UCLA Stein Eye Institute | DOHENY EYE INSTITUTE

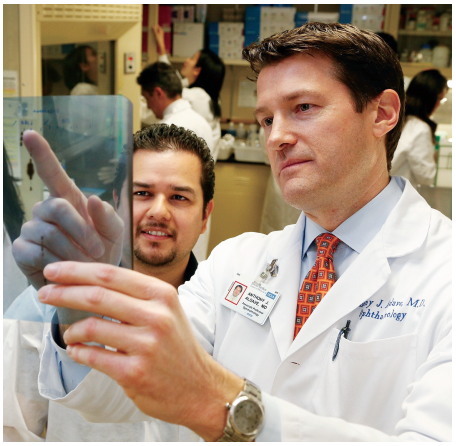
CLINICAL UPDATE

Research Paving the Way Toward Better Treatments and Outcomes for Patients with Corneal Disorders

Advances in corneal transplantation have improved results and expanded indications for what is already the most common and most successful type of human transplant surgery. UCLA's Stein Eye Institute is among the leaders in these efforts, under the direction of Anthony J. Aldave, MD, Walton Li Chair in Cornea and Uveitis, and chief of the Cornea and Uveitis Division, as well as director of the Institute's Cornea Genetics Laboratory.

Dr. Aldave's clinical research focuses on optimizing outcomes for some of the most complicated corneal transplantation cases through the use of Boston keratoprosthesis (Boston Kpro) and Descemet stripping endothelial keratoplasty (DSEK) surgery. He is widely known for his expertise in the Boston Kpro, the most commonly performed artificial corneal transplant procedure, for patients who are not candidates for traditional corneal transplantation. "The artificial cornea has gone from being considered experimental a decade ago to an accepted treatment modality for a variety of indications," Dr. Aldave says. "Patients who previously had no hope of seeing after experiencing repeated corneal transplant failure now have a viable alternative that can reestablish vision for a meaningful period of time."

Among the most challenging indications for artificial corneal transplantation is Stevens-Johnson Syndrome (SJS), a potentially fatal disease of the skin and mucous membranes that can also lead to visual impairment and blindness. The primary problems have been the melting of the donor corneal tissue that carries the artificial cornea, as well as infection. But Dr. Aldave's group, working with surgeons in Calcutta, India, and Manila, Philippines, has found that although the donor cornea may thin and require replacement, complications leading to the permanent loss of vision are



Dr. Aldave (right) and Ricardo Frausto, a senior research associate in the Cornea Genetics Laboratory, review results of a research project.

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Orbital Vascular Disease Center Establishing New Standards of Care for Challenging Disorders

Orbital vascular diseases—rare disorders of the eye socket characterized by abnormal blood vessel growth—can be devastating to patients, leading to both disfigurement and vision loss. They are also extremely challenging to treat.

The Stein Eye Institute's Orbital Vascular Disease Center, part of the UCLA Orbital Disease Center, has emerged as a leader in managing these complex cases. Using a multidisciplinary-team approach, the Center has adopted and developed innovative treatments that have become the standard of care at UCLA and other specialized centers—including surgical approaches to the orbital vasculature that enable direct access to the lesions for endovascular treatment, as well as nonsurgical interventions, such as the use of sclerosing injections and glues.

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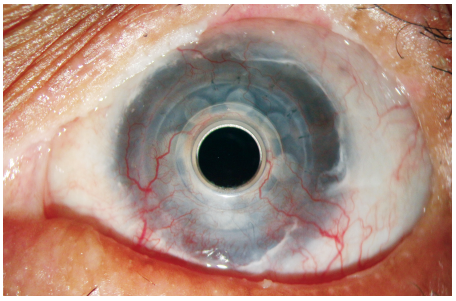

Left eye of a patient with Stevens Johnson Syndrome, who maintains 20/30 vision six years after Boston type I keratoprothesis implantation.

extremely rare. In a review of 234 Boston Kpro procedures performed in the three countries, 40 of which were in patients with SJS, the researchers found that 96 percent of SJS patients had a final vision of better than 20/200 vs. 63 percent of patients who did not have SJS. Prior to the surgery, none of the SJS patients had better than 20/200 vision—and most experts would have predicted that they would fare far worse than the non-SJS patients, Dr. Aldave notes.

"This indicates that although postoperative complications are common in SJS patients, they are typically not complications that cause permanent loss of vision," Dr. Aldave says. "In the hands of experienced surgeons who proactively manage the postoperative complications that will occur, patients with SJS can do very well with this surgery."

Among the concerns about artificial corneal transplants are the long-term results of the surgery. "There is a perception that these patients may do well for a few years, but eventually lose vision from glaucoma or another cause," Dr. Aldave says. With colleagues from Johns Hopkins University, the University of Rochester, and other institutions, Dr. Aldave recently reported on patients with follow-up as long as 10 years, showing that long-term retention of vision following Boston Kpro implantation is much better than many would have predicted. In a separate long-term outcomes study analyzing 68 Boston Kpro procedures that he performed between 5 and 10 years ago at the Stein Eye Institute, Dr. Aldave found that 52 percent of patients had corrected vision better than 20/200 at their final postsurgical follow-up vs. only 7 percent before surgery. A total of 71 percent of all patients had better vision at their final follow-up than before the surgery. "When you compare this data to what we know about the alternatives, it's really a no-brainer that the majority of these patients see better with an artificial cornea than they would with a repeat corneal transplant that would likely fail again," Dr. Aldave says.

Glaucoma, which is present prior to surgery in most individuals who undergo artificial corneal transplantation, is the primary cause of loss of vision over time for these patients. Dr. Aldave's group is investigating new strategies to prevent the glaucoma from progressing, including performing glaucoma surgery at the time of the transplant. Dr. Aldave has also published studies on outcomes of DSEK in patients who have had previous glaucoma surgery.

In the laboratory, Dr. Aldave and colleagues have sought to discover the genetic basis for a variety of inherited disorders of the cornea toward the goal of developing cell-based therapeutic alternatives to corneal surgery for future patients. Using next-generation sequencing to perform DNA analysis in members of a large Menonite family in Pennsylvania, they recently identified the genetic basis of posterior amorphous corneal dystrophy (PACD), a rare dominantly inherited disorder affecting the cornea and iris. The finding has broader implications, Dr. Aldave notes, since the genes involved play important roles in the maintenance of corneal clarity. Dr. Aldave's group is also using this sophisticated technique to look into the genetic basis of Lisch corneal dystrophy, which affects the epithelial layer of the cornea; and posterior polymorphous corneal dystrophy type 1 (PPCD1), an inherited condition of the corneal endothelium.

In a separate project that is also funded by the National Eye Institute, Dr. Aldave is working with a researcher at Cedars-Sinai Medical Center to identify genetic factors that contribute to keratoconus, the most common indication for corneal transplant in many countries throughout the world and one of the leading indications in the United States. The work could have a dramatic impact: Patients with clinically undetectable early-stage keratoconus who have corneal refractive surgery are likely to develop corneal ectasia and may require corneal transplantation. "If we can identify the genetic factors that predispose to keratoconus, it may become part of standard clinical practice to screen for those factors prior to refractive surgery," Dr. Aldave says.

Dr. Aldave's group is also investigating inherited corneal disorders for which the genetic basis is known, specifically elucidating the molecular pathways that lead to the corneal endothelial dystrophies. Research projects in this area are currently focused on the role of a particular gene, *ZEB1*, in posterior polymorphous corneal dystrophy type 3 (PPCD3); and Fuchs endothelial corneal dystrophy (FECD), which is the most common indication for corneal transplantation in the United States. "Finding a gene that causes an inherited disorder is not the end of the search; it's the beginning," Dr. Aldave says. "If we can better understand what genes are responsible for maintaining corneal clarity and figure out how dysfunction of these genes leads to the diseases that we see in our clinics, we will identify new targets for intervention."

"Although artificial corneal transplants continue to make a significant impact on patients' lives," Dr. Aldave concludes, "ultimately the goal is to find less invasive and more effective approaches."

Establishing New Standards of Care *continued from cover*

Dr. Jack Rootman (right) lecturing on orbit dissection at the Stein Eye Institute's annual Aesthetic Eyelid and Facial Rejuvenation Course.

The most common orbital vascular diseases are venous varices, lymphaticovenous anomalies, and arteriovenous malformations, but research has found that orbital vascular diseases occur along a spectrum. "The classic descriptions of a varix or a lymphangioma, for example, are probably not robust enough to describe what's really going on, since there are often abnormalities involving many different types of vessels," says Robert Alan Goldberg, MD, Karen and Frank Dabby Endowed Chair in Ophthalmology, chief of the Orbital and Ophthalmic Plastic Surgery Division, and director of the UCLA Orbital Disease Center. Dr. Goldberg notes that the cause of these diseases is believed to be embryologic—something that occurs during development that results in the vessels forming abnormally. Often the diagnosis is made at birth, but in some patients, the abnormality isn't detected until early childhood or even adolescence or later. Although the disorder is almost always present at birth, in rare cases it can be acquired as a result of other diseases or trauma.

As the blood vessels grow into normal tissues, the mass and infiltrative effects and growth of these lesions can become a substantial problem for patients—both functionally and cosmetically, Dr. Goldberg explains. In addition, he notes, the intrinsic, sometimes turbulent blood flow can cause problems such as thrombosis, hemorrhage, pressure, and inflammation, resulting in congestion and potential ischemia.

Treatment of ocular vascular diseases has been challenging for several reasons, Dr. Goldberg explains. Because the blood is typically flowing through the lesions, standard surgical techniques can be hampered by concerns about intraoperative bleeding. In addition, the lesions are often diffuse—spread throughout the normal tissues—making them difficult to surgically remove. Finally, for reasons that are not entirely clear, they often return even after surgery appears successful. "The majority of these processes don't respond well to traditional surgical treatment," Dr. Goldberg says.

Through its research and clinical efforts, the UCLA Orbital Disease Center has developed new surgical and nonsurgical approaches. From the surgical standpoint, the Center has long featured advanced instrumentation and techniques to perform the delicate types of surgeries required to remove orbital vascular lesions. The program has pioneered minimally invasive, small-incision techniques that take advantage of advanced endoscopy and microsurgery to operate on the lesions through less-invasive approaches, often under local anesthesia.

To develop nonsurgical techniques, the Orbital Vascular Disease Center takes advantage of its multidisciplinary team. Interventional radiologists map the orbital vascular disorders using advanced techniques to provide a detailed picture of the vascular anomalies. The Center has developed medical treatments based on this information, including sclerosing agents that effectively kill the inside of the abnormal vessels, causing them to collapse; and glues to seal off the inside of the lesion—often facilitating surgery to remove the rest of the lesion. "This is work that we started 15 years ago, and it has become standard treatment," Dr. Goldberg says. Researchers at the Center are currently investigating glues that would treat the lesions without the need for surgery, as well as sclerosing agents that are more specific to different types of vessels, as strategies for reducing side effects of the treatment.

Orbital Vascular Disease Center researchers are also exploring the potential use of biologic agents. "We are beginning to better understand the chemicals and proteins that regulate blood vessel development in the embryo and in adults," says Dr. Goldberg, "and we are using that understanding to study agents that might be able to control those proteins and turn off the signal that is making the lesions grow." Initially, this could augment the current therapies. Eventually, Dr. Goldberg believes such treatments could replace the existing ones. "The field is evolving toward nonsurgical, specific kinds of therapy," he says.

The Center's clinical faculty was recently bolstered by the recruitment of Jack Rootman, MD, a world-renowned authority in orbital vascular diseases. The team features interventional radiologists known for innovative approaches to vascular lesions; head and neck surgeons and neurosurgeons who participate in the surgical management; basic scientists who are unraveling the molecular biologic features of orbital vascular diseases; and pediatricians, neurologists, dermatologists, and other specialists who are brought in as needed. "By bringing together these experts, we are making headway against a very complex group of disorders."

The Center is also training the next generation of leaders through a two-year fellowship program in orbital and ophthalmic plastic surgery that provides trainees with a unique experience in the multidisciplinary environment.

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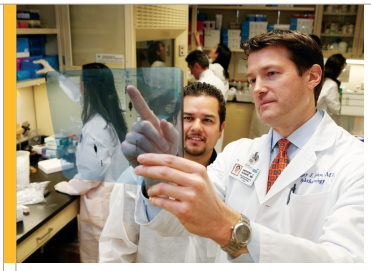

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