A new round of clinical tests offers the promise of major advances in the U.S. Department of Energy’s (DOE) Artificial Retina Project—a collaborative, multi-institutional quest to help restore sight for people blinded by retinal diseases.

With approval from the U.S. Food and Drug Administration to move ahead with clinical trials, surgeons at the Doheny Eye Institute (University of Southern California Medical Center) are enrolling subjects blinded by retinitis pigmentosa (RP) to receive an Argus II—the latest model of an artificial retina. Other select implantation sites in the United States, Europe, and Latin America are also enrolling subjects for clinical trials.

Described as a group of inherited eye diseases that affect the retina, RP causes degeneration of the photoreceptor cells that enable sight by capturing and processing light. As the cells degenerate, patients experience progressive vision loss. The implant, manufactured by Second Sight Medical Products Inc., a private company, takes the place of the damaged photoreceptors. These devices are experimental and not yet commercially available.

The current clinical trial follows on the heels of earlier human implant tests that indicated the safety and long-term reliability of first-generation Argus I. During the testing phase, which began in 2002, six people received retinal prostheses. Each of these previously blind individuals has since been able to detect light, identify objects in the surrounding environment, and even perceive motion (see graph above). Although one implant had to be removed for unrelated health reasons, and one patient passed away, the remaining four patients continue to use the device at home (see sidebar, p. 2).

To date, Argus I is the only retinal prosthesis developed worldwide that continues to work over a period of...
This is a great example of how the unique talents and resources at the DOE national laboratories can be used to advance the development of instrumentation to help the blind to see,” says Dean Cole, program manager for the DOE Artificial Retina Project. Clinical trials on the third model are expected to begin in 2011.

Another Step Forward
The second-generation retinal prosthesis incorporates revolutionary DOE national laboratory technologies. Designed to last a lifetime, the compact device contains 60 electrodes—nearly 4 times as many as the initial 16 electrodes—embedded in a tiny array. The array is surgically attached to the retinal surface and used in conjunction with an external camera and video-processing system to provide rudimentary sight to the implanted subjects.

Fitting neatly into the eye’s socket, the new prosthesis is only about a fourth the size of the original retinal implant, thereby dramatically reducing surgery and, potentially, recovery times.

“It’s aimed for patients with little or no light perception, hopefully to provide them with unaided mobility,” says Mark Humayun, a surgeon at Doheny who is leading the DOE effort. What’s key is that, like the Argus I, this device processes information in real time.

“We can’t afford to have images coming back 5 to 10 seconds later when a person is trying to cross a street,” Humayun explains.

Leveraging DOE Know-How
A third implant model, under development, will incorporate cutting-edge, dual-use DOE technologies (see Lawrence Livermore National Laboratory, p. 3). It will be even smaller and have 4 to 5 times more electrodes embedded in the array. Eventually, the DOE collaborators hope to produce a 1000-electrode device that potentially could restore enough sight to enable facial recognition and even the ability to read large print, in addition to unaided mobility (see graph, p. 1).

To date, participants in the clinical studies have had little or no light perception due to RP. Ultimately, however, millions suffering from dry, age-related macular degeneration, or AMD, also stand to benefit because the disease strikes the same photoreceptor cells as RP.

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Normal vision begins when light enters and moves through the eye to strike specialized photoreceptor (light-receiving) cells in the retina called rods and cones. These cells convert light signals to electric impulses that are sent to the optic nerve and the brain. Retinal diseases like age-related macular degeneration and retinitis pigmentosa destroy vision by annihilating these cells.

With the artificial retina device, a miniature camera mounted in eyeglasses captures images and wirelessly sends the information to a microprocessor (worn on a belt) that converts the data to an electronic signal and transmits it to a receiver on the eye. The receiver sends the signals through a tiny, thin cable to the microelectrode array, stimulating it to emit pulses. The artificial retina device thus bypasses defunct photoreceptor cells and transmits electrical signals directly to the retina’s remaining viable cells. The pulses travel to the optic nerve and, ultimately, to the brain, which perceives patterns of light and dark spots corresponding to the electrodes stimulated. Patients learn to interpret these visual patterns. ■
Pioneering work with polymer-based microfabrication methods at Lawrence Livermore National Laboratory (LLNL) is feeding into the primary component of the Artificial Retina Project—namely, development of a flexible, biocompatible microelectrode array.

A key LLNL technique for making thin metal lines “allows us to pack many more electrodes into a much smaller device than previous models,” says Satinderpall Pannu, who is leading the LLNL effort. This technique, coupled with integrated-circuit and wireless technologies, drives development of the Department of Energy’s advanced retina prosthesis. The current goal is to develop an array with hundreds of electrodes.

**Micrometer Sizing**

As part of LLNL’s Center for Micro- and Nano-Technology, Pannu and his team are applying their expertise to microelectromechanical systems (called MEMS) that integrate micrometer-sized mechanical elements, sensors, actuators, and electronics through microfabrication technology.

The metal traces forming the electrodes and electronics in the array are less than a micrometer thick—less than 1% the thickness of a human hair. Embedded in such soft, moldable substrates as silicone, the array conforms easily to the curved shape of the retina.

Pannu’s group also is developing methods for integrating complementary metal oxide silicon (called CMOS) electronics into the retinal prosthesis to reduce its overall size and complexity. These electronics send electrical signals to microelectrodes to stimulate the retina, a function normally generated by the eye’s photoreceptor cells. In blind people suffering from retinitis pigmentosa and age-related macular degeneration, however, this process has broken down. The microelectrode array mimics the function of the photoreceptor cells by electrically stimulating the remaining healthy bipolar and ganglion cell layers (see graphic at right).

Additionally, LLNL’s expertise is being tapped to develop advanced ocular surgical tools that will allow surgeons to place the microelectrode array precisely on the retina with minimal tissue damage (see image, p. 8).

**Dual-Use Technology**

Many of the technological advances forming the basis of this research stem from LLNL’s role as a national security laboratory.

“This project is a great example of LLNL’s multidisciplinary approach to science,” says Cherry Murray, LLNL’s deputy director of Science and Technology.

Previously, LLNL researchers used silicone as a substrate for microfluidic devices such as biosensors to detect and identify chemical and biological pathogens in waterways.

Since silicone is a biocompatible material, more recent work has focused on developing processes for embedding metal microelectrodes and electronics within silicone for use in biomedical devices. …continued on page 8
When Terry Byland began having trouble seeing in the dim light of dark restaurants and nightclubs, he wasn’t overly concerned. Soon after, however, the problem began to affect his night driving. A year later, he went to an ophthalmologist to have his eyes checked. He wasn’t prepared for the grave diagnosis: Retinitis pigmentosa (RP).

“What’s going to happen to me?” Byland asked his doctor, who told him that eventually he could go blind.

RP is a group of relatively rare inherited eye diseases that attack the photoreceptor cells in the retina, affecting about 1 in 4,000 people. Symptoms begin with night blindness, generally progressing to tunnel vision years or decades later and, finally, to complete blindness in some affected individuals. Millions more become blind each year from age-related macular degeneration (AMD), which strikes the same photoreceptor cells but begins with loss of central vision. There is no cure for RP and, as yet, no treatment.

In Byland’s case, the full progression took only 7 years, leaving him blind when he was 45. Forced to retire from a job he loved selling tools and parts and no longer able to play the sports he enjoyed, Byland struggled through bouts of depression, anger, and despair. “My family saw me at my worst and didn’t know from one day to the next what emotional state they’d find me in,” Byland says.

Little by little, he began to pick himself up, learning how to cope with the new life he’d unwillingly been handed. “Blindness robs you in so many ways, and either it deals with you or you deal with it,” he explains. He started visiting the Braille Institute, an advocacy organization for the blind, and soon realized he wasn’t alone. Since then, Byland has built up an extensive support network of other people with RP.

Nearly 11 years after blindness closed in, Byland learned about the Department of Energy’s Artificial Retina Project through a friend who’d had a cornea problem checked out at the nearby
Doheny Eye Institute of the University of Southern California Medical Center. Passing a series of medical tests, Byland found he was a suitable implant candidate. A few weeks later, he was on the operating table—the last of six patients to receive the first experimental device.

The decision to go through the surgery wasn’t difficult, he says, even though doctors at Doheny and Second Sight Medical Products Inc., the implant manufacturer, weren’t sure what he might be able to see with the device. In the end, it came down to, “What have I got to lose? If there’s a chance I can help myself and others down the road, I’ve got to do this,” Byland explains.

The 16-channel implant that Byland received allows him to see images transmitted from a tiny camera mounted on a pair of dark glasses. Seeing only bits and pieces of light at first, Byland was guardedly optimistic that eventually he’d make some sense of it all.

“Let’s be honest, this isn’t a cure-all, but it could be; it just needs good people to get it started,” he says.

Path of Discovery
He never expected—nor did his doctors—that he’d come as far as he has. When a person has been blind for some time, a portion of the brain goes dormant and has to be retrained. During 3 years of extensive laboratory testing, the visual cortex of Byland’s brain appears to be relearning how to translate what it’s seeing.

His doctors conducted scores of tests to see whether the electrodes were working right, adjusting to different levels of current. In the beginning, Byland had trouble distinguishing whether the bars he was seeing were horizontal or vertical and whether the light was in the upper left or lower right corner.

After awhile, though, being able to identify the light source became second nature to him, and, every time he uses the device, his brain is storing information again.

He can’t make out shapes yet, but he can see the edges of light and dark objects. When he walks down a street, for example, the edge of a tree branch blocking his way will appear as a white line, alerting him that something’s in his way.

“Before, I would’ve walked right into it,” Byland says. After dark, he can flip on a switch and see light emanating from a chandelier on the ceiling or make out changes in the light as action figures move across a television screen.

“It sounds pretty primitive to a sighted person,” Byland admits, “but for a blind person like me, it’s really amazing to see anything at all.” Especially exciting was being able to see his 18-year-old son’s shadow as he passed by on a sidewalk. “It was the first time I’d seen anything of him since he was 5 years old,” Byland explains.

The retinal implant has given him more confidence to go alone to unfamiliar places. He can see light coming in through windows and tell where a door is and whether it’s closed or open. He also enjoys impressing the ladies when he can. “They think it’s pretty cool when I can tell whether they’re wearing dark or light clothing or if there’s a pattern on their blouse,” which he determines from contrasts between light and dark.

Future Promise
Byland is hopeful that he’ll get a more advanced artificial retina in the future. “It’s inspiring to know that one day blind people won’t be stuck with darkness,” Byland says. He’s also excited to have been part of developing the implants and of letting people know that hope is on the way. “It had to start somewhere, and we’re the roots of that,” he adds.

Retinal implant recipient Terry Byland visits the World War II memorial on a recent trip to Washington, D.C. The insights gleaned from this first device are being integrated into newer models that will offer more visual perceptions and higher-resolution vision.

“We’re unlocking doors and giving doctors the keys to unlock more doors.”
–Terry Byland

Clinical Trials continued from page 2

Other Projects Worldwide
Other efforts to develop retinal prostheses are ongoing in the United States, Germany, Japan, and elsewhere. These programs pursue many different designs and surgical approaches. Some show promise for the future but have yet to demonstrate practicality in terms of adapting to and lasting long term in a human eye. Thus far, Second Sight is the only company that has demonstrated visual acuity in preliminary testing of some implanted blind individuals.
RETINAL IMPLANT CLINICAL TRIALS

How to Participate

Retinal implant clinical trials are now open for enrollment of candidates affected by a group of inherited eye diseases known as retinitis pigmentosa (RP).

These clinical studies are being conducted by the Doheny Eye Institute at the University of Southern California Medical Center and other select sites in the United States. Testing will evaluate the safety and usefulness of Argus II, the latest model of a retinal prosthesis, in providing visual function to blind subjects with severe-to-profound RP.

Individuals interested in enrolling as implant candidates in this clinical trial must

- Have a confirmed history of retinitis pigmentosa, with remaining visual acuity of bare light perception or worse in both eyes.
- Have functional ganglion cells and optic nerve, as determined by a measurable electrically evoked response or documented light perception.
- Have a history of prior useful vision.
- Be 50 or older.
- Reside within 2 hours of land transport from a clinical site.
- Be able to communicate verbally in English.

The study requires each subject to be followed for at least 3 years, with visits to the implanting center up to twice a week. Those with optic-nerve disease, glaucoma, diabetic retinopathy, ocular trauma, or a history of retinal detachment are not suitable candidates.

For more information, contact Second Sight at patients@2-sight.com or 818.833.5027 or go to www.2-sight.com/Patients.htm

These devices are experimental and not yet commercially available. Extensive, preclinical testing preceded the human implant clinical trials.
**Second Sight Wins NIH Award**

Second Sight Medical Products Inc. (SSMP) has been awarded a renewal of its National Institutes of Health (NIH) Bioengineering Research Program (BRP) grant, administered by the National Eye Institute (NEI). The renewal is for 5 years and $13.3 million and extends the total grant period to 10 years and $26.5 million. The renewal grant will support basic science research in animal models, psychophysical testing in patients, and technology development and integration. Second Sight BRP partners include the Doheny Eye Institute, Salk Institute for Biological Studies, and Alfred Mann Foundation.

During the first funding period, SSMP manufactured the Argus I devices that were implanted in six patients, and integrated the technologies developed by BRP partners and others into the Argus II device now in clinical trials. Robert Greenberg (SSMP’s president, CEO, and lead investigator for the BRP) says, “The generous support by NEI not only validates our capabilities and progress to date but will enable the development of more clinically useful devices for our patients.”

BRP grants, which support both basic and applied research, enable technologies to move from the lab to the clinic. SSMP, which also receives substantial support from private investors including its founder, Al Mann, began clinical trials for its new 60-channel Argus II retinal prosthesis this summer. Greenberg adds, “We have been very pleased with the results from our 16-electrode Argus I device—the world’s only powered retinal prosthesis in daily use by patients today—and are optimistic that our second-generation implant will prove even more effective.”

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**New Book in Press**

Advanced ocular surgical tools developed at Lawrence Livermore National Laboratory are used to tack the thin-film electrode array into the retinal tissue.

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