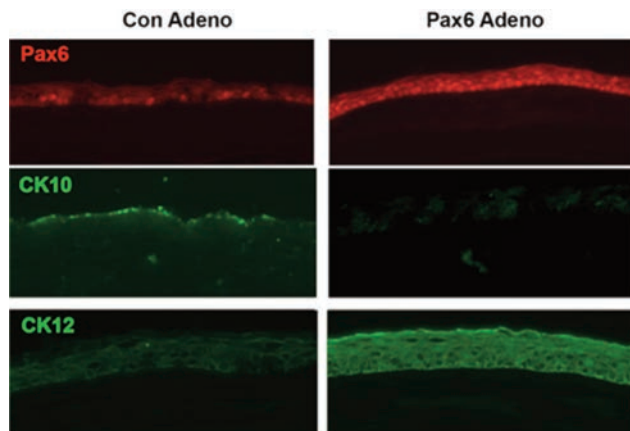


Figure 3 Pax6 adenovirus restores corneal phenotype in Aire KO mice. (A) Immunostaining of corneal transcriptional regulator Pax6 (red), epidermal cyokeratin, CK10<sup>+</sup> (green), and corneal cyokeratin, CK12<sup>+</sup> (green) in Aire KO mice 5 days after injection with Pax6-adenovirus (Pax6 Adeno) or control (Con Adeno). Aire KO mice experience a phenotype switch from corneal (CK12<sup>+</sup>) to epidermal (CK10<sup>+</sup>) lineage, leading to an altered state of differentiation that is associated with epithelial disruption and pathological keratinization. Forced expression of Pax6, restores Pax6 levels and restores corneal phenotype (CK12<sup>+</sup>/CK10<sup>-</sup>).

## Early Detection of Lung Cancer in Smokers

Cigarette smoke, containing 60 established carcinogens, increases the risk of developing lung cancer by 20-fold and is responsible for 87% of lung cancer deaths. The 5-year survival rate of lung cancer is very poor (~6-15%) mainly because symptoms of the disease do not present until it is at an advanced and incurable stage. Five-year survival rates are much higher (~67-75%) when lung cancer is detected earlier. Thus, a key to improving lung cancer survival is early diagnosis.

Dr. McNamara's lab has worked to gain a better understanding of molecular events leading to lung carcinogenesis in the smoker's airway. To accomplish this, they developed an 3-dimensional, experimental model of pseudostratified human bronchial epithelial (HBE) cells to simulate the in vivo airway. Cells are exposed to cigarette smoke using a fast, easy, and reproducible method, which offers the opportunity to perform manipulations at a molecular level. Using this model, they have shown that smoke has aberrant, tumor-promoting effects on membrane-bound mucin 1 (MUC1) and adherens junction (AJ) components E-cadherin (E-cad), -catenin ( -ctn) and p120-catenin (p120ctn).<sup>5-8</sup> MUC1 is overexpressed in many epithelial cancers (including lung cancer) where it promotes the immortality and invasion of tumor cells. Notably, the serum level of soluble MUC1-N is routinely applied as a tumor marker in the diagnosis of breast and ovarian cancer.

Dr. McNamara's lab showed that cigarette smoke induced the aberrant glycosylation of MUC1's N-terminus (Figure 4A) and that altered glycosylation provoked the early events of malignant transformation that ultimately leads to tumor foundation. Moreover, smoke provoked a time-dependent accumulation of shed glycosylated MUC1-N into the culture medium (Figure 4B), thereby mimicking mucin shedding into the blood and body cavity of human patients that are readily detectable in serum and ascites.

## DR. NANCY MCNAMARA'S RESEARCH (cont'd)

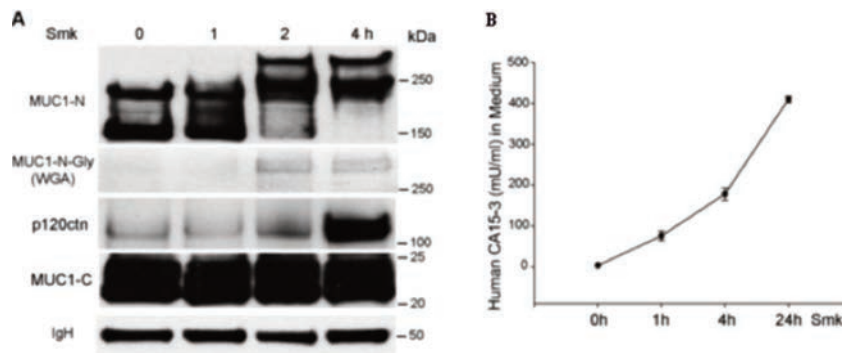


Figure 4. Smoke induced MUC1-N glycosylation and shedding in pseudostratified HBE cells. (A) Smoke stimulated a shift in molecular weight indicating aberrant glycosylation of MUC1-N. Cells exposed to smoke-concentrated medium (Smk) were harvested and immunoprecipitated using anti-MUC1-C. The immunoprecipitates were probed with anti-MUC1-N (VU4H5), anti-p120ctn, anti-MUC1-C and biotinylated wheat germ agglutinin (WGA). (B) Smoke induced time-dependent shedding of glycosylated MUC1-N. Media was collected after Smk exposure for indicated time points.

These data point to smoke-specific glycosylation of MUC1-N as an initiating event in the malignant transformation of airway epithelial cells induced by cigarette smoke. The specificity of this glycosylation event to airway cells exposed to smoke, together with the apparent functional role of glycosylation in provoking premalignant events, suggest it may provide a novel tool for screening, and perhaps even the treatment of lung cancer in smokers. Dr. McNamara's lab is working to develop a monoclonal antibody directed against the smoke-specific glycosylation domain of MUC1-N (referred hereon as SmkMab). SmkMab will differ from MUC1 antibodies currently in clinical use and development because it will be generated using endogenous MUC1-N on primary, human bronchial epithelial cells isolated from the in vivo airway and aberrantly glycosylated by cigarette smoke. Following its development, they will explore SmkMab's diagnostic potential by examining MUC1-N glycosylation in sera and lung tissue specimens of non-smokers, long-term smokers and long-term smokers with lung cancer provided by the Lung Tissue Research Consortium.

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Top: Lighting deepas in the Meenakshi Temple in Madurai, India.

Bottom: Dr. Keenan examines a woman in Nepal.



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The Insignia of the Francis I. Proctor Foundation for Research in Ophthalmology is the ancient Egyptian symbol known as the "Wedjat Eye" or "the sound eye of Horus." The symbol is derived from the ancient myth in which the eye of Horus was torn into fragments by the wicked god Seth. Later the god Thoth miraculously restored the injured eye by joining together its parts, whereby the eye regained its title as the "sound eye."

As such the Wedjat Eye represents the myth of the restoration of the eye, its parts, its precision, and the skill and art needed for its restoration. It is a symbol of great antiquity, familiar to the world's first ophthalmic specialists of Egyptian medicine."