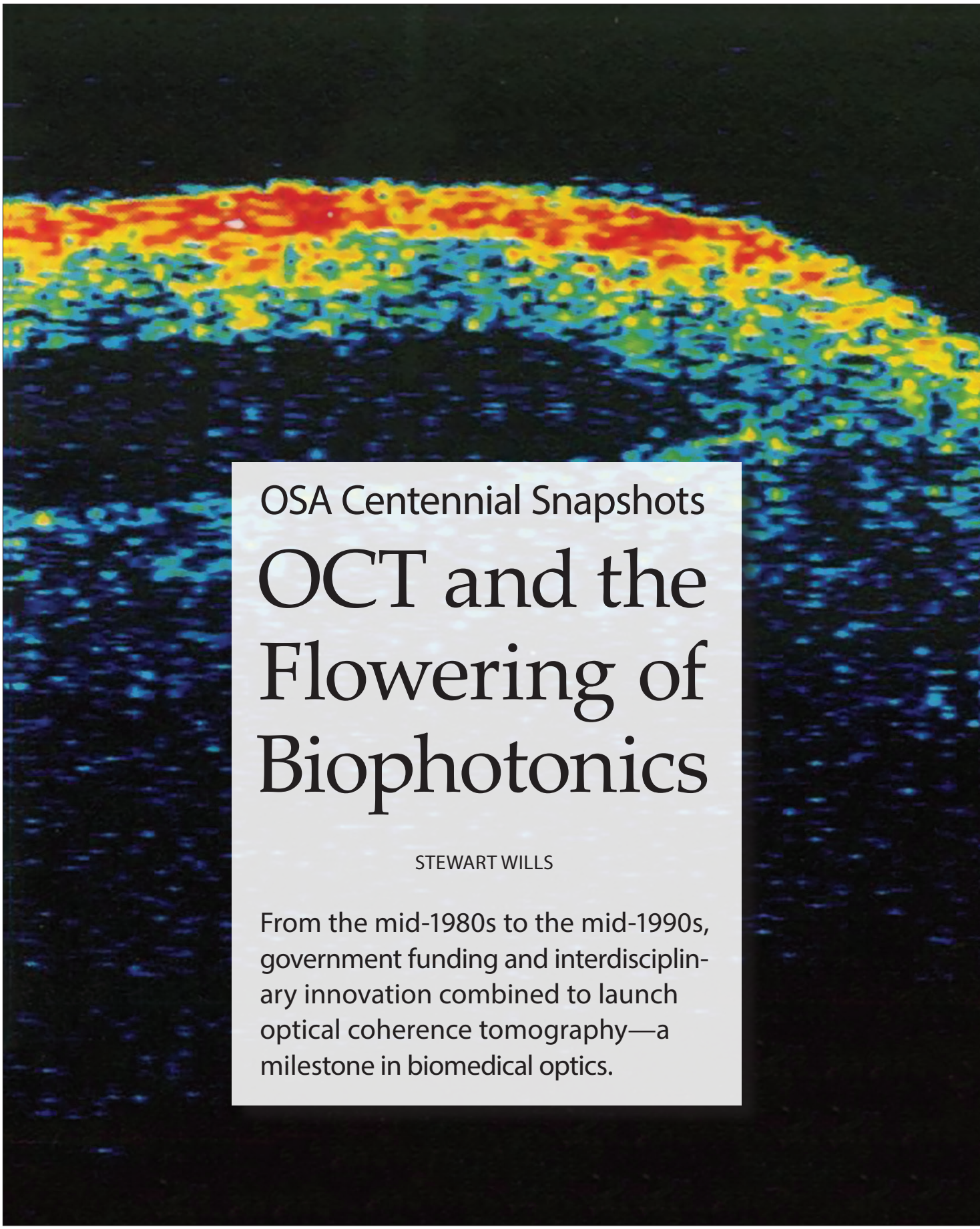
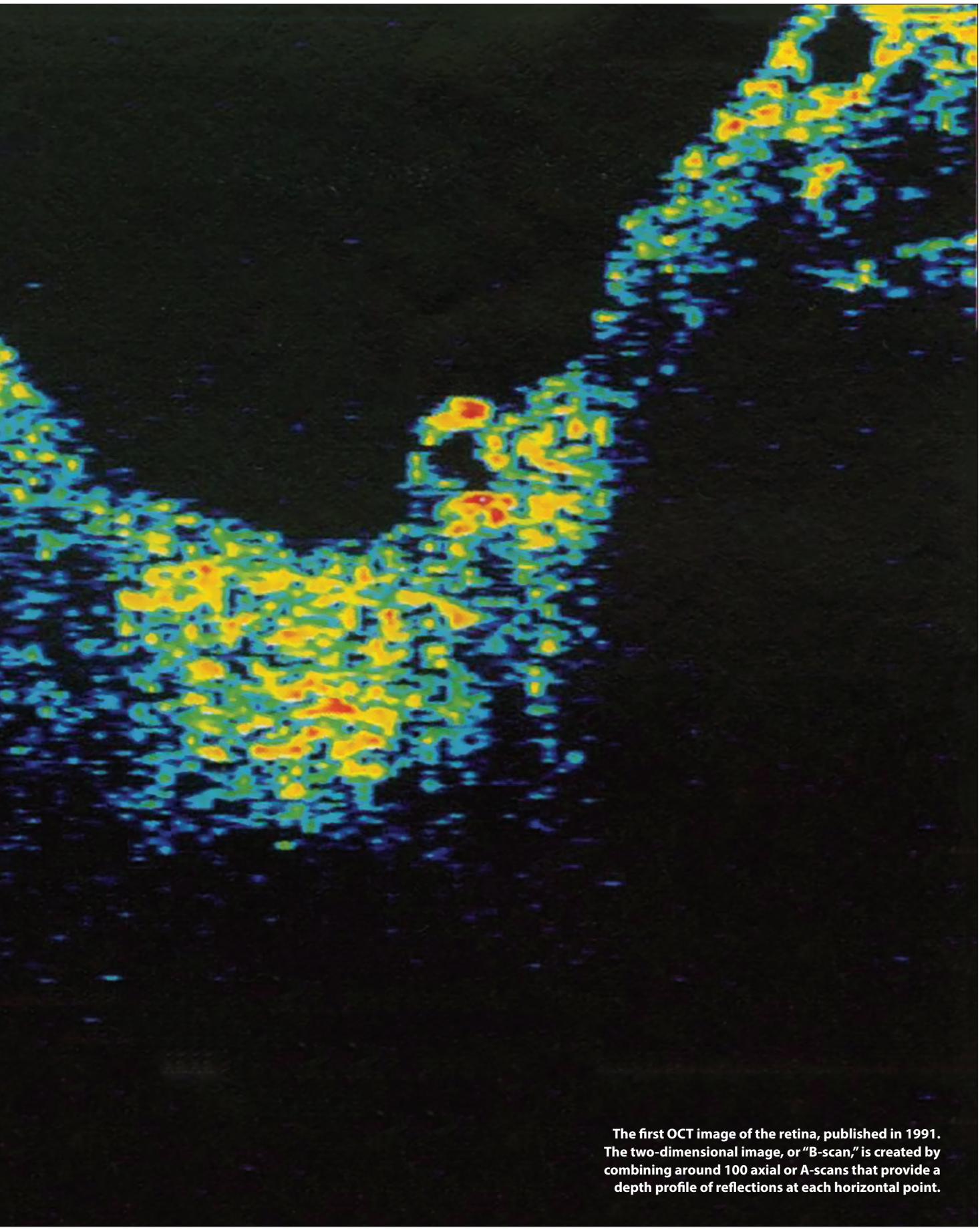


OSA Centennial Snapshots

OCT and the Flowering of Biophotonics

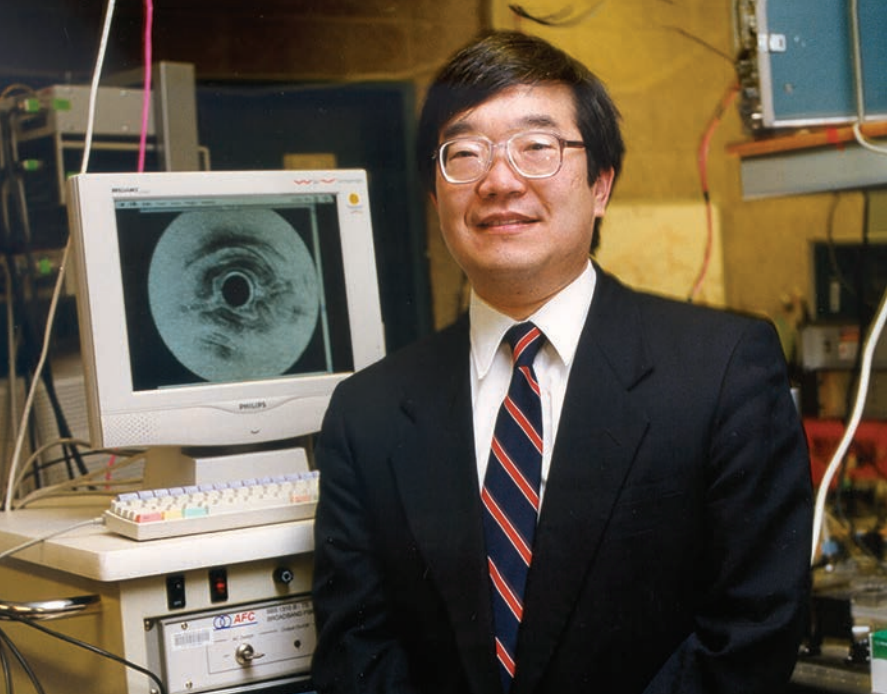
STEWART WILLS

From the mid-1980s to the mid-1990s, government funding and interdisciplinary innovation combined to launch optical coherence tomography—a milestone in biomedical optics.



The first OCT image of the retina, published in 1991. The two-dimensional image, or "B-scan," is created by combining around 100 axial or A-scans that provide a depth profile of reflections at each horizontal point.

Fom Huang et al., Science, doi: 10.1126/science.1957169. Reprinted with permission from AAAS.



James Fujimoto at his MIT lab, in a photograph taken in the early 2000s.
John Cook / RLE

Twenty-five years ago this month, the editors of *Science* accepted for publication a research paper titled "Optical Coherence Tomography." That three-word phrase (and its punchier abbreviation, OCT) heralded a revolution in ophthalmology—one that would spawn a billion-dollar-a-year market, and affect millions of people.

The birth, commercialization and ultimate impact of OCT stand out as landmark accomplishments even amid the abundant advances in biophotonics during the 1980s and 1990s. For this eighth installment in its "OSA Centennial Snapshots" series, OPN talked with some OCT pioneers about those early days, and the revolution the technology has wrought ever since.

The birth, commercialization and ultimate impact of OCT stand out as landmark accomplishments even amid the abundant advances in biophotonics during the 1980s and 1990s.

The quest to "see through skin"

At a basic level, OCT is analogous to ultrasound imaging: a series of 1-D scans, showing the time delay and magnitude of waves echoing from tissue layers at depth, is stitched together to form a 2-D, cross-sectional image. But in OCT, the "echoes" being read are echoes of light, not sound. And the technique used to measure the delay time is low-coherence interferometry (LCI).

The first application of LCI to a biomedical problem took place in the laboratory of Adolf F. Fercher at the University of Vienna, Austria, where LCI was used to precisely measure distances within the eye (see "Vienna: Measuring eye length," p. 45). But the path to actual OCT imaging was marked out in the lab of James Fujimoto at the Massachusetts Institute of Technology (MIT), USA, beginning in the mid-1980s.

Fujimoto had already achieved some renown in ultrafast optics as a doctoral student of Eric Ippen, using mode-locked dye lasers and nonlinear optics to generate pulses on the order of 16 fs. Fujimoto and Ippen began to consider possible applications of ultrashort pulses in biological systems, and they teamed up with an ophthalmologist, Carmen Puliafito of the Harvard Medical School, and several other researchers.

Particularly interesting to the team was the prospect of "seeing through skin"—inside biological tissues—with "echoes" of light, analogous to ultrasound imaging. The idea had been suggested as early as 1971 by M. A. Duguay and A. T. Mattick, who argued that such light-based echograms would be possible "if subpicosecond pulses become readily available."

Using 65-fs pulses from a ring dye laser, Fujimoto and the others applied nonlinear cross-correlation gating, which harnesses second-harmonic generation to measure the time delay of light bouncing off of a tissue layer relative to a reference pulse. They were able to obtain an axial scan (or, in later parlance, A-scan) of a rabbit's eye—essentially, a 1-D profile of backscattering versus depth that clearly showed prominent reflections at the front and back of the cornea. But additional efforts with human skin, a much more optically scattering medium, proved less successful.

While the first results, published in *Optics Letters* in 1986, were encouraging, the ultrafast-pulse

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approach promised to be expensive. "Ultrashort-pulse lasers were some of the most complicated technology on the planet, and still are," notes Joseph Izatt, now at Duke University, USA, who joined the Fujimoto lab as a postdoc in 1991. So, in the late 1980s, Fujimoto and the team began exploring LCI, coupled with techniques then being developed independently in fiber optics and telecomunications, which involved much simpler, cheaper components and promised better scalability.

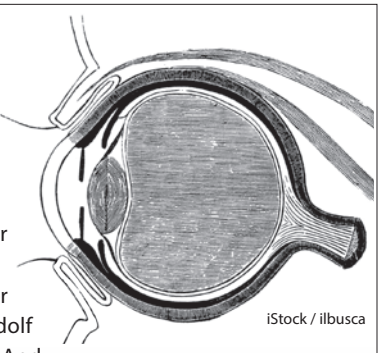
At about this time, the team added two new members, each of whom would play a key role in OCT's development. One of them, David Huang, was an M.D./Ph.D. student at MIT who was casting about for a thesis project in biophysics. Fujimoto's lab "was very nearby—my master's thesis lab was on the same floor of the adjacent building," says Huang. "And I liked the laser lab because the physics seemed really cool, and the setup was pretty amazing." So Huang went to work in the Fujimoto lab.

The other new collaborator was Eric Swanson, a staff member working on intersatellite and fiber optic communications at MIT's Lincoln Laboratory, where Fujimoto had worked as a consultant. One day, Swanson recalls, Fujimoto "asked me if I would be interested in collaborating with his group at MIT campus in biomedical optics." Ironically, Swanson—who would become central to the development, commercialization and success of OCT—almost declined the invitation, as he was already quite busy and the new work seemed far afield from his mission area at Lincoln Lab.

The birth of OCT imaging

Initially, says Huang, Fujimoto put him to work on projects related to femtosecond laser surgery, but then Huang was switched to the LCI

Vienna: Measuring eye length



iStock / ilbusca

The first published use of low-coherence interferometry (LCI) in ophthalmology, for "intraocular ranging"—essentially, measuring the internal length of the eye, a key parameter for cataract surgery—came from the lab of Adolf F. Fercher at the University of Vienna, Austria. And, according to Christoph Hitzenberger, who joined the lab as an assistant professor in 1987, "this was then considered a very exotic field."

At the time, Hitzenberger—whose background was in electron microscopy and solid-state physics—had "no idea about ophthalmic optics," he says. "But I thought, 'Well, this is something like using lasers in ophthalmology, and that sounds very interesting' … I applied for the position, and luckily I got it."

Fercher himself, who hailed from Germany, had joined the university only a year earlier to set up his new Institute of Medical Physics, bringing with him a proof of concept for measuring eye length using LCI. As Hitzenberger was joining the lab, Fercher and colleagues were wrapping up an *Optics Letters* paper on the interferometric eye-ranging technique that would be published the following year.

The system used lasers and a Fabry-Pérot interferometer to analyze light reflected from the eye's back wall and from the anterior surface of the cornea. The distance between the interferometer plates was manually adjusted until an interference pattern between the two reflected beams became visible, at which point the intra-plate distance equaled the eye's optical length.

But the new scheme had to clear a big hurdle before it could be practical: it was slow and complicated to undertake. "A single measurement took about 15 minutes in a healthy person," says Hitzenberger. Fercher handed him the task of hammering that time down to make the technique feasible in a clinical setting.

Hitzenberger's solution was to apply a principle from telecommunications and signal processing—heterodyne detection—to Fercher's setup. Specifically, rather than manually shifting one of the interferometry plates in incremental steps, and looking for interference fringes at each step, Hitzenberger's refinement moved the plate at a constant velocity, and modulated the intensity of the interference pattern by the Doppler frequency shift.

The setup—which used a photodiode to convert the data into an electrical signal—proved far more amenable to computer processing than Fercher's original one. And, crucially, it cut the time for a single measurement from 15 minutes down to less than 3 seconds.

"That was the breakthrough for intraocular ranging," says Hitzenberger, adding that the group was ultimately able, using the technique, not only to measure eye length, but also to get retinal thickness measurements and profiles of the ocular fundus (the eye's interior surface, opposite the lens). By 1993, they had shown that the technique could be used at scale in the clinic on patients. Eventually, the Carl Zeiss Company built an instrument based on the technology, the IOL Master, that sold thousands of units.

Nonetheless, Hitzenberger stresses, the Vienna group's early work was firmly in the realm of intraocular ranging. "We didn't come at this from the imaging side," he says. "The idea to take images came later," from James Fujimoto's lab on the other side of the Atlantic Ocean.

Huang had hit upon the idea of the B-scan—lining up a series of 1-D A-scan profiles to create a cross-section, or tomogram, of the retina's structure at depth.

project. At that point, he says, "we were going to do some trivial things, like measuring corneal thickness and the depth of radial keratotomy." An undergraduate student at MIT, John Apostolopoulos, had already done a bachelor's thesis in 1989 in which he used a modified Michelson interferometer to generate 1-D echograms, or A-scans, of the cornea, but the measurements suffered, Huang says, from a low signal-to-noise ratio.

Huang picked up where Apostolopoulos had left off, and, working with Swanson, set up a new, benchtop interferometer that used single-mode fiber in a way that significantly boosted the signal-to-noise ratio. Huang then started scanning a collection of *ex vivo* eyes provided by Puliafito's group at Harvard. In addition to corneal thickness, he says, "we were thinking we could also measure the thickness of the retinal layers." But he found that the retinal signal was plagued by speckle noise. "I couldn't tell one layer from another."

In considering the noise problem, Huang recalls, "I thought if we make an image—if we scan the beam over hundreds of positions, and compile the axial scans into a false-color image—then despite the noise, the layers will become apparent … And then it occurred to me that this was actually a new imaging modality, because nobody had described these kinds of images before."

Huang had hit upon the idea of the B-scan—lining up a series of 1-D A-scan profiles to create a cross-section, or tomogram, of the retina's structure at depth. Using the concept, he created tomographic images with a 15-micron axial resolution of the retina and the coronary artery (from *ex vivo* samples), and was able to match structures on the tomograms with histological images of the same tissues. The team published the images in a landmark paper in *Science* on 22 November 1991 (which, at last count, has garnered more than 6,500 citations on ISI's Web of Science). Optical coherence tomography was born.

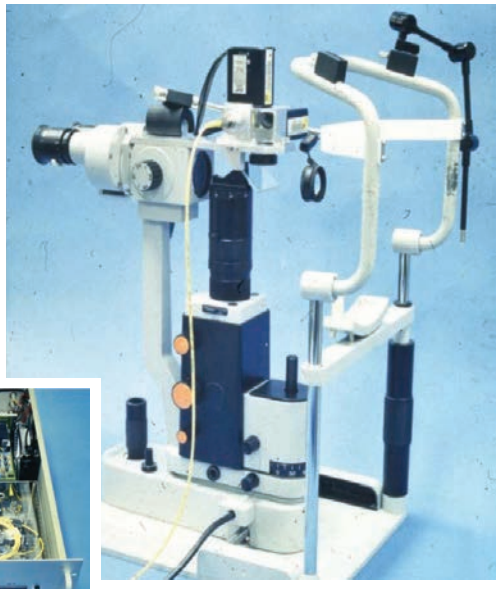
The need for speed

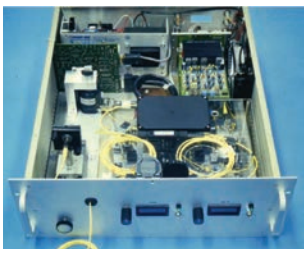
Work on commercializing the technology commenced almost immediately, with Fujimoto, Puliafito and Swanson creating the first OCT start-up company, Advanced Ophthalmic Diagnostics (AOD), in 1992. But, exciting as the initial *Science* images had been, the team had much to do to engineer the technology for clinical testing, let alone widespread clinical use.

The time the procedure took was a critical first hurdle. For the images in the *Science* paper, it had taken at least 190 seconds to obtain a B-scan consisting of 100 A-scans—fine, Huang notes, for working with *ex vivo* tissue, but far too long for *in vivo* use in the clinic, where the patient's eye motion

would hopelessly muddle the results. "The goal," he says, "was to increase the speed to something like 100 A-scans per second."

Toward that end, Eric Swanson's expertise in optical communication technology became crucial. It was, Swanson recalls, "a little surprising—the heart of an OCT system ended up looking very much like the intersatellite transceivers we were building. They were coherent (or interferometric); had high dynamic range, low noise and dual balanced detection; used a combination of fiber optics and bulk optics; even used galvanometric beam scanners to scan laser beams. All these technology and system concepts," he says, "although we didn't realize it at the very start, translated well to exactly what OCT needed."





Retinal imaging prototype setup designed by Eric Swanson, for use in the 1993 clinical tests.

Courtesy of Eric Swanson

Using those concepts, the MIT team built a relatively compact prototype that increased the imaging speed a hundred fold. Joseph Izatt and Ph.D. student Michael Hee (an author on the original *Science* paper, and today a practicing eye surgeon and consultant in the San Francisco area), collaborated on the control software and clinical studies.

The moment had come for the first clinical tests. "We had official approval to image normal subjects," says Izatt. "Which were ourselves." Eric Swanson vividly recalls the moment of those first tests with a setup that, until then, had never been tested on humans—and how Fujimoto calmly sat down to expose his own eyes to the apparatus as test subject number one.

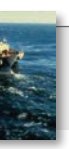
Those sessions produced the first *in vivo* clinical images from the U.S. group, published in several papers in 1993. Fercher's group in Vienna published its own *in vivo* OCT image in the same year. As Christoph Hitzenberger, who was involved with the work, notes, the Vienna group used an instrument based on bulk optics and optimized for ocular biometry. That meant a lower signal-to-noise ratio and a slower speed for imaging applications than the setup of the MIT group, which was engineered for clinical use, having high-speed optical scanning and real-time display.

The MIT group's initial *in vivo* experiments led, with support from the U.S. National Institutes of Health, to clinical studies involving more than 5,000 patients. These studies, published in a variety of papers in 1995 and 1996,

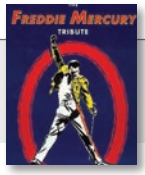
1990
Optics News is renamed *Optics & Photonics News*

1993
OSA Recognizes Educational Excellence with Beller Medal

1995
CLEO Branches Out to Europe



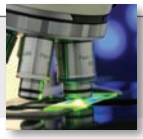
1989
Exxon Valdiz Spills 11 Million Gallons of Oil



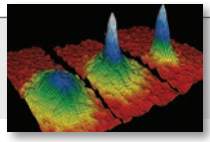
1992
Over One Billion People View AIDS Concert

1994
Nelson Mandela Elected President of South Africa

1990
The Hubble Space Telescope Launches

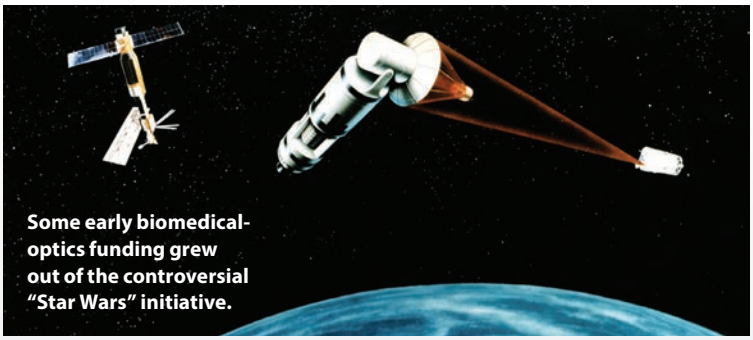


1993
Betzig and Colleagues Home in on Single Cell Imaging



1995
Cornell and Wieman Create World's First Bose-Einstein Condensate

Source: Wikimedia Commons, OSA Historical Archives and iStock



Some early biomedical-optics funding grew out of the controversial "Star Wars" initiative.

Wikimedia Commons

Funding and the biophotonics bloom

As Gregory Faris documents in the recently published *OSA Century of Optics*, OCT was only one of many applications of photonics to biological research and medicine that began to take off in the mid-1980s and 1990s. A number of factors—maturing technology, commercial developments, even the boom in molecular biology and biotech—all contributed to this biophotonics bloom. Yet James Fujimoto, generally viewed as the father of OCT, points to one factor as particularly crucial.

"In the United States, funding from the Air Force Office of Scientific Research had a major impact," he says. The funding—which, Fujimoto notes, was a spinoff of the Reagan administration's controversial Strategic Defense Initiative (SDI), colloquially known as "Star Wars"—was, in his judgment, "the major driving force for development of lasers in medical applications during this period."

What got the Air Force interested in that topic? William P. Roach, who heads up AFOSR's physical and biological sciences branch, says that the attention of the Air Force and other armed services stemmed partly from progress in weapons technology. "There was a medical need to look at injury, particularly eye injury," says Roach, in light of the development of new battlefield technologies such as laser rangefinders. That, in turn, raised a need to understand, protect against, and treat new kinds of retinal injuries.

At that time, Roach notes, "there *were* no academic biomedical engineering departments, and there *was* no recognized biomedical optics academic track"—those areas didn't yet exist as formalized disciplines. Within that environment, Roach credits much of the early development of the U.S. government's biomedical-optics funding to the vision of one person: Howard Schlossberg, AFOSR's program manager for optical sciences, who joined the office in 1978. During the mid-1980s, Roach notes, "Schlossberg, was pretty much on his own, and was funding lasers and biology," as well as programs in what today would be labeled biomedical optics.

Those initial efforts were followed up in 1988 with the creation of the Medical Free Electron Laser Program. That program—led by the U.S. Office of Naval Research under Michael Marron, and including AFOSR (Schlossberg) as a reviewer—arose through a congressional earmark of US$15 million in annual funding (and later more) that had crept into the SDI budget. A third defense funding component, focused on ultrashort laser pulse technology and its effect on human eyes, came on stream in 1991.

"To me," says Roach, "those three programs"—Schlossberg's early efforts and the two large government projects that followed—constituted "sort of the 'forcing function' that would help create the new disciplines" that today make up biomedical optics. Roach recalls that in 1992, only one professional society, SPIE, had put together a small interdisciplinary group on biomedical applications of lasers and optics. Within five years, all other major professional societies, including OSA, had followed suit—a development Roach believes was strongly aided by the military interest. "It's out of these programs, in my opinion," says Roach, "that these disciplines were helped to be strongly positioned to be born."

firmly established OCT's ability to shed light on a variety of retinal diseases—as did the publication in 1996 (spearheaded by Carmen Puliafito) of the first atlas of OCT and ocular diseases.

Meanwhile, the Carl Zeiss Company had purchased the AOD start-up in 1994, and by 1996 the company had released the first commercial OCT unit. "At that point," says Swanson, "I think it was very clear that OCT had a promising future."

Events afterward would bear out that perception. Although the earliest Zeiss OCT instruments met with a cool response in the ophthalmic market in the late 1990s and early 2000s, the company stayed the course, and with the unveiling of the third-generation StratusOCT instrument, in 2002, Zeiss had a major hit on its hands. By 2006, an estimated 6,000 StratusOCT units had been sold, and some 20 million ophthalmic OCT procedures had been done worldwide.

Toward next-gen OCT

Even as this first generation of OCT was becoming clearly established as a clinical standard of care, the foundation of the technology's second generation was being laid. First-generation OCT used time-domain detection (TD-OCT), involving mechanical scanning of the reference arm of an interferometer. But it was clear early on that, given the right technology advances, systems could also be built that worked in the Fourier domain, and that used spectrometry and high-speed digital cameras to measure the interference and capture OCT images—an approach that came to be called spectral-domain OCT (SD-OCT). And tunable lasers offered the possibility of another Fourier-domain implementation, using an interferometer and a frequency-swept laser, called swept-source OCT (SS-OCT), with the potential of even higher speeds.

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While Fujimoto's group was heavily involved during the early 1990s in technology development and clinical studies to establish TD-OCT, the team also actively investigated both types of Fourier-domain OCT starting in the early 1990s, with patents outlining both SS-OCT and SD-OCT submitted as early as 1991 and 1996, and several papers on SS-OCT in 1997.

The first published paper outlining SD-OCT, meanwhile, came from Fercher's Vienna group in 1995. Christoph Hitzenberger, the second author on that paper, notes that the study—which has gone on to be cited more than 900 times in the literature—was largely overlooked initially. The reason: although SD-OCT potentially had a huge sensitivity advantage over time-domain detection, that advantage wasn't demonstrated until 2003 "because the CCD cameras that were available earlier were not good enough" to exploit that advantage. Then, in a rush of papers in 2003, the Vienna group along with colleagues at Copernicus University, Toru'n, Poland, as well as researchers at Duke University and at Massachusetts General Hospital, all independently demonstrated SD-OCT's powerful sensitivity and speed advantages. (The Duke paper also showed similar advantages for SS-OCT.) The Vienna group, notes Hitzenberger, followed up with the first clinical imaging with SD-OCT, published in *IOVS* in 2005.

Once camera technology had caught up, SD-OCT would constitute a sort of second revolution in OCT, starting with the introduction of the first commercial system approved by the U.S. Food and Drug Administration, by Optovue, in 2006. Today, SD-OCT is the standard technology for ophthalmic instruments, and SS-OCT has become the dominant technique for ultra-high-speed OCT imaging. "Sometimes," concludes Hitzenberger, "people have ideas, or do some experiments, before the time is ripe."

A thriving ecosystem

This installment of our "OSA Centennial Snapshots" series must end at this point. But the larger OCT story has continued and picked up speed in the years since the mid-2000s. Revenue associated with OCT systems is approaching US$1 billion a year. And new applications—ranging from imaging in other clinical specialties such as cardiology, dermatology and gastroenterology, to non-biomedical uses from industrial sensing to art history sleuthing and restoration—continue to open up, seemingly on a daily basis.

Swanson credits the success of OCT over the past two decades to the development of a robust OCT ecosystem. That ecosystem is, critically, anchored by solid physics and a long-term government funding commitment (on the order of half a billion U.S. dollars over the past ten years), and includes other interconnected stakeholders such as researchers, clinicians, entrepreneurs, venture capitalists, and companies small and large.

Yet the birth of OCT also marks an early triumph of something now taken for granted in biomedical optics. "Today, interdisciplinary research in biomedical optics is the standard," says Swanson. "And that was less common 25 years ago." A lot of innovation, he points out, "happens at the boundaries of disciplines. OCT is such a rich combination of disciplines—in optics, mechanical systems, electronics, software, medical devices, clinical medicine. That's one of the reasons there's been so much innovation in OCT, and that there's so much more to come."

David Huang, now on the faculty of ophthalmology and biomedical engineering at the Oregon Health and Science University, USA, agrees. Much of his own career success, he notes, has stemmed from being able to see both the clinical and the engineering sides. And the birth of OCT "was possible because there were people who were knowledgeable about both clinical applications and the technology," Huang says. "The big progress got made at the intersection between disciplines." OPN

Stewart Wills (swills@osa.org) is the editor and content director of *Optics & Photonics News*.

References and Resources

A complete list of references and resources can be found in the online version of this article, at www.osa-opn.org/link/snapshots-oct .

Two articles in a special issue of *Investigative Ophthalmology and Visual Science* published in July 2016 to mark the 25th anniversary of OCT (http://iovs.arvojournals.org/ss/octissue.aspx) provide a more detailed scientific perspective (and copious references) on the development of OCT technology, including the events described in this feature:

- J. Fujimoto and E. Swanson. "The development, commercialization, and impact of optical coherence tomography," IOVS **57**, OCT1 (2016).
- C.K. Hitzenberger et al. "Key developments for partial coherence biometry and optical coherence tomography in the human eye made in Vienna," IOVS **57**, OCT460 (2016).

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