Jules Stein Eye Institute
U C L A

Clinical Update

September 2006
Volume 15, Number 3

Jules Stein Eye Institute
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JSEI Clinical Research Highlighted

The Jules Stein Eye Institute's Clinical Research Center, dedicated in 1998, provides core support to faculty members who are conducting patient-based research studies. This support involves vital, behind-the-scenes activities that facilitate the clinical research process. Center staff members serve as liaisons with granting agencies and government regulatory bodies, assist with the preparation of grant applications, participate in the design and management of clinical studies, and perform data collection and analysis functions.

"The Clinical Research Center was established to assist investigators with their research activities," says Gary N. Holland, MD, Professor of Ophthalmology and Director of the Center. "Our aim is to help investigators work efficiently, accomplish more, and achieve higher-quality results."

Institute faculty are currently conducting over 44 clinical research studies ranging from natural history studies to clinical trials involving patient intervention to investigate new therapies for eye disease. Two current clinical investigations are highlighted below.

Multicenter Uveitis Steroid Treatment (MUST) Trial: **Comparing Two Treatments for Uveitis Patients**

The Jules Stein Eye Institute is participating in the Multicenter Uveitis Steroid Treatment (MUST) Trial, an NIH-funded study that compares two currently available treatments for patients with vision-threatening, non-infectious, intermediate uveitis, posterior uveitis, or panuveitis for whom oral corticosteroid therapy is one appropriate treatment option.

In developed countries such as the United States, a substantial majority of intermediate uveitis and panuveitis cases, and about one-half the posterior uveitis cases that present for care to uveitis practices, are presumed to be "autoimmune," based on the lack of evidence for infection, and a salutary response to corticosteroid or other anti-inflammatory therapies.

Non-infectious uveitis, regardless of cause, often requires long-term anti-inflammatory therapy with corticosteroids or immunosuppressive drugs. Traditionally, these drugs are given systemically, placing patients at risk for complications of drug therapy, despite the fact that, often, the disease involves only the eye. An alternative method for disease treatment is implantation of a device that slowly releases corticosteroid into the eye. Although effective, these

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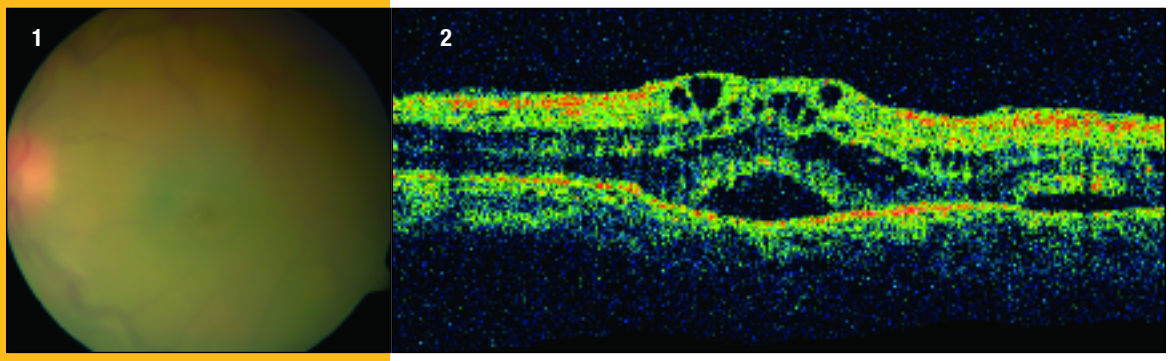


1. A vitreous inflammatory reaction in a woman with severe panuveitis obscures view of the left fundus.
2. Optical coherence tomography (OCT) demonstrates macular edema in the same eye.

http://www.jsei.org

UVEITIS PATIENTS

(*continued from page 1*)

implants are associated with high rates of cataract and glaucoma as side effects, which can result in a need for additional surgery.

In the MUST trial, systemic therapy, consisting of oral corticosteroids and supplementary immunosuppressive drugs, will be compared to treatment using the FDA-approved intraocular fluocinolone acetonide implant. Patients will be randomized to either a systemic treatment or the implant during the trial, which will last from one to four years.

The MUST trial is designed to investigate the relative risk and benefits of these two very different approaches to treating non-infectious uveitis, each with its own unique side effects. Also, it may help to assess whether systemic regulation of immune responses is important, even though disease is limited to the eye.

The primary outcome variable for the study is visual acuity. Additional outcome measures include other aspects of visual function, success in controlling uveitis, retinal morphologic outcomes, quality of life, cost effectiveness, and occurrence of potential ocular and systemic complications of uveitis and of therapy.

Investigators:

Gary N. Holland, MD,
Anurag Gupta, MD,
Ralph D. Levinson, MD,
Susan S. Ransome, MD

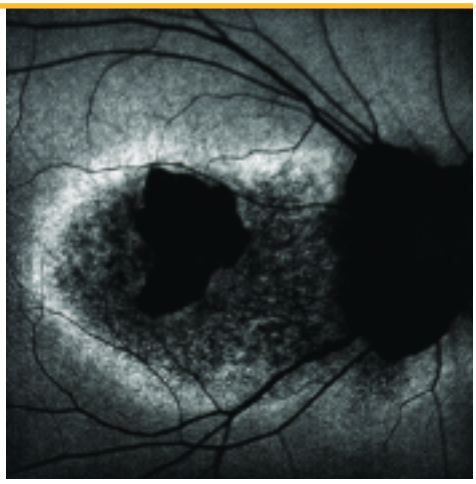
Clinical Characterization, Genetic Testing, and Visual Function in Patients with Stargardt Disease

The primary goal of this research investigation is to perform comprehensive ophthalmic examinations, visual function testing, autofluorescence imaging, and genetic testing in patients diagnosed with recessive Stargardt macular degeneration.

Stargardt disease is an early onset form of macular degeneration caused by mutations in the ABCR gene. Mutations in this gene cause defective retinoid trafficking within the visual cycle resulting in the accumulation of lipofuscin, a common feature of Stargardt disease. An understanding of the underlying mechanism of disease action in Stargardt disease has led to the development of a potential treatment strategy aimed at slowing or stopping progression of the disease by blocking the accumulation of lipofuscin. Researchers at the Jules Stein Eye Institute are working closely with Sirion Therapeutics, Inc., to develop pharmacologic interventions for macular degeneration. Recent progress using animal models offers hope that a treatment will soon be available for Stargardt disease.

In preparation for a clinical trial, the Institute is identifying and characterizing Stargardt patients and documenting their disease states using a broad range of clinical and functional tests. Patients undergo a comprehensive ophthalmologic examination that includes a complete medical, ophthalmic and family history, a standardized measurement of visual acuity with protocol refraction, and a complete eye examination, all designed to confirm a clinical diagnosis of Stargardt disease. Visual function is evaluated in the UCLA Visual Physiology Laboratory using a broad range of electrophysiological and psychophysical tests. Retinal function is evaluated with full-field and multi-focal electroretinograms, electro-occulography, dark-adaptometry, and visual fields. In addition, patients receive standard fundus photography, fluorescein angiography, optical coherence tomography (OCT), and autofluorescence imaging with a modified scanning laser ophthalmoscope to detect the bisretinoid fluorophores of lipofuscin that are common in Stargardt disease.

Despite the array of ophthalmic and functional abnormalities observed in Stargardt patients, there is no clear consensus as to which of the assays described above will be the most sensitive indicator of visual change, particularly with regard to an outcome measure for a clinical trial.



Retinal image showing fluorescent ring of lipofuscin fluorophores in Stargardt disease.

By testing patients on a yearly basis using the protocols described above, this study hopes to elucidate the most appropriate outcome measure for a trial. The data also will help clarify the sequence of biochemical and physiological events leading to disease expression in Stargardt macular dystrophy.

Clinical Investigators:

Steven Nusinowitz, PhD,
Steven D. Schwartz, MD,
Allan E. Kreiger, MD,
Debora B. Farber, PhD, DPhhc

Basic Science Investigators:

Dean Bok, PhD, Gabriel H. Travis, MD,
Debora B. Farber, PhD, DPhhc,
Steven Nusinowitz, PhD,
Xianjie Yang, PhD

JSEI Clinical Research

The clinical research studies on the following pages are in the active stage of collecting data and/or recruiting patients. Information about referral of subjects for study participation can be obtained by contacting the designated investigators.

CATARACT

Morcher Iris Diaphragm

The Institute has obtained a compassionate use Individual Device Exemption from the U.S. Food and Drug Administration to use the Morcher Iris Diaphragm implant in patients with partial or complete aniridia, and to evaluate its preliminary effectiveness. The implant is designed to limit the amount of light coming into the eye, like a natural iris, reducing symptoms of light sensitivity and glare. Patients will be followed on an outpatient basis for one year following surgery.
Investigators: *Kevin M Miller, MD, Michael Olson, OD, PhD*
(310) 206-9951

Ophtec Iris Reconstruction Lens

The Institute is participating in a multicenter clinical investigation designed to evaluate the safety and effectiveness of the Ophtec Model 311 Iris Reconstruction Lens for the treatment of visual disturbances (glare, halos, and photophobia) related to the absence of part or all of the iris. This study is designed to determine the level of reduction in visual disturbances and improvement in uncorrected and best spectacle corrected visual acuity associated with Model 311 lens implantation. The implant is designed for patients who are aniridic and either aphakic or in need of cataract surgery. Patients will be followed on an outpatient basis for a three-year period.
Investigators: *Kevin M Miller, MD, Michael Olson, OD, PhD*
(310) 206-9951

CORNEAL DISEASE

Genetic Basis of Posterior Polymorphous Corneal Dystrophy

The Institute is participating in a study to identify the gene(s) responsible for posterior polymorphous dystrophy, an inherited corneal endothelial disorder that may result in irreversible corneal swelling and loss of vision.
Investigator: *Anthony J. Aldave, MD*
(310) 206-7202

Understanding the Genetics of Inherited Eye Disorders

The Institute is participating in a study to search for the gene(s) that are responsible for inherited disorders of the cornea, such as keratoconus and the corneal dystrophies.
Investigator: *Anthony J. Aldave, MD*
(310) 206-7202

EYE INFECTIONS/INFLAMMATIONS

Multicenter Uveitis Steroid Treatment (MUST) for Uveitis

The study compares two currently available treatments for uveitis. Systemic treatment utilizing medications (corticosteroids or immunosuppressive drugs) taken orally, by injection, or by intravenous infusion will be compared to treatment with an intraocular implant containing corticosteroid that is placed surgically. Neither is experimental. Both treatment approaches are known to be effective for treating uveitis, but have different potential adverse events. (See expanded description on page 1.)
Investigators: *Gary N. Holland, MD, Anurag Gupta, MD, Ralph D. Levinson, MD, Susan S. Ransome, MD* (310) 794-5602

Longitudinal Studies of the Ocular Complications of AIDS (LSOCA)

LSOCA is a multicenter, NIH-supported epidemiological study designed to investigate the nature of HIV-related eye diseases since the introduction of potent anti-retroviral therapies. Nearly 2,000 people are being followed nationwide.
Investigators: *Gary N. Holland, MD, Susan S. Ransome, MD*
(310) 794-5602

Factors Related to the Severity of Ocular Toxoplasmosis

Toxoplasmosis is a common parasitic disease that can cause a vision-threatening infection of the retina. Severity varies from asymptomatic lesions to extensive destruction of the retina, with blindness. Individuals with and without ocular toxoplasmosis are being evaluated with a blood test to determine whether (1) people can have a genetic predisposition to severe disease when infected with the parasite, or (2) there is a particular strain of parasite that causes more severe disease.
Investigators: *Gary N. Holland, MD, Ralph D. Levinson, MD*
(310) 206-7202

Relation between NK Receptor Genes and CMV Retinitis

Institute faculty are studying why some people with AIDS develop CMV retinitis, an infection of the retina, while others do not. People are at risk for CMV retinitis when the number of circulating CD4+ T-lymphocytes drops substantially and there is a high number of HIV particles in the blood. This study is

designed to determine whether genes that control Natural Killer (NK) cell activities differ between HIV-infected individuals who develop CMV retinitis and those who do not, despite similar risk factors otherwise.
Investigators: *Ralph D. Levinson, MD, Gary N. Holland, MD*
(310) 794-7770

GENERAL OPHTHALMOLOGY

New Tests of Vestibular Function

Investigators are conducting clinical and laboratory studies of vestibular-ocular reflexes in patients with disorders of the inner ear or cerebellum. The study is sponsored by the National Institute of Deafness and Communicative Diseases.
Investigator: *Joseph L. Demer, MD, PhD*
(310) 206-6354

Subfoveal Choroidal Neovascularization for Pathologic Myopia

The purpose of this study is to evaluate the safety and efficacy of Combretastatin A4 Phosphate given by infusion for the treatment of subfoveal choroidal neovascularization in subjects with pathologic myopia.
Investigator: *Christine R. Gonzales, MD*
(310) 794-9921

GLAUCOMA AND OPTIC NERVE DISEASES

Ahmed Valve Implant vs. Baerveldt Implant in Glaucoma

Tube shunt devices for glaucoma have received little comparison. This study compares the long-term efficacy and safety of the two most commonly used glaucoma tube shunt surgical devices in clinical settings.
Investigators: *Simon K. Law, MD, PharmD, Joseph Caprioli, MD, Anne L. Coleman, MD, PhD*
(310) 825-0146

Clinical Measurements of the Optic Nerve in Glaucoma

Accurate assessment of optic nerve and nerve fiber layer is important to the early detection and timely treatment of glaucoma. Studies are underway to develop novel structural measures of the optic nerve and nerve fiber layer, which are sensitive and specific for early and progressive, glaucomatous optic nerve damage.
Investigators: *Joseph Caprioli, MD, Anne L. Coleman, MD, PhD, Simon K. Law, MD, PharmD*
(310) 825-0146

MACULAR DEGENERATION

Clinical Characterization, Genetic Testing, and Visual Function in Patients with Stargardt Disease

The Institute is identifying and characterizing Stargardt patients and documenting their disease state using a broad range of clinical and functional tests. Subjects are given the option of having their information entered into a database to be contacted should a treatment become available. (See study description on page 2.)
Clinical Investigators:
Steven Nusinowitz, PhD, Steven D. Schwartz, MD, Allan E. Kreiger, MD, Debora B. Farber, PhD, DPhhc
(310) 206-0496

Early Age-Related Macular Degeneration Lesion Study

Retina faculty are undertaking a prospective, open-label, multicenter trial evaluating the safety and efficacy of 0.3 mg eye intravitreous injection of pegaptanib sodium (Macugen) given every six weeks for 54 weeks in patients with exudative age-related macular degeneration.
Investigators: *Christine R. Gonzales, MD, Anurag Gupta, MD, Allan E. Kreiger, MD, Marc O. Yoshizumi, MD, Peter H. Win, MD, Amish R. Purohit, MD* (310) 794-9921

Intravitreous Injections of Macugen for Wet Age-Related Macular Degeneration

The Institute is participating in a two-year, multicenter trial that compares the safety and efficacy of two pegaptanib sodium (Macugen) treatment regimens: Macugen injections combined with photodynamic treatment and Magugen injections alone, for wet age-related macular degeneration.
Investigators: *Christine R. Gonzales, MD, Anurag Gupta, MD, Allan E. Kreiger, MD, Marc O. Yoshizumi, MD, Tara A. Young, MD, Peter H. Win, MD* (310) 794-9921

MACULAR EDEMA

Intravitreous Injections of Macugen for Diabetic Macular Edema

The Retina Division is participating in a multicenter trial to compare the safety and efficacy of intravitreous injections of pegaptanib sodium (Macugen), given as often as every six weeks for three years, to patients who have diabetic macular edema. The three-year study will compare Magugen injections in three doses to placebo injections for diabetic macular edema.
Investigators: *Christine R. Gonzales, MD, Anurag Gupta, MD, Allan E. Kreiger, MD, Marc O. Yoshizumi, MD, Tara A. Young, MD, David Sarraf, MD, Peter H. Win, MD, Amish R. Purohit, MD, Eric Lee, MD, Scott Oliver, MD* (310) 794-9921

Dexamethasone Injections in the Treatment of Diabetic Macular Edema

Retina faculty are participating in

(*continued on page 5*)

JSEI CLINICAL RESEARCH (*continued from page 4*)

a study to assess the safety and efficacy of 70 mg and 350 mg dexamethasone posterior segment drug delivery system in the treatment of patients with diabetic macular edema. The three-year multicenter study compares 350 mg and 70 mg dexamethasone injections (slow release) to placebo injections for diabetic macular edema.
Investigators: *Anurag Gupta, MD, Christine R. Gonzales, MD, Allan E. Kreiger, MD, Tara A. Young, MD, Peter H. Win, MD, Amish R. Purohit, MD, Eric Lee, MD, Scott Oliver, MD* (310) 206-5004

Dexamethasone Injections in the Treatment of Macular Edema Due to Retinal Vein Occlusion

The Institute is participating in a study to assess the safety and efficacy of 700 mg and 350 mg dexamethasone posterior segment drug delivery system in the treatment of patients with macular edema following retinal vein occlusion. The one-year multicenter study compares dexamethasone injections in two doses to placebo injections for macular edema due to retinal vein occlusion.
Investigators: *Anurag Gupta, MD, Christine R. Gonzales, MD, Allan E. Kreiger, MD, Amish R. Purohit, MD, Eric Lee MD, Scott Oliver, MD* (310) 206-5004

MACULAR TELANGIECTASIA

A Natural History Study of Macular Telangiectasia: The MacTel Study

Retina faculty are conducting a study to better understand the natural history of macular telangiectasia, a rare eye disorder that results in slow vision loss beginning in adulthood. Little medical information is known about this condition at this time. This study examines how the clinical manifestations of macular telangiectasia changes over time through a variety of tests. No medical treatment currently exists for this disease.
Investigator: *Steven D. Schwartz, MD* (310) 206-7474

OCULAR MELANOMA

Molecular and Cytogenetic Studies of Ocular Melanoma

The goal of this research is to study ocular melanoma tumor tissue, and identify key molecular and genetic features that could help predict those patients who may by at high risk for metastasis. A sample of tumor tissue will be removed at the time of radioactive plaque placement surgery or tumor resection and used for molecular and genetic testing. Patients will be informed of the results and, depending on the outcome, will have increased monitoring to detect metastasis at the earliest possible stage and the opportunity to participate in clinical trials of experimental treatments that might not normally be offered to patients with ocular melanoma.
Investigators: *Tara A. Young, MD, Bradley R. Straatsma, MD, Ben J. Glasgow, MD, Lynn K. Gordon, MD, PhD, Nagesh P. Rao, PhD* (310) 206-7484

Optical Coherence Tomography of Regional Abnormalities Associated with Choroidal Nevus, Choroidal Melanoma, and Choroidal Melanoma Treated with Iodine-125 Brachytherapy

Optical coherence therapy (OCT) imaging is performed during regularly scheduled visits on patients with choroidal nevus, choroidal melanoma, and choroidal melanoma treated with iodine-125 brachytherapy. The purpose of this study is to (1) study the structure and function of the retina overlying the tumor and the macula, (2) evaluate the effects of radiation on the retina, and (3) compare OCT imaging to other imaging procedures.
Investigators: *Bradley R. Straatsma, MD, Tara A. Young, MD, Melissa Chun, OD, Jennie Kageyama, OD, Dan Bourla, MD* (310) 825-5051

PET/CT Imaging for Early Detection of Ocular Melanoma Metastasis

Subjects with ocular melanoma undergo a series of combined position emission tomography (PET)/CT scans. Results are studied to evaluate the use of this new imaging procedure and compared to CT scanning alone. This information may be useful in detecting metastasis (spread of tumors) at an early stage. The research may ultimately provide new knowledge that will be used to develop better ways of monitoring for tumor spread and allow for early treatment if metastasis is found.
Investigators: *Tara A. Young, MD, Bradley R. Straatsma, MD, Johannes Czernin MD, Antoni Ribas, MD* (310) 206-7484

ORBITAL AND PLASTIC SURGERY

Hydrogel Lacrimal Stent Study

Faculty in the Orbital and Ophthalmic Plastic Surgery Division are evaluating the use of the Hydrogel Lacrimal Stent in dacryocystorhinostomy (DCR) surgery. DCR surgery creates an ostium or drainage hole between the tear duct and the nose, bypassing obstructed tear ducts. A stent is inserted following surgery to maintain the ostium. The new lacrimal stent made of Hydrogel, a medical plastic that can absorb more than 90 percent of its weight in water, absorbs fluid from surrounding tissue to expand to a diameter of approximately one-fifth inch in a spherical fashion. This fluid-absorbing property allows the stent to be inserted small and expand after insertion, thus minimizing scarring within the nasal cavity.
Investigators: *Robert A. Goldberg, MD, Raymond S. Douglas, MD, PhD* (310) 794-7459

Thyroid-Related Orbitopathy

In this research, cells from the orbital tissue of patients with Graves disease, removed as part of surgery, are harvested and grown in the laboratory. Molecular biologic features of the disease identified in these cells are correlated with clinical parameters of the disease. It is hoped that this research will lead to better therapies and more specific tests to determine the effectiveness of therapies.

Investigators: *Robert A. Goldberg, MD, Terry J. Smith, MD, Raymond S. Douglas, MD, PhD*
(310) 794-7459

STRABISMUS AND PEDIATRICS

Biomechanical Analysis in Strabismus Surgery

Now in its second decade of support from the National Eye Institute, this study aims to develop new diagnostic tests and computer models that will lead to improvements in strabismus surgery. Tests of binocular alignment and eye movements, as well as magnetic resonance imaging (MRI) of the extraocular muscles, are performed in the Institute's Clinical and Basic Science Ocular Motility Laboratory before and after strabismus surgery. Selected patients undergo molecular genetic studies of the extraocular muscles and orbital connective tissues. Results are correlated with state-of-the-art anatomic studies done in the laboratory and with comparative anatomic studies in volunteers who do not have strabismus.

Investigator: *Joseph L. Demer, MD, PhD*
(310) 206-6354

Genetic and Anatomic Basis of the Fibrosis Syndrome

The long-term goal of this National Eye Institute-sponsored project is to determine the cause of congenital fibrosis of the extraocular muscles, a rare, inherited condition resulting in strabismus and drooping eyelids. A collaborative investigation is being conducted with investigators from Children's Hospital in Boston. Nerve versus muscular causes of this syndrome are being studied in individual families around the country and linked through molecular genetics testing of blood samples to the causal genes.

Investigator: *Joseph L. Demer, MD, PhD*
(310) 206-6354

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