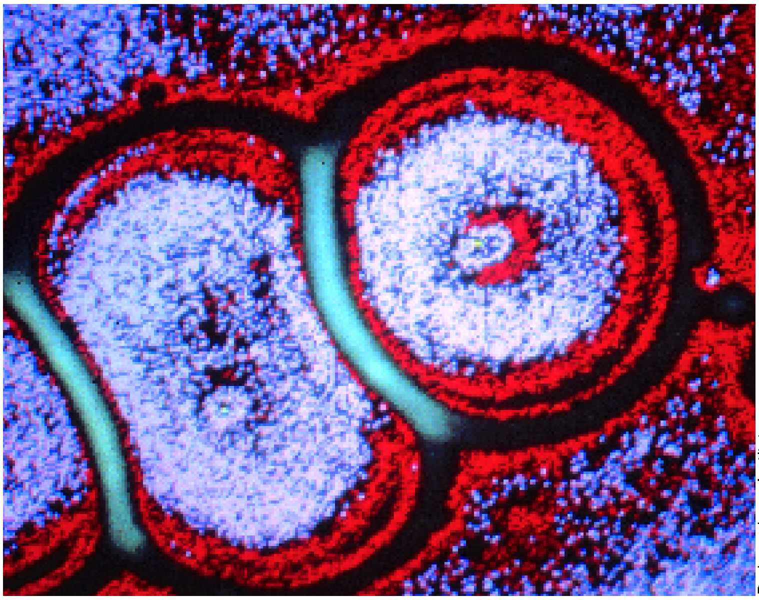
by Jennifer Ouellette

Lasers Open Up the Life Sciences

Over the past two decades, laser technology has expanded the scope of eye surgery and the treatment of kidney stones and certain cancers. The development of more advanced techniques, such as “laser scissors” and “laser tweezers,” will push the borders of the frontier even further, enabling scientists to use laser light for artificial insemination, to cut and paste chromosomes, and to sequence genes.

“When you look at the history of surgery, the Egyptians, ancient Indians, and the Chinese only had one tool: a knife,” says Rangaswamy Srinivasan, founder and president of UV Tech Associates (Ossining, NY), a pioneer in the surgical applications of ultraviolet lasers. “The only other new cutting tool introduced in the intervening millennia was cautery, in which a hot metal tip is used to burn off tissue locally.” With ultraviolet laser ablation, surgeons now have a tool that doesn’t touch the surface, yet “it can remove tissue with a precision doctors never imagined”—cutting to one-hundredth the thickness of a human hair, Srinivasan adds. Laser procedures used today are so precise that they can remove a single layer of cells without affecting neighboring cells.

Ophthalmology—and eye surgery in particular—has benefited from an explosion of new lasers and techniques for treating myopia (nearsightedness), hyperopia (farsightedness), astigmatism, glaucoma, and diabetic retinopathy, which is the leading cause of blindness in adults. Precision lasers can stop and sometimes reverse damaging changes in retinal blood vessels to prevent blindness in diabetics. They are also used to repair small tears in the retina that often lead to retinal detachment. Most recently, ophthalmologists have begun using lasers to sculpt the surface of the cornea to correct vision (Figure 2).



Beckman Laser Institute

Figure 1. A pulsed laser has been used to drill a hole only 0.1 µm in diameter in the center of each of these two living red blood cells. The holes appear as tiny dark spots within the light colored disks in this computer-enhanced image.

Laser refractive eye surgery has its roots in the mid-1800s, when surgeons sought to flatten the cornea with a blow from a spring-mounted mallet delivered through a closed eyelid. More than 100 years later, serious surgical investigation began using excimer lasers. While at IBM in the early 1980s, Srinivasan demonstrated that ultraviolet laser pulses could vaporize tissue without damaging surrounding cells, which paved the way for the eventual use of excimer lasers in eye surgery. Srinivasan describes the process, called ablative photodecomposition, as “an exquisitely controlled explosion in the sense that the patient feels as if someone is touching the eye momentarily.”

Development of ablative photodecomposition led to the formation in 1986 of two companies, VISX (Santa Clara, CA) and Summit Technology (Waltham, MA), which introduced the excimer laser to U.S. eye surgeons. The U.S. Food and Drug Administration (FDA) approved the initial use of lasers for the correction of myopia in 1995, and it has since approved procedures for treating eyes that have both myopia and astigmatism. Market analysts project that as many as 700,000 laser procedures will be performed a year for vision correction in the United States, with a total market value of $1 billion, by the year 2000. Laser surgeons have treated more than 1 million eyes outside the United States since the late 1980s.

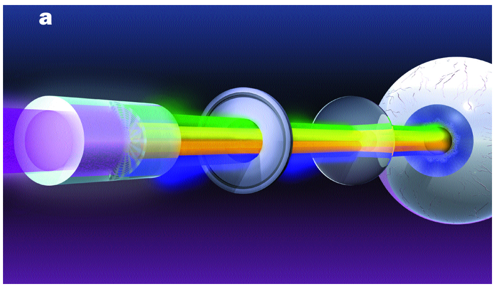
Lured by a large profit potential, other laser companies are entering the ophthalmology market: Nidek, a Japanese company with offices in Fremont, California, LaserSight (Claremont, CA), and Chiron Vision (Orlando, FL), a subsidiary of Bausch and Lomb, are all awaiting FDA clearance for their systems. Autonomous Technologies (Orlando, FL), which recently merged with Summit, received FDA approval for its laser system late last year. It features an eye-tracking system to reduce error caused by patient eye movements during the procedure.

Two types of laser surgery dominate vision correction. The FDA-approved photorefractive keratectomy (PRK) treats myopia by using laser energy to flatten the front surface of the cornea, which shortens the length of the eyeball and refocuses light on the retina. Laser-assisted in situ keratomileusis (LASIK) combines traditional surgery with laser treatment. In LASIK, a surgeon uses an instrument called a microkeratome to create and lift up a thin “flap” of tissue about a third of the thickness of the cornea. The laser is then used to resculpt the internal corneal tissue, similar to the procedure used in PRK, and the flap is repositioned over the cornea. PRK and LASIK are quickly replacing radial keratotomy, in which a surgeon reshapes the cornea by using a hand-held blade to make a pattern of incisions.

LASIK has become increasingly popular worldwide because it causes no postoperative pain and vision improves immediately following surgery. However, the FDA currently categorizes LASIK as an "off-label" procedure, which means that the agency has not approved its use but physicians can legally perform the operation. LASIK costs more than PRK because it is more complex and time consuming, and it requires an additional instrument, the $50,000 microkeratome.

Innovations

New procedures under development include using LASIK to correct hyperopia. The technique is similar to standard LASIK except that it requires a larger flap to allow the laser energy to reach the periphery of the cornea. VISX recently received FDA approval to market this new procedure for the treatment of mild hyperopia and accompanying astigmatism. Hyperopic PRK, a procedure in which the curve of the central



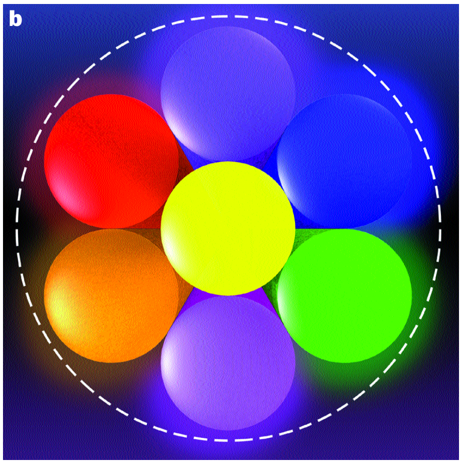
cornea is steepened by removing a ring of peripheral tissue, is also being investigated.

Sunrise Technologies International (Fremont, CA) is developing laser thermal keratoplasty (LTK), which changes the refractive power and properties of the cornea by applying holmium laser light to modify the structure of its collagen fibers. Rather than removing large numbers of corneal cells, the laser gently heats supporting tissue that lies within the cornea but outside the optical path. LTK is quick and leaves the central corneal surface untouched; and it seems that vision improvement is almost instantaneous. Sunrise received FDA premarket approval in February for its system, and now awaits final marketing approval.

Smooth corneal ablation is critical in vision-correction surgery. VISX recently unveiled its VISX STAR S2 laser system, which uses a rotating split-laser-beam configuration to produce a smoother ablation. Last year, FDA approved Summit's innovative Apex Plus excimer laser system for treating low to moderate myopic astigmatism. According to Robert Palmisano, Summit's chief executive officer, the Apex Plus system includes a disk that fits over the eye and precisely directs the laser beam, delivering smooth corneal ablations without the need for expensive, complicated optomechanical or computer tracking systems.

Other specialties

Newer laser technologies are seeping into other medical specialties, fueled by key advances in supporting technology. Although lasers have been used to treat liver, head,



and neck tumors, physicians have had less success applying them to breast tumors because neither standard magnetic resonance imaging (MRI) nor ultrasound enables surgeons to determine exactly where a tumor ends. But Steven Harms, director of imaging research at the University of Arkansas Center for Medical Science and chief of radiology at Central Arkansas Veterans Healthcare System in Little Rock, has developed a promising new therapy that combines interactive MRI and laser ablation to destroy breast tumors without surgery.

Called rotating delivery of excitation off-resonance (RODEO), the system uses a computer software adaptation of MRI that accentuates the contrast between normal and cancerous breast tissue to make it plainly visible to doctors. "Prior to ablation, tumors look like bright stars in a dark sky," says Harms. "The laser heat spreads in a sphere, and the image turns dark when the tumor is destroyed." A needle is placed in the tumor, through which a fiber-optic wire is inserted to deliver laser heat until the tumor is destroyed, which takes about 10 minutes.

Results of a preliminary study of breast tissue experimentally treated after it was surgically removed confirmed the destruction of all cancerous tissue identified by the MRI. "It's early and more studies are necessary, but it is a very promising alternative for women who want to avoid disfiguring surgery," says Harms. The next development step is to use the MRI-guided laser technique instead of surgical lumpectomy to treat breast cancer in patients.

Controlling the temperature of the target

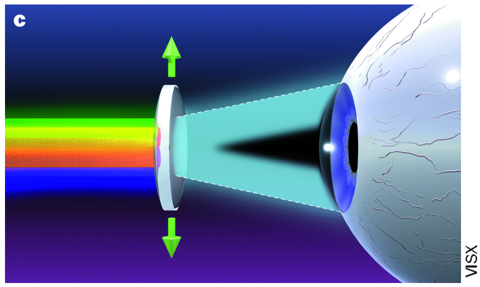


Figure 2. In order to minimize surface irregularities in corneal surgery, this excimer laser system splits a single beam into seven smaller-diameter beams (a). For myopia (b), the seven beams rotate and flatten the cornea. For hyperopia (c), an orbiting lens directs the beam around the edge of the cornea to steepen it.

tissue is critical for any laser surgical application, notes Peter Celliers of Lawrence Livermore National Laboratory (LLNL). For example, in tissue welding, laser energy forges bonds between tissue surfaces and fuses them. Overheating damages cells and slows the healing process; too-little heat prevents bonds from forming. Researchers in LLNL's medical technology program have developed a two-color, fiber-optic infrared sensor to measure tissue temperatures between 50 and 800° C and the emissivity of tissue, which is an indicator of how well a target emits infrared radiation (heat).

Tissue welding has a broad range of surgical applications, including vessel grafts and repair, skin-wound closure, and nerve repair. LLNL's scientists are collaborating with Conversion Energy Enterprises (Spring Valley, NY) and the University of California campuses at San Francisco and Davis to apply this technique to repair congenital defects in aortas in infants. Studies by LLNL and the Beckman Laser Institute and Medical Clinic at the University of California, Irvine, may lead to a useful laser tool that will eventually replace metal dental drills.

In conjunction with Conversion Energy Enterprises, LLNL researchers are investigating techniques for doing optical biopsies. Such a diagnostic technology would enable researchers to reliably interpret the optical signatures of both healthy and diseased tissue. And researchers with the Biomedical Engineering Center at the University of Texas (UT) Medical Branch in Galveston are collaborating with several clinicians and industrial partners to develop a medical imaging modality called the laser optoacoustic imaging system (LOIS). This system uses laser-induced acoustic signals to create images of greater contrast and sensitivity than those that can be obtained from conventional ultrasound.

"Biomedical optics researchers have found that optical contrast between various human tissues—including normal and malignant tissues—may be substantially greater in many cases than any other type of contrast used in such modern imaging modalities as X-ray radiography, MRI, or ultrasound," says Alexander Oraevsky, director of the Optoacoustic Imaging and Spectroscopy Laboratory at UT–Galveston.

Wide-band ultrasonic waves help in delivering signals from tumors to the tissue surface. As a result, small breast tumors invisible in conventional mammograms may be detected and localized. Other potential applications of LOIS include imaging early gastrointestinal cancers, brain tumors, hematomas, and internal bleeding. Although still in initial clinical testing, Oraevsky says that the technology could become available for clinical diagnostic applications in the next decade.

New frontiers

Revolutionary developments are bringing laser technology into the interior of single cells, achieving feats of precision far beyond the surgeon's scalpel. Michael Berns, director of the Beckman Laser Institute, is building on his pioneering work with laser scissors in the 1970s and the more recent work of Arthur Ashkin and Steven Chu in optical trapping of molecules to advance the use of laser scissors and tweezers to the intracellular level. The combination makes possible unprecedented manipulations of organelles and entire cells.

"Much as medical surgeons guide micromachined tweezers and scissors through endoscopes to perform minimally invasive surgery on organs, the cell biologist can now use laser tweezers and laser scissors to perform minimally invasive manipulations on living cells and their organelles," says Berns. Laser tweezers (the equivalent of forceps) allow photons from a pair of laser beams to immobilize cells and structures within them, while a separate beam (laser scissors) cuts and manipulates cell components (Figure 1).

Laser beams can hold an object in their grasp because laser light has momentum that can be imparted to a target to make it remain stationary. "The refraction of any pair of symmetric laser light rays within the beam produces forces," Berns explains. Although these forces are quite small, "they are large enough to influence biological processes at the subcellular level, where the masses of objects are infinitesimal."

Laser scissors are currently being tested in a multicenter study to assist human in vitro fertilization using the technology of Cell Robotics (Albuquerque, NM). Once an egg has been fertilized in a laboratory dish to become a zygote, the laser scissors cut a small trench in the zona pellucida, the zygote's protective cover. The zygote is then placed in the womb, where the thinning of the zona appears to abet its implantation in the uterine wall, Berns says. This laser-aided technique, called "assisted hatching," may prove particularly useful to women over 30 because the zona pellucida appears to toughen as women age. A group at the Associated Research Institute for Human Reproduction in Rome, Italy, found a more than 50% increase in pregnancy rates among 200 women who had undergone laser zona thinning, compared with women who had not.

Laser tweezers have also been used to grasp two human myeloma cells, while laser scissors cut the adjoining cell membranes, causing the two to merge into a single hybrid cancer cell containing the genomes of both. "Fused cells can combine valuable attributes within one entity, such as one cell's ability to produce a useful product with another's ability to divide indefinitely," says Berns. He has used laser scissors to cut chromosomes in the midst of mitosis (cell division) and then employed laser tweezers to move the fragments within the cell. This technique will enable scientists to study, without destroying the cell, the machinery that pulls replicated chromosomes to opposite ends of a cell as it divides.

Berns, in collaboration with another UC–Irvine group, is using laser scissors to open a single cell and analyze its chemical components at the moment it is opened. Potential applications in single-cell analytical chemistry include determining the exact identities and concentrations of proteins that are important in cancer at the individual cell level. Today, "optical tools incorporating lasers enable biologists to become cell surgeons," says Berns. "The application of these technologies has far-reaching implications for medicine, developmental biology, the study of cell structure and function, and for the unraveling and manipulation of the human genome."

Further Reading

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Srinivasan, R., "Ablation of Polymers and Biological Tissue by Ultraviolet Lasers," *Science,* Vol. 234, 1986, pp. 559–565.