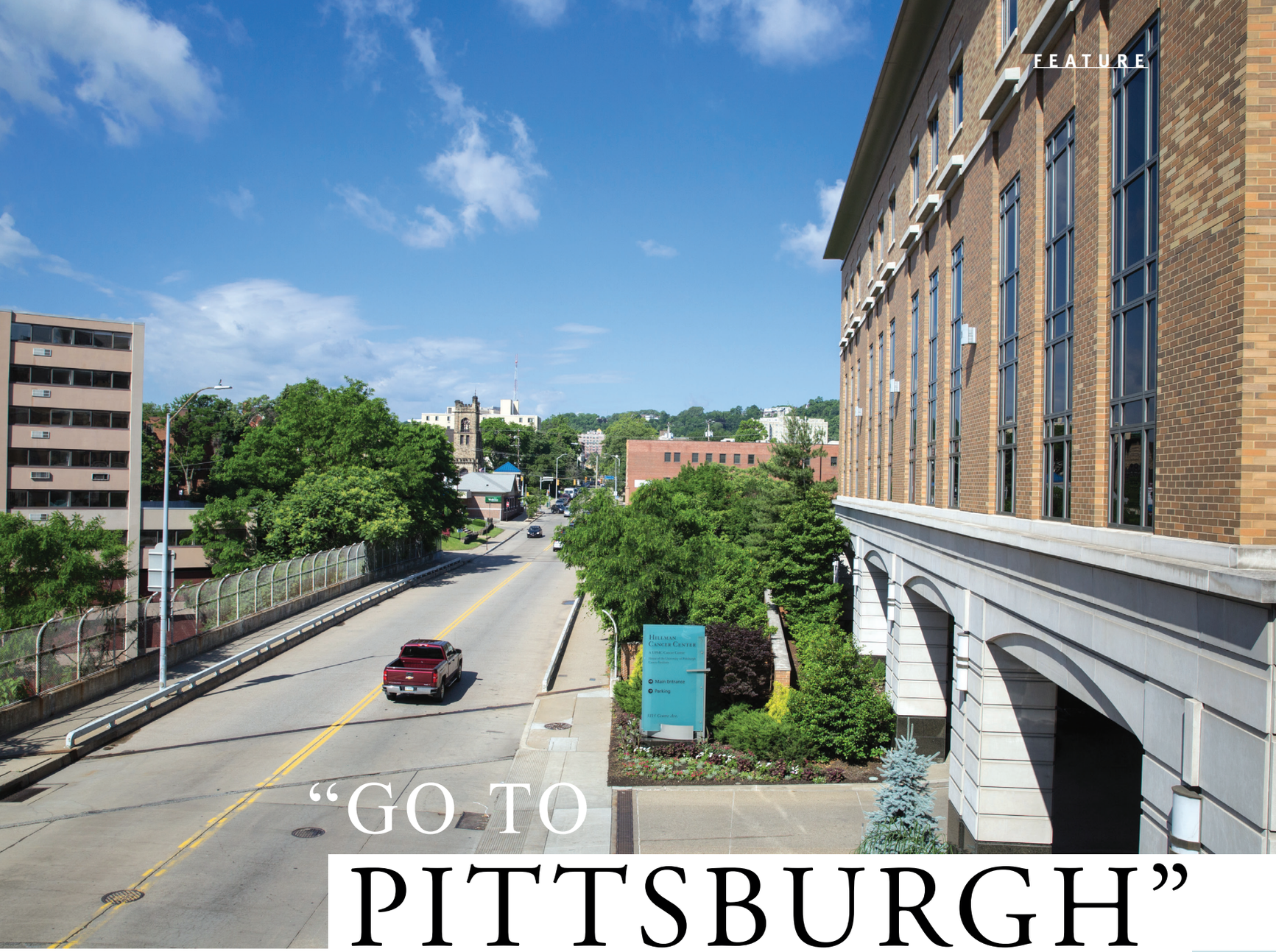


"GO TO PITTSBURGH"

HOW A CANCER INSTITUTE CAME OF AGE

BY JULIE SCHWIETERT COLLAZO

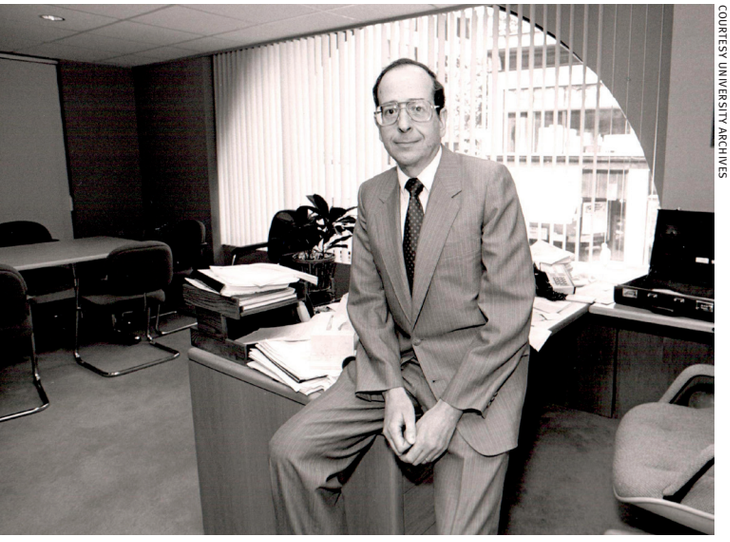
Louis Bodek, a retired teacher from Northern Cambria, Pa., went to a Walmart Vision Center for what he hoped would be a routine checkup in October 2014.

"I had this little faint gray mark that was in my field of vision, in my left eye," he recalls. "I wanted the optometrist to take a look." Right away, it became clear that the visit would be anything but routine.

"Something's not right there," the optometrist told Bodek.

"He made me get on a better machine," Bodek, 62, recounts. "He groaned when he looked at it. He said, 'Oh boy, I want you to go to Pittsburgh immediately. I'll call for you; they have better equipment.'"

Bodek went the same day to retina specialists in Pittsburgh, and by that evening, he had a diagnosis: ocular melanoma, the most common eye cancer in adults (though far less common than skin melanoma). With a metastasis rate of approximately 50 percent, ocular melanoma is often fatal. A procedure to eliminate the tumor from his eye was successful, but doctors told him the cancer had spread to his liver. They would try to get him in to see the University of Pittsburgh Cancer Institute's melanoma and skin cancer program director John Kirkwood, an MD, who is Pitt's Sandra and Thomas Usher Professor of Melanoma.



COURTESY UNIVERSITY ARCHIVES

Under Ronald Herberman, UPCI became an NCI-Designated Cancer Center in record time.

By Thanksgiving 2014, Bodek had met Kirkwood. "When he walked in, I knew this was a serious man who'd put it all on the line for me. He told me, 'You have cancer. It has spread, and it's at stage 4.' Dr. Kirkwood told me about the 5–10 percent success rate and said, 'Here's what we can do for you.'"

Kirkwood initially put Bodek in a clinical trial on interleukin-2. It fought the cancer, but, says Bodek, "It did a number on my heart."

Kirkwood was leading another trial examining the efficacy of a new class of drugs called immune checkpoint blockers. These drugs work by not allowing cancers to turn on the immune system's built-in brakes. So Kirkwood took Bodek off of interleukin-2 and in its place, introduced pembrolizumab, an immune checkpoint blocker approved by the FDA for certain advanced melanoma regimens in just the past two years.

The introduction of immune checkpoint blockers to cancer care represents "really a remarkable change," Kirkwood says. Prior to this, for melanoma cases that are advanced and inoperable "there was not a single therapy which we knew had an effect upon survival, and only one treatment that had any ability to stop the disease more than 10 percent of the time." One of Kirkwood's current research projects seeks to identify the mechanisms of resistance to immune checkpoint blockers.

Kirkwood has been on the front lines of the fight against melanoma since UPCI's very beginning. The institute turned 30 last year; in many ways, the melanoma program mirrors UPCI's strengths as it's matured—notably advancing research at the bench and seeing that through to its translation into promising new therapies. And there are thousands of stories like Bodek's at UPCI; from across the region and beyond, people facing the diagnosis of almost every type of cancer come to Pitt specialists for world-class care and the chance to be part of experimental therapies.

Kirkwood, who was there in the early days, recalls that the center's origins were indeed quite humble—though the center was founded by Ronald Herberman, an MD who'd been a leading figure in cancer immunology at the National Cancer Institute.

"When I arrived, the Cancer Institute had just about four rooms in the refurbished Eye and Ear Hospital," which, Kirkwood says, was one of the wings of the old Presbyterian Hospital. It had no medical oncologists.

UPCI, now ranked sixth among National Institutes of Health–funded university cancer centers, began in a janitor's closet—depending, that is, "upon which version of the story you believe," says Nancy Davidson, MD director of UPCI; she is also the Hillman Professor of Oncology and a Distinguished Professor of Medicine at Pitt.

In the 2016 fiscal year, UPCI received $147 million in research funding. It's made stronger by, and in turn strengthens, the UPMC CancerCenter network—which includes 40-plus clinical sites today, with 2,000 specialists and 15 disease-focused care centers. More than 74,000 patients pass through CancerCenter doors each year.

How did it rise so quickly?

Already, the University was home to Distinguished Professor Bernard Fisher, MD '43, whose contributions to understanding breast cancer and its progression were changing how people thought about cancer and treating it.

And: "Pitt was famous for its achievements in organ transplantation," says Olivera Finn, a PhD, Distinguished Professor, and founding chair of immunology at the School of Medicine, who's been a member of the UPCI for 25 years. "The goal of the leadership was to catch up and to surpass that fame . . . in cancer research and treatment, as well."

Prominent local families rallied to the cause. After conversations with Pitt's Thomas P. Detre, MD and former senior vice chancellor for the health sciences, George Taber of the Richard King Mellon Foundation set up the funding that permitted the recruitment of Herberman to direct what was then called the PCI, or Pittsburgh Cancer Institute, in 1985. Herberman served in that capacity until 2009, when Davidson, renowned for her breast cancer work at Johns Hopkins, was appointed director. (By the way, based on her research contributions, Davidson was elected president of the American Association for Cancer Research this year.)

In the early years, Kirkwood says, Herberman's team "put out grant proposals every month or two. In quick succession, we got several." By 1988, UPCI had gained the vaunted status of a National Cancer Institute (NCI) Designated Cancer Center, which recognizes excellence in basic science, clinical research, translational science, education, and outreach. Last year, that core grant was renewed once again—with reviewers noting that UPCI's application was "outstanding." Thanks to its substantial translational research activity, the institute has been one of NCI's Comprehensive Cancer Centers since 1990, which is an even more prestigious designation. Today, Pitt faculty hold a total of 166 NCI grants.

During Herberman's tenure, the dream of a new research facility became a reality, thanks to the Hillman Foundation. In 1999, it supported the construction of the Hillman Cancer Center, which would become PCI's home on the UPMC Shadyside campus. The Hillman Family Foundations, providing almost $24 million in gifts for research funding since 2004, have also helped UPCI attract and retain top investigators.

Davidson describes those gifts as "pivotal." She notes that the Hillman Center layout facilitates the relationships between researchers and clinicians—a bridge and other common areas connect clinical and research spaces, which now total nearly 450,000 square feet.

Those close links remain central to UPCI's work: "Everyone uses the same lobby—the researchers, the patients, the nurses, the doctors," Davidson says, "and it helps us keep a focus on why we're all here."

Many of the patients at Hillman, UPCI's flagship center, are probably unaware of just how much the people with whom they cross paths are contributing to the understanding, treatment, and prevention of cancer. Kirkwood says that in the area of melanoma alone, the advances during his time at UPCI have been astounding.

"I really think we can take some significant credit for the fact that we have 10 new FDA-approved treatments for melanoma," he says.

Pitt is home to three SPORE projects (Specialized Programs of Research Excellence)—those are focused on cancers of skin (led by Kirkwood), the head and neck (led by Robert Ferris, an MD/PhD, UPMC Professor of Advanced Oncologic Head and Neck Surgery, and professor of otolaryngology, with former Pitt faculty member Jennifer Rubin Grandis (MD '87, Res '88, Fel '92, Res '93), and the lung (led by James Herman, MD professor of medicine). Make that three-and-a-half—Pitt also shares a SPORE grant on ovarian cancer with Roswell Park Cancer Institute (Pitt's lead is Robert Edwards, MD professor and chair of obstetrics, gynecology, and reproductive sciences). NCI designed these grants to quickly move promising research findings along to therapeutics, "as well as to determine the biological basis for observations made in individuals with cancer or in populations at risk for cancer," according to the agency.

UPCI is home to hundreds of federally supported programs beyond the SPORE initiatives. Those investigations include probing for the best ways to detect breast cancer and using broccoli sprout extracts to prevent oral cancer, to name just a couple. Faculty efforts to understand the basic workings and biology of cancer—including the roles played by viruses, the immune system, and mitochondria—have produced a flood of revealing results (for instance, identifying two of the seven viruses known to cause cancer). Pitt has built a head-turning genome stability group that's just published a string of papers in *Nature* and other top journals; those investigators look at how cancer can unfold when DNA's repair machinery is threatened. And UPCI's clinical trial presence—hundreds at any given time—is dizzying. (An online tool that taps into current trials and findings guides CancerCenter physicians in suggesting the most appropriate evidence-based approaches.) UPMC's own $100 million investment in pursuing personalized medicine focused first on cancer—and helped Pitt gain notice for President Barack Obama's Precision Medicine Initiative.

Just this August, UPCI learned it will receive up to $10 million throughout the next five years from NCI for preclinical research—that means researchers here are now involved in every NCI drug development stage, from screening drugs to determining dosage to all phases of clinical trials.

Nancy Davidson
has led UPCI through seven years of tremendous growth; UPCI investigators received a total of $147 million in funding in 2016.

PORTRAITS BY CIDDE

John Kirkwood
could add "informal memory keeper" to his many roles at UPCI. His team's progress in melanoma through the past few decades mirrors UPCI's strengths.

UPMC CancerCenter also has seven international initiatives. Not surprisingly, UPCI's reach is also global. Davidson points to the work of faculty like Jian-Min Yuan, an MD/PhD and a highly respected epidemiologist who was hired in 2011 to serve as UPCI's associate director for cancer control and population sciences and leader of the Cancer Epidemiology, Prevention, and Control Program. When Yuan, who now holds the Arnold Palmer Chair in Cancer Prevention, arrived at UPCI, he was already the principal investigator of four NCI-funded studies. One of them is a longitudinal study still in progress that tracks more than 80,000 research participants in Shanghai and Singapore.

"Dr. Yuan has been following these people for over 25 years now," says Davidson. "He took people when they were healthy and spent time getting histories, data, and samples from time to time. He was looking at the question: What happens to people that they would become cancer patients?" The significance of this study is profound, Davidson says, because cancer rates are skyrocketing in Asia.

Kirkwood notes that in the field of melanoma, modern research has produced a great deal of information that can be used for early detection, yet the utility of that information is constrained when providers aren't aware of it. So he and his colleagues have embarked on an effort to train more than 500 primary care clinicians in the UPMC system through an online education program, and it's working. Melanomas detected by the program's trained physicians were, on average, half the thickness, and therefore had a better prognosis, as those found by the physicians in the control group.

READY FOR LIFTOFF

In his 2016 State of the Union address, President Barack Obama announced the National Cancer Moonshot initiative—a program led by Vice President Joe Biden that aims to put cancer research on the fast track, to accomplish in five years what is usually done in 10. Pitt people are among the experts from around the country who have been called on to help with the liftoff:

- **As a National Cancer Advisory Board member, Pitt's Distinguished Professor of Pathology, Yuan Chang, an MD, will review the Blue Ribbon Panel's recommendations to the vice president on the initiative.**
- **With Peter Ellis, an MD and director of UPMC CancerCenter's Medical Oncology Network, Nancy Davidson, UPCI director and Hillman Professor of Oncology, has been meeting with representatives of the vice president's office.**
- **Davidson, an MD, led a congressional briefing on progress in cancer research and the opportunities that lie ahead. She was joined by UPCI's Kara Bernstein, PhD assistant professor of microbiology and molecular genetics. (Davidson also attended the National Cancer Moonshot summit hosted by Vice President Biden in Washington, D.C.)**
- **UPCI hosted the region's Cancer Moonshot Summit in June. It was organized by UPCI's deputy director and professor of medicine Edward Chu, an MD; Maryann Donovan, PhD research administration associate director; and Linda Robertson, an RN, DrPH, assistant professor of medicine, and associate director of health equity, education, and advocacy. A special guest star also stopped by the summit: the Stanley Cup. (The Penguins' Mario Lemieux, a cancer survivor, has long been an important supporter of UPCI.)** ***—Ali Greenholt***

In addition, physicians who did the online training were more likely to detect melanomas. (The study involved 330,000 patients who were screened at UPMC in 2014.) Prevention is occupying Kirkwood's time as much as treatment does these days.

The Eye and Ear Hospital ward where Kirkwood once worked feels a lifetime away now that he is an international melanoma expert at a top cancer center. The fact that such a transition occurred in a few short decades is somewhat remarkable, he admits; but what is even more impressive to him is what UPCI has accomplished, particularly in the past five years.

Now, he says, "we can actually understand what we're doing at ground zero in the tumor, and in the blood, and in other tissues of the body, so as to move novel clinical trials forward in months." Previously, he points out, "this would have taken us many years and, more often, more than a decade, to make progress."

Bodek understands he's part of a clinical trial, but he believes the immune checkpoint blocker represents his best chance, pointing out that pembrolizumab is the same drug former President Jimmy Carter was given to treat melanoma, which had metastasized to his liver and brain. Carter recently announced he is cancer free. "If it worked for a 92-year-old man, maybe it will work for a 62-year-old man," Bodek says, laughing.

"I feel optimistic. I really feel like it's going to come to a good conclusion."

IN ITS PRIME

UPCI TURNED 30 LAST YEAR. DURING THOSE FEW DECADES, IT HAS GROWN TREMENDOUSLY—AND SO HAS ITS ABILITY TO REDUCE THE BURDEN OF CANCER.

GRANTS AND FUNDING

- $147 MILLION IN 2016
- RANKED SIXTH IN NIH FUNDING AMONG UNIVERSITY RESEARCH RECIPIENTS
- $10 MILLION FROM NCI OVER THE NEXT FIVE YEARS TO SUPPORT PRECLINICAL RESEARCH IN DRUG DEVELOPMENT
- 166 CURRENT NCI GRANTS
- 3 UPCI FACULTY MEMBERS HONORED WITH OUTSTANDING NCI INVESTIGATOR AWARDS IN 2015 AND 2016
- FIRST DEEMED AN NCI-DESIGNATED CANCER CENTER IN 1988; SINCE 1990, ONE OF NCI'S 47 COMPREHENSIVE CANCER CENTERS

RESEARCH PUBLICATIONS

- 5,000 IN LAST FIVE YEARS

FACULTY INVESTIGATORS

- 344

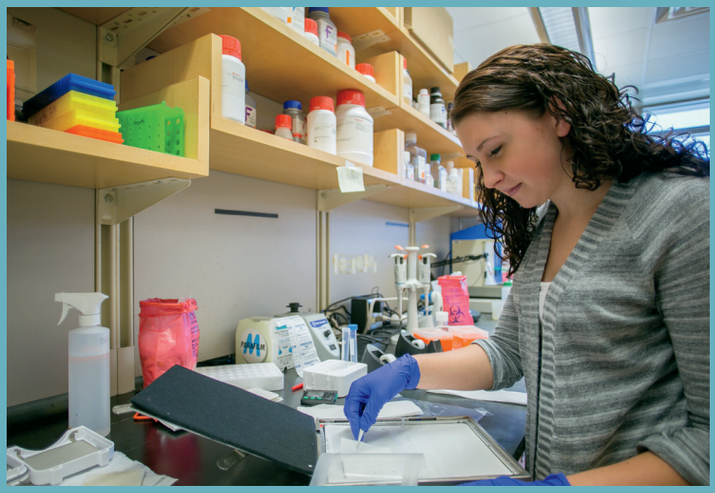
CLINICAL TRIALS

- 458 ACTIVE TRIALS

ITS CLINICAL PARTNER, UPMC CANCERCENTER, LAYS CLAIM TO . . .

- MORE THAN 25,000 NEW PATIENTS EACH YEAR
- 2,000 EXPERTS
- 40+ TREATMENT CENTERS IN WESTERN PENNSYLVANIA AND OHIO
- 7 INTERNATIONAL CLINICAL INITIATIVES (IN IRELAND, ITALY, CHINA, COLOMBIA, KAZAKHSTAN, LITHUANIA, AND MYANMAR)

SOURCE: UPCI/UPMC CANCERCENTER



UPCI has aged well. Shown here—scenes from its home, the Hillman Cancer Center. Pedestrian walkways, bridges, and an atrium connect research and clinical areas. Pictured: Immunology research technician Ashley Menk.

NETWORKING

Among the many clinical studies in which UPCI participates are those in the National Cancer Institute's National Clinical Trials Network and the Experimental Therapeutics Clinical Trials Network. For both of these efforts, UPCI is an academic lead. That means Pitt doctors "provide scientific leadership in the development and conduct of clinical trials," according to the NCI.

More importantly, says Edward Chu, an MD and deputy director of UPCI, with hundreds of ongoing clinical trials, "we're able to offer patients an entire continuum of drugs that are being tested at all levels of development." And because of "the breadth and depth of clinical trials that our cancer patients in western Pennsylvania have access to . . . they don't have to go outside our region. They can come right to Pittsburgh." *—AG*

PHOTOGRAPHY BY JOHN ALTDORFER (EXCEPT WHERE NOTED)