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 Santa 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 STATEMENT
The mission of the Foundation is the prevention of blindness world wide through research and teaching focused on infectious and inflammatory eye disease.

EXECUTIVE SUMMARY
The past several years have been an exciting time at the Proctor Foundation as our relatively young faculty matures into a seasoned group of collaborative clinicians educators and scientists, and as we continue to remodel and strengthen our infrastructure, all the while staying true to our mission firmly established by those before us: Drs. Thygeson, Hogan, O’Connor, Nozik, Ostler and Dawson.

Our International Programs, headed up by Tom Lietman, are thriving with very active research programs in Niger, Ethiopia, India, and Thailand. The focus of these programs is on effective diagnosis and treatment of trachoma, fungal keratitis, non-infectious uveitis, acanthamoeba keratitis, and CMV retinitis. And through their success the trachoma programs have even extended to cover malaria and childhood mortality.

In the labs our faculty are developing molecular assays for acanthamoeba keratitis, working out the mechanisms behind epithelial keratinization in dry eye disease, investigating the mechanisms behind corneal scar formation and developing novel in vitro methods for studying neuronal infection with herpes simplex virus. And our UC Berkeley colleagues have pushed forward the frontiers on our understanding of corneal lymphangogenesis and pseudomonas keratitis.

In the clinics our faculty are carrying out clinical investigations on uveitis, infectious keratitis, corneal epithelial wound healing, meibomitis and ocular pain, a component of the Foundation that has grown over the past 5 years and which is tightly coupled to active growth of the Proctor Medical Group and hiring of Sally Tsang as our Practice Manager.

The past year, however, has not been without its challenges and sadness. In addition to further financial cutbacks by the NIH and the University of California, we learned of the untimely passing of Chandler Dawson, a true gentleman and past Director of the Foundation. To me, tributes to Dr. Dawson on the Proctor listserv not only served to forge a lasting memory of the man who mentored many of us, but also demonstrated the strength of the Proctor academic community throughout the world. From many conversations that I had with Chan in his later years I can tell you that he was very proud of how the Proctor Foundation had evolved with the times.

All my best wishes for a wonderful 2013.

Sincerely,

Todd P. Margolis, MD, PhD
Research

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
- Clinical practice guidelines

Training

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.

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 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.
The Proctor Clinical Diagnostic Laboratory is certified by the State of California and CLIA for specialized bacterial, viral, and cytologic, tests including molecular diagnostic tests. Dr. Todd Margolis is Director of this laboratory. Vicky Cevallos is the Senior Clinical Laboratory Technical Specialist, and Cathy Donnellan is a Technical Specialist.

Vicky Cevallos  
Sr. Clinical Laboratory Technical Specialist

Cathy Donnellan,  
Clinical Laboratory Technical Specialist

Josephine Gesulga  
Lab Assistant
IV. RESOURCES

A. 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.

1. 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.

2. 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.

3. HARRY WILLIAM HIND LIBRARY: Room PF-314, 95 Kirkham Street, which serves as a library, conference room, and seminar room.

4. ELIZABETH C. PROCTOR LIBRARY: Room S318, Medical Sciences Building

B. ENDOWMENT

The F.I. Proctor Foundation endowment provides base support for the Foundation. As of June 30, 2012 the endowment had a market value of $35,553,813, which represents a 6% decrease over the prior year. Other endowment funds used to support foundation activities 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
C. Grants and Contracts

Grants and contracts are the major source of funds supporting expenses and personnel costs associated with research projects. In 2011-2012, $3,484,331 was available in direct costs to the Foundation from grants and contracts. This represents an increase of 2% from the prior year. Federal awards funded 73% 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 Pratt Foundation, the Harper-Inglis Fund Memorial Fund for Eye Research, the J. Cox Fund, 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, the Tumori Foundation, Brooks Family Foundation, the IBM International Foundation, and individual donors.

D. 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.

PERSONNEL

- BOARD OF GOVERNORS
- FACULTY
- STAFF
- PROCTOR FELLOWS

Board of Governors

The Board of Governors is comprised of three members:

Chancellor, UC San Francisco
Susan Desmond-Hellmann, MD, MPH
(Represented by Executive Vice Chancellor and Provost, Jeffrey Bluestone, PhD)

Chair, Department of Ophthalmology, UC San Francisco
Stephen D. McLeod, MD

Independent Governor
John P. Whitcher, MD, MPH
F.I. PROCTOR FACULTY
FRANCIS I. PROCTOR FACULTY
Faculty with Primary Appointments in the F.I. Proctor Foundation

DIRECTOR
Todd P. Margolis, MD, PhD
Professor, Department of Ophthalmology and Director Francis I. Proctor Foundation

Nisha Acharya, MD, MS
Associate Professor, Department of Ophthalmology and the Francis I. Proctor Foundation

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

Chandler R. Dawson, MD
Professor Emeritus, Departments of Ophthalmology, Epidemiology & Biostatistics, Microbiology, and the Francis I. Proctor Foundation

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

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

Thomas M. Lietman, MD
Professor, Departments of Ophthalmology, Epidemiology and Biostatistics, and the Francis I. Proctor Foundation
Niger

Left Photo: Anthropometrists measure the mid-upper arm circumference of a study participant.

Right Photo: A team member registers a study participant.

F.I. Proctor Faculty

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

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

Bennie Jeng, MD
Associate Professor and Co-Director of Cornea Service, Department of Ophthalmology and the Francis I. Proctor Foundation, and Chief of Ophthalmology San Francisco General Hospital

Stephen McLeod, MD
Chairman, Department of Ophthalmology, Theresa M. Caygill, Wayne M. Caygill Endowed Chair and Professor of Ophthalmology and the Francis I. Proctor Foundation

Ayman Naseri, MD
Associate Professor of Ophthalmology and the Francis I. Proctor Foundation, and Chief of Ophthalmology, San Francisco V.A. Medical Center

Julius Schachter, PhD
Professor, Departments of Laboratory Medicine, Epidemiology & International Health, and the Francis I. Proctor Foundation

Clinical Faculty WOS Appointments

Kenneth Chern, MD, MBA
Assistant Clinical Professor, Department of Ophthalmology and the Francis I. Proctor Foundation

Douglas Holsclaw, MD
Assistant Clinical Professor, Department of Ophthalmology and the Francis I. Proctor Foundation

Robert Nasser, MD
Assistant Clinical Professor, Department of Ophthalmology and the Francis I. Proctor Foundation

Robert Kim, MD, MBA
Associate Clinical Professor, Department of Ophthalmology and the Francis I. Proctor Foundation
Faculty with Primary Appointments at Other U.C. Campuses

Lu Chen, MD, PhD
Assistant Professor of Optometry, U.C. Berkeley

Suzanne M.J. Fleiszig, OD, PhD
Professor of Optometry and School of Public Health, U.C. 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

Proctor Fellows 2012-2013

Elizabeth Grace, MD
Cornea Fellow

Vincent Lam, MD
Uveitis Fellow

Waroonchat Issariyapat, MD
International Research Fellow

Jennifer Rose-Nussbaumer, MD
Cornea Fellow
Admin Staff

Proctor Staff

Leslie Aguayo
Administrative Director

Joey Bernal
Fellows Affairs and Communications Manager

Pauline Chin
Financial Manager

Connie Chong
Accounting and Payroll Assistant

Susan Ford
Assistant, International Programs

Liz Obana
Accounting Assistant
Proctor International Programs Staff and Personnel

Stephanie Chin
Research Associate

Arezu Haghigi
Medical Student

Gelareh Homayounfar
Medical Student

Earnest Maningding
Medical Student

Michael Melgar
Medical Student

Natalie Nardone
Research Coordinator

Kieran O’Brien
Research Coordinator

Kathryn Ray
Statistician

Nicole Stoller
Study Coordinator
Proctor International Programs Staff and Personnel (cont’d)

Zhaoxia Zhou
Study Coordinator

Lina Zhong
Laboratory Assistant

Sun Yu
Study Coordinator

Catherine Sun
Medical Student

Zhaoxia Zhou
Study Coordinator

Wayne Enanoria, PhD
Research Scientist

Seth Blumberg, MD, PhD
Visiting Fellow

Daozhou Gao, PhD
Postdoctoral Fellow

Nick Sippl-Swezey
Associate Specialist

Fengchen Liu, MS
Associate Specialist

Porco Lab Personnel
McNamara Lab Personnel

Feeling Chen
Research Associate

Ying Ting Chen
Postdoctoral Scholar

Marianne Gallup
Senior Research Associate

Lili Zhang
Postdoctoral Scholar

Trinka Vijmasi
Assistant Specialist

Heintz Lab Personnel

Nicole Giordani
Postdoctoral Fellow

Aye Aye Ma
Research Associate
Proctor Medical Group Staff

Veronica Alvarez
Patient Services Coordinator

Nancy Lee, OD
PROSE Senior Optometrist

Salena Lee, OD
Senior Optometrist

Earnestine Reagan
Billing Specialist

Delilah Trail
Medical Record Assistant

Sally Tsang
Practice Manager

Ethiopia

Left Photo: After an examination, study participants return home.

Right Photo: Local village women singing and dancing.
**RESEARCH**

- Overview
- Todd Margolis’s Research
- Nisha Acharya’s Research
- Matilda Chan’s Research
- Ira Wong’s Research
- Suzanne Fleiszig’s Research
- Lu Chen’s Research
- David Hwang’s Research
- Bennie Jeng’s Research
- Nancy McNamara’s Research
- Tom Lietman’s Research
- Jeremy Keenan’s Research
- Travis Porco’s Research
- Bruce Gaynor’s Research

**OVERVIEW**

**Todd Margolis, MD, PhD**  
Ralph and Sophie Heintz Laboratory

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 development and evaluation of molecular diagnostics for infectious eye disease. A third line of investigation focuses on the use of telemedicine to screen AIDS patients for CMV retinitis in developing countries.

**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.

**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, smoking and uveitis, and clinical trials on corneal ulcers 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 focuses on defining molecular and cellular mechanisms of corneal inflammation and transplantation immunity, particularly those related to lymphatic and blood vessel formation and regulation.

Suzanne M.J. Fleiszig, OD, PhD

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 bacteria interact with the epithelial cells that line the surface of the cornea on which contact lenses are placed.

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 3-year, federally-funded clinical trial investigating a novel compound for the treatment of persistent epithelial defects. 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. However, there is no treatment that can be relied upon to consistently improve outcomes in PED and to relieve
OVERVIEW (cont’d)

Bennie H. Jeng, MD (cont’d)

the severe disability experienced. The purpose of this study is to evaluate the safety and efficacy of NEXAGON, a novel therapeutic agent, in the healing of PED from any of the above listed causes. This compound would potentially add a powerful non-surgical treatment option for a condition that is difficult to treat and that often results in poor visual outcomes.

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 Myanmar; and (3) diagnosis and treatment of acanthamoeba keratitis.

Thomas M. Lietman, MD

Dr. Thomas Lietman is investigating what community-treatment strategies are most effective in eliminating trachoma, in collaboration with the Proctor trachoma team. 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. These studies are in the Amhara Zone of Ethiopia and the Mata-maye District of Niger, in areas where 1/2 of children in a village may have active trachoma infection. Dr. Lietman and Dr. Nisha Acharya are running 2 large fungal ulcer trials in collaboration with the Aravind Eye Care System in South India.

Stephen 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.
OVERVIEW (cont’d)

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 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.

Ayman Naseri, MD

Dr. Naseri has two primary research interests: cataract surgery and resident education. His work within cataract surgery has been focused primarily on the prophylaxis of endophthalmitis, and specifically on the cost implications of antibiotic prophylaxis. The next phase of his collaboration with Dr. Travis Porco is to complete a cost-utility analysis of endophthalmitis prophylaxis. With respect to resident education, Dr. Naseri is particularly interested in outcomes of resident-performed surgery. By studying the results of resident-performed surgery, he hopes to improve the care of patients while also improving resident surgical education.

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.

Ethiopia

Left Photo: Exam station.

Right Photo: During sample collection training, Mike Seider plays the role of a study participant while an Ethiopian team member demonstrates how to properly flip an eyelid.
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 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. Through the use of HSV-1/HSV-2 intertypic recombinants we have found that a fragment of the viral LAT in HSV-2 clearly dictates specificity for preferential productive viral infection in A5+ neurons and latent infection in KH10+ neurons. A major focus of current research is to use our in vitro system to study the molecular mechanisms by which this cis acting mechanism regulates both the differential permissiveness of A5+ and KH10+ neurons for productive infection in vitro as well as the establishment of latent infection in vivo. 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.
In the past we developed molecular assays to aid in the diagnosis of HSV1, HSV6, HSV7, VZV, CMV, toxoplasmosis eye diseases and have moved these assays into the clinical laboratory at the Proctor Foundation.

We are currently using molecular diagnostics to help determine the cause of SHAPU, a seasonal panuveitis of children in Nepal. We have recently reevaluated optimal conditions for detecting VZV in corneal samples and for acanthamoeba keratitis.

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 also found that patients presenting to the eye clinic in Chiang Mai had much more advanced, active disease, including a very high prevalence of bilateral eye disease and frosted branch angiitis at the time of their presentation as compared to what is seen in developed countries.

We currently have ongoing 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. Patient recruitment is complete and we are now evaluating the data. We are also evaluating the ability of non-medical professionals in both the US and Thailand to evaluate the digital fundus photos. 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.
HEINTZ (cont’d)
Telemedicine for CMV Retinitis

If successful we hope to place the job of take screening for CMV retinitis into the hands of HIV care providers. In establishing telemedicine screening centers we believe that will we be able to provide improved care for more individuals as well as establish a network of centers for future studies on the most cost-effective ways of managing CMV retinitis in patients that are initiating HAART. 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 diagnosing CMV retinitis without the need of a highly trained ophthalmologist.

DR. NISHA ACHARYA’S RESEARCH

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

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. The FAST pilot is a randomized, masked clinical trial comparing methotrexate to mycophenolate as initial therapy in patients requiring immunosuppressive therapy. Eighty patients have been enrolled in the pilot study at Aravind Eye Hospital in Madurai and Coimbatore, and results will be available in 2012. In 2012, we will be starting a larger trial to compare these therapies, as well to assess rates of success on the second therapy after failing the first. This trial will enroll patients at the Proctor Foundation, Casey Eye Institute in Oregon, and at Aravind Eye Hospital in India.
ACHARYA (cont’d)  
Multi-Center Uveitis Steroid Treatment Trial (MUST)  
N. Acharya, I.G. Wong, T. 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 on a protocol committee to help design future trials to be conducted with the MUST network.

Epidemiologic Studies on Uveitis  
N. Acharya, N. Nardone, W. Enanoria, T. Porco and V. Tham

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. Another area of research is investigating risk factors for developing ocular inflammation, including exposure to cigarette smoke. The smoking study is being done in collaboration with Kaiser Hawaii and Dr. Viven Tham, a Proctor alumna.

Predicting and Improving Clinical Outcomes in Corneal Ulcer Patients  
N. Acharya, T. Lietman, S. McLeod, J. Whitcher, K. Ray, C. Oldenburg, M. Zegans, S. Fleiszig, M. Srinivasan and other collaborators at Aravind Eye Hospital in South India

There is ongoing controversy regarding the use of steroids in treating bacterial corneal ulcers. Additional data is needed to help clinicians understand the risks vs. benefits. The Steroids for Corneal Ulcers Treatment (SCUT) trial is a randomized, placebo-controlled trial enrolling patients at the Proctor Foundation at UCSF, Aravind Eye Hospital in South India and Dartmouth-Hitchcock Medical Center. The main objective of SCUT is to study the effect of topical steroids on bacterial corneal ulcers. This study of 500 patients was completed in 2011. Overall, there was no difference in visual acuity outcomes between patients receiving adjunctive corticosteroids or not, but steroids were associated with better visual outcomes in patients presenting with the most severe ulcers. Ancillary studies are now being conducted to compare baseline characteristics and clinical outcomes by organism (Pseudomonas aeruginosa vs. all others), and by genetic differences (invasive vs. cytotoxic P. aeruginosa).

Mycotic Ulcer Treatment Trials  
M. Chan, J. Li, A. Bertrand, J. Lin, I. Maltseva, S. Rosen, Z. Werb

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 aims to determine which topical antifungal treatment, voriconazole or natamycin, results in better visual acuity in patients with fungal corneal ulcers. MUTT 2 is studying whether adding oral voriconazole to topical voriconazole improves clinical outcomes in severe fungal ulcers. Following completion of a 120 patient pilot study, we have started both MUTT 1 and 2 multicenter trials. MUTT 1 was completed in 2012, and MUTT 2 is still ongoing.
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.

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.
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 (Figure 2).

The inflammation from uveitis can lead to sight-threatening complications. In particular, glaucoma and cataract formation are the leading complications.

We have studied the complications occurring in a cohort among the 3 million Kaiser Permanente Health Care program members of Northern California over a five year period. Almost 4% of the cases had uveitic glaucoma and about 5% had combined mechanism glaucoma and these patients were more often diagnosed with chronic uveitis than acute uveitis. Cataracts affected 6% of the uveitis patients, cystoids macular edema 3% and epiretinal membranes 0.5%. Fortunately, retinal detachments, phthisis, subretinal neovascularization and vitreous hemorrhage occurred only in a handful of cases.

Clinical Trials

Dr. Wong continues to participate in the Multicenter Uveitis Steroid Treatment Trial. This prospective, randomized clinical trial compares current steroid and immunomodulatory therapy to an intraocular implant that releases steroid over 30 months.

Novel Drug Delivery Device for Ocular Surface Disorders

Dr. Wong is currently developing a novel device to deliver therapeutic agents to the ocular surface. In this device the fluid stored in a reservoir is delivered to the ocular surface using a programmable pump providing intermittent or continuous drug therapy.
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.**
   - This long standing aim is focused on understanding the molecular factors that prevent bacterial penetration of 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 the system is compromised. Traditionally researchers have used "infection models" to study tissue interactions with bacteria. These involve deliberately compromising the tissue to induce enable susceptibility to infection. During the past few years, the Fleiszig lab has worked towards developing new models that do not bypass the need for bacteria to penetrate the epithelium, which is the event the laboratory seeks to understand. The Fleiszig laboratory has also successfully developed several in vivo and in vitro methods that together enable epithelial cell penetration by bacteria to be studied. In addition, novel imaging technologies are now enabling bacterial interactions with the epithelium to be imaged in living intact eyes.

Utilizing these technologies, in the past year the laboratory has been working towards determining virulence factors used by bacteria to traffic through the epithelium when it becomes susceptible. New data show that the type III secretion system, a toxin delivery system that bacteria use to inject proteins across host cell membranes, is critical for bacteria to penetrate the corneal epithelium.

- In the past year, the laboratory has continued its efforts to develop therapies to prevent any type of infection of any body site based on eye derived molecules. The first year of the project revealed that human tear fluid modifies the biology of the corneal epithelial cells to enhance their resistance to microbes. In the past year, the laboratory worked on understanding the mechanisms by...
which tear fluid modifies epithelial cell immunity. Data show that tear fluid alters the expression of microRNAs, a rapid method by which gene expression can be modulated within tissues. Further, the laboratory has discovered that the corneal epithelial cells express a previously unknown class of antimicrobial peptides. The existence of these molecules helps to understand how epithelia resist infection, and could be used to develop new therapies to prevent or treat infection. Laboratory members who have contributed to this work are Drs. Connie Tam and James Mun, and UC Berkeley undergraduate student volunteers Gary Chan and Jong Hun Kim.

- Another project in the laboratory is to understand the relationship between dry eye and susceptibility to infection. The knowledge gained is furthering our understanding of how the eye normally defends itself against infection, while also contributing to our knowledge about how dry eye impacts the biology of the ocular surface. New data show that dry eye in a healthy mouse does not predispose the eye to infection, and that this is related to upregulation of known defense factors. This project is being conducted by Assistant Specialist Susan Heimer, who is also an Assistant Professor at Touro University-California College of Pharmacy. She is being assisted by undergraduate volunteer Kelsey Li-Chinn Liu.

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

The goal of the project is to determine the mechanisms used by invasive P. aeruginosa to survive inside corneal epithelial cells, and the relevance of intracellular survival to disease. Previously, the laboratory had found that ExoS, a protein encoded only by invasive P. aeruginosa strains, enables this capacity involving its ADP-ri activity. New data show ExoY, another protein also secreted by invasive strains into host cells can also participate, but that it uses a completely different enzymatic (adenylate cyclase) activity. Other data reveal new insights into how the host responds to internalization by bacteria; for example that bacteria lacking the capacity to secrete these molecules are targeted to degradative compartments inside cells where they do not thrive.

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

A project nearing completion is an offshoot of the SCUT (Steroids in Corneal Ulcer Therapy) study being conducted at the Proctor Foundation in collaboration with a number of other international organizations. The role of the Fleiszig Laboratory is to classify P. aeruginosa strains isolated from infections to determine if they are invasive or cytotoxic. The hypothesis is that invasive and cytotoxic strains, which differ in how they interact with cells, are associated with different treatment outcomes in patients, as previously found by the Fleiszig laboratory in a study utilizing mice. Lab members 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. Chen’s research focuses on the molecular and cellular mechanisms of ocular inflammation and transplantation immunity, particularly those involved in lymphatic and blood vessel development and regulation.

Her projects include the following research efforts which have led to a number of publications during the last year.

1. **Role of VLA-1 in lymphangiogenesis and high-risk transplant immunity**
   
   It has been found that VLA-1 directly mediates processes of lymphangiogenesis. Its gene depletion suppresses several functions of lymphatic endothelial cells in vitro. Moreover, anti-VLA-1 treatment inhibits corneal inflammatory lymphangiogenesis and transplant rejection.

2. **Role of VEGFR-3 in lymphangiogenesis and high-risk transplant immunity**
   
   It has been shown that VEGFR-3 plays a significant role in high-risk corneal transplant immunity. Its blockade modifies high-risk host beds and promotes transplant survival.

3. **Interaction between lymphatic factors**
   
   Several studies have been performed to demonstrate that lymphatic factors interact with each other. Combined blockade of VEGFR-3 and VEGFR-2 suppresses both early- and middle-stage lymphangiogenesis, and combined blockade of VEGFR-3 and VLA-1 markedly promotes 90% survival of high-risk transplants. A strong association is also identified between high-risk transplant rejection and high-degree of lymphangiogenesis in grafted corneas.

4. **Lymphangiogenesis in infant corneas**
   
   Infant corneas reject transplants at accelerated rate. It has been demonstrated that corneal lymphangiogenesis, hemangiogenesis, and macrophage infiltration occur at a greater scale in infants than in adults.

5. **Lymphatic valve formation during corneal inflammatory lymphangiogenesis**
   
   It has been discovered, for the first time, that corneal lymphatic vessels develop luminal valves during inflammatory lymphangiogenesis. These valves increase in number and mature in structure as corneal lymphangiogenesis proceeds. The fundamental roles of these valves in lymphatic drainage and transplantation immunity will be further studied.

6. **Spontaneous lymphatic formation and regression during corneal development**
   
   It has been discovered, for the first time, that the cornea is not devoid of lymphatic vessels from its embryogenesis. Spontaneous lymphatic formation and regression occur in this tissue before it matures. Given that lymphangiogenesis can be reactivated in adult cornea after a pathological stimulation, the cornea is the first tissue ever identified to possess a full range of plasticity in lymphatic formation and regression.
7. LYVE-1 in hyaloid vascular system
LYVE-1 is the most widely used marker for lymphatic vessels. It has been found that this molecule is expressed in the transient hyaloids vascular system in developing eyes. The LYVE-1+ cells co-express F4/80, indicating a macrophage lineage. This study identifies a new and natural model to study functions of the LYVE-1 pathway.

8. Podoplanin in retinal pigment epithelial cells
Podoplanin is a transmembrane protein which has been widely used as a molecular marker for lymphatic endothelial cells. It has been demonstrated that this molecule is highly expressed in retinal pigment epithelial cells and plays a significant role in several functions, including cell proliferation and cell-cell contact.

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.
The Ophtec 311 intraocular lens is a large diameter PMMA posterior chamber intraocular lens that has a rim that is colored to simulate an iris.

This lens was designed to treat patients who have missing irides for various reasons in order to reduce the patients’ symptoms of glare. We have designed a prospective observational study to evaluate the safety of this device, as well as the patient outcomes. We are currently enrolling for this trial.

Postoperative infection is a rare but serious complication of penetrating keratoplasty (PK). Optisol-GS is still the most commonly used corneal storage medium in the United States; however it currently does not include an antifungal additive. In this study, we will evaluate the efficacy of adding voriconazole or amphotericin B to Optisol-GS corneal storage media in reducing viable fungal colony counts and to assess the optimal concentration of voriconazole or amphotericin B needed to achieve eradication of viable fungal colonies. We will also evaluate the potential impact of voriconazole or amphotericin B in the storage media on the health of the donor corneal endothelium during storage.

Recently, the Northern California Kaiser Permanente Health System made autologous serum an approved and covered benefit. This has allowed for patients who are not as severe in the disease process to receive the potential benefits of autologous serum since cost is not a factor. This study evaluated all of the patients in this population who received autologous serum for treating their ocular surface disease, and the results suggest that it is efficacious.

Published epidemiologic studies have evaluated various ocular diseases, but all in insured populations (e.g. Kaiser Permanente Health Care System, Olmstead County, Veteran’s Affairs Medical Centers). Few, in any, studies have focused on the uninsured population in the United States. We have investigated the epidemiology of corneal ulcers and of uveitis in the uninsured population of San Francisco. Preliminary results suggest that the incidences of these disorders is lower than in other populations.
Blepharitis is a chronic disease for which there are numerous potential treatment modalities. We performed a retrospective chart review to evaluate the safety and efficacy of oral azithromycin in the treatment of blepharitis, and our preliminary results suggest both safety and efficacy.

One of the recent advances in endothelial keratoplasty is the utilization of eye bank personnel to pre-cut the donor cornea tissue. This costs more, but saves surgeon and operating room time. We undertook a study to determine the cost-effectiveness of eye bank-cut versus surgeon-cut tissue.

The recent increase in popularity of implantation of the Boston Type I keratoprosthesis (KPro) has underscored the lack of a reliable method of intraocular pressure (IOP) measurement for these cases. While corneal pathology may render corneal-based IOP readings unreliable, limbal and scleral measurements may be of benefit. This study examined whether scleral IOP measurements can aid in estimating true IOP. Similar analyses were performed before and after KPro placement to ascertain if measuring scleral IOP is a reliable alternative to measuring true IOP in KPro eyes.
Pathological keratinization of the ocular surface, also known as squamous metaplasia (SQM) causes a debilitating and vision-threatening disease that can eventually progress to complete corneal opacification and blindness (Figure 1).

It occurs in severe, autoimmune-mediated disorders, such as Stevens-Johnson syndrome (SJS), ocular cicatricial pemphigoid (OCP) and Sjögren’s syndrome (SS). These diseases present some of the most challenging clinical cases facing eye care today and targeted therapies that can be used as treatment alternatives to systemic immunosuppression are not currently available.

Very little is known about the specific mechanisms mediating SQM in the setting of autoimmunity. Over the past several years, Dr. McNamara and her colleagues have worked to identify mediators of chronic inflammation that set off the process of keratinization. They identified small proline rich protein 1B (SPRR1B), a protein specific to keratinized epithelia, as a surrogate biomarker for keratinizing SQM in human patients with SS that was highly correlated with clinical disease severity and inflammation (Figure 2). Using tear proteomics they identified cytokines upregulated in the tears of patients with active ocular cicatricial pemphigoid and discovered that increased protein levels of interleukin 1 alpha (IL1α) and IL1β were correlated with dry eye symptoms in SS patients.
In an animal model of autoimmune dry eye, ocular SQM was dependent on autoreactive CD4+ T cell infiltration and local signaling via the IL-1 receptor. Macrophages are a major source of IL-1 during inflammation and Dr. McNamara’s group identified a pathological role for macrophages in autoimmune dry eye. They depleted macrophages using clodronate liposomes both locally, via subconjunctival injection, and systemically, via intraperitoneal injection. In mice with autoimmune dry eye, subconjunctival clodronate restored ocular surface integrity while systemic treatment normalized tear secretion. These studies suggested that depletion of macrophages in the setting of autoimmune dry eye significantly reduced inflammation and ocular damage while increasing tear secretion (Figure 3). In future studies, Dr. McNamara’s group will explore the mechanism whereby macrophages contribute to autoimmune-mediated ocular surface disease and the usefulness of modifying macrophage function or blocking their recruitment as a novel treatment strategy.

Most recently, Dr. McNamara’s group identified a role for stem cells in SQM pathogenesis. They discovered that corneal stem cells become activated in SQM disease and this activation drives the aberrant program of cellular differentiation that leads to SQM. Altered stem cell activation appears to occur when corneal cells lose their master regulator, Pax6. They are testing the hypothesis that ocular stem cells and Pax6 are the cellular and molecular links between chronic inflammation and ocular SQM disease. In preliminary studies, forced expression of Pax6 in diseased eyes using adenoviral transfer normalized stem cell activity and restored the tissue phenotype. The biological significance and therapeutic implications of this work are evident and strategies geared to restore ocular health at the stem cell level may prove helpful in the treatment of autoimmune diseases that promote ocular surface disease.
Dr. McNamara’s experience in the area of autoimmune ocular surface disease extends into the clinical arena through her work with SICCA. As a SICCA investigator since 2006, she collects clinical data and biospecimens for the Sjögren’s Syndrome Registry and participates in the preparation of scientific manuscripts. Most recently, the SICCA group established important associations of the labial salivary gland biopsy focus score with phenotypic ocular and serological components of SS, as well as developing new classification criteria for the diagnosis of SS.

Smoking represents the single most important carcinogenic exposure and is the leading cause of cancer-related mortalities. An estimated 219,440 Americans were diagnosed with lung cancer in 2009, 87% of which were directly attributable to cigarette smoke. In order to identify drug targets that can be exploited by pharmaceutical companies to alleviate and/or prevent lung cancer caused by tobacco smoke, Dr. McNamara’s lab uses a novel, 3-dimensional experimental model of stratified bronchial epithelial cells to simulate the in vivo airway. Cells are exposed to smoke using a fast, easy, and reproducible method, which offers the opportunity to perform manipulations at a molecular level. Using this model, they have identified an essential role for structural units that maintain the polarity of airway epithelial cells in the pathogenesis of lung cancer. Membrane-bound mucins on the apical cell surface and sub-apical junctional complex components E-cadherin, β-catenin and p120 catenin, establish a structural barrier that protects the airway from infectious, inflammatory and noxious stimuli (Figure 4). As an early step in tumorigenesis, tobacco smoke disrupts cell-cell interactions, liberating β-catenin and p120 catenin from their junctional complexes. Once liberated, catenins function as tumor promoting oncogenes through their interactions with the cytoplasmic tail of MUC1 (MUC1-CT). MUC1-CT chaperones β-catenins to the nucleus where it turns on pro-tumor genes in response to smoke, while 120 catenin promotes migration of airway epithelial cells. In addition to its role in cell migration, p120 catenin interacts the MUC1-CT to induce the transformation of normal mucosal epithelial cells to tumor cells. Using a MUC1-CT blocking peptide, PMIP, the laboratory was able to restore polarity of the airway mucosa and prevent early events that promote tumor formation. A deeper understanding of smoke-induced cell transformation and migration may provide a platform for screening new drug candidates that suppress tumor formation, progression and migration in metastatic disease.
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, may provide useful information, but will take years to complete and may be prohibitively expensive. Our research focuses on the use of mathematical models to determine 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 (see below) 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 *C. trachomatis*, azithromycin 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, Lietman, and Cyrus Maher have used mathematical models of chlamydia and streptococcus transmission to estimate the amount of drug resistance caused by trachoma programs.

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 TANA 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 that annual treatments. Future studies will determine if infection will return after treatments are discontinued.

We are just starting a new research program funded by the Gates Foundation which determines whether complete elimination in the entire community is possible by only treating a core group of children. This 3-year study is taking place in Matamaye District, Niger, in collaboration with the Programme National de Lutte Contre la Cécité.

In our Ethiopian trachoma studies, we also monitored 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 of trachoma is not a lethal disease. We are in the process of setting up a community-randomized clinical trial to confirm this reduction in mortality. This trial will need to be far larger than the previous study, and be performed in an area with ~400,000 individuals.

Fungal Ulcer treatment: the Mycotic Ulcer Treatment Trials

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. For example, they make up 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 of 120 ulcers, funded by That Man May See, and are in the midst of two large, NIH-funded trials of 600 cases. The Aravind Eye Hospital in Tamil Nadu is the ideal partner for this project.
Dr. Jeremy Keenan's Research

Optimal Trachoma Control after Mass Antibiotic Distributions

Trachoma, caused by repeated ocular chlamydial infection, is the leading cause of infectious blindness worldwide.

The WHO recommends repeated mass antibiotic treatments for trachoma, and researchers from the Proctor Foundation, led by Dr. Tom Lietman, are currently conducting clinical trials in Ethiopia to determine the best strategy for mass treatments. We are currently studying several ancillary aims from these trials. For example, we found that an RNA nucleic acid amplification test is a more sensitive indicator of ocular chlamydial infection than a DNA test. Using this RNA test, we found that an important risk factor for persistent ocular chlamydial infection was lack of treatment with mass antibiotics—arguing for the importance of antibiotic treatment programs for trachoma elimination. In the upcoming year, we will assess the cost effectiveness of various treatment strategies for trachoma, and further study the role of mass azithromycin distributions for childhood mortality.

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. Along with Dr. Todd Margolis and researchers at a district hospital in Chiang Mai, Thailand, we are testing whether an HIV clinic can use telemedicine to identify CMV retinitis. Another option would be training HIV providers how to use an indirect ophthalmoscope to visualize the retina. In a study in Myanmar, we found that non-ophthalmologists were able to effectively diagnose CMV retinitis after a 4-day workshop. In the following year, we plan on following a cohort of patients with CMV retinitis to better determine optimal treatment practices.

Diagnosis and Treatment of Acanthamoeba Keratitis
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.
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) continued 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.

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 colleague Jim Scott.

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.

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.
Trachoma, caused by an infection with Chlamydia trachomatis, remains the most common cause of infectious blindness, and affects over 80 million people worldwide. Mass antibiotic treatments with oral azithromycin are effective: the WHO global elimination campaign advocates mass treatments. However, much remains unknown, including: what the frequency and total number of treatments should be; whether complete elimination is possible; and if elimination is not possible, why? The goal of this project is to improve our understanding of mass antibiotic distributions for trachoma assessing populations in which trachoma was presumably eliminated. We will utilize the most sensitive rRNA-based amplification assay that is currently available, in addition to the traditional DNA-based test. This study will use populations from two trials: TANA (Trachoma Amelioration in Northern Amhara, NEI U10) and PRET (Partnership for the Rapid Elimination of Trachoma, Gates Foundation). These studies will be performed in Ethiopia and Niger utilizing local and international partner institutions including The Carter Center and PNLCC (Programme National de Lutte Contra la Cecite.) This project is being done in collaboration with Jeremy Keenan, Jack Whitcher, Thomas Lietman, and Travis Porco.

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. Outcome measurements include malaria thick blood smear and hemoglobin assessments in children aged 0-72 months. We aim to determine if antibiotics with antimalarial activity can have long-lasting impacts on malaria, at least during periods of low transmission.

Antimicrobials are used primarily to treat infectious disease, but they have other effects. We are assessing anthropometry measurements in children in 24 communities who have received mass azithromycin treatments in a randomized clinical trial in Niger. We are measuring wasting, low MUAC, stunting, and underweight in communities which receive different mass treatments. There is a high prevalence of undernutrition in the communities in Niger where our research is taking place. Changes in growth and nutrition may explain observed reductions in mortality that the Proctor Foundation team has previously observed.
Recent Publications


Hwang DG. Closing the gaps in surgical infection control. Topics in Ocular Antimicrobials 2011;19: 5-7.


Keenan JD, Mandel MR, Margolis TP. Peripheral ulcerative keratitis associated with vasculitis manifesting...
Recent Publications (cont’d)


Recent Publications (cont’d)


