UT Southwestern
Harold C. Simmons
Comprehensive Cancer Center

GAME CHANGERS

Leading the Next Generation of Lung Cancer Discoveries

Cover photos (clockwise from top)

Dr. Robert Timmerman (left) is pioneering the use of stereotactic ablative radiotherapy in inoperable early-stage lung cancer patients and in metastatic lung cancer. He trains physicians from around the world in stereotactic radiotherapy techniques.

Dr. Hak Choy (right) is recognized globally for his expertise in radiation and chemoradiation therapy for lung cancer. As Radiation Oncology Chairman, he has assembled the latest radiotherapy technologies along with talented oncologists to ensure the most appropriate therapy is best utilized to target each individual's cancer.

Dr. Kemp Kernstine is a leader in minimally invasive chest procedures and techniques, including video-assisted lobectomy and robotic lobectomy. Dr. Kernstine trains colleagues and provides consultation for hospital surgical programs around the world.

Dr. Joan Schiller, whose research focuses on experimental therapeutics for lung cancer, is also founder and president of Free to Breathe, which aims to double lung cancer survival by the year 2022 through promotion of clinical trials to find more and better personalized treatments for patients.

Dr. John Minna (left) is the principal investigator of a National Cancer Institute Specialized Program of Research Excellence in lung cancer, one of just four in the U.S. His research focuses on understanding the molecular pathogenesis of lung cancer and on exploiting tumor genetics to better individualize treatments.

Dr. Adi Gazdar (right) studies molecular events leading to cancer's onset and driver mutations responsible for tumors' growth and spread. He is among the top 1 percent of scientists most cited in 2002-12 in their field, placing him on Thomson Reuters' list of the World's Most Influential Scientific Minds.

James K.V. Willson, M.D.
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Changing the Game

Pervasive and particularly deadly, lung cancer has remained intractable even as other cancers have yielded more readily to treatment advances. But science is steadily shedding light on therapeutic approaches that may begin to turn the odds of beating the disease in lung cancer patients' favor.

Identifying effective treatments, and speeding their delivery to patients who need them now, has been a defining mission of lung cancer physicians and scientists at UT Southwestern for nearly a quarter-century. That's when Drs. John Minna and Adi Gazdar arrived from the National Cancer Institute—bringing with them an expanding collection of lung cancer cell lines, curated by Dr. Gazdar and linked with clinical data, that today is used in scientific investigations worldwide. At UT Southwestern, the collection has been a functional and symbolic centerpiece of a diverse and far-reaching lung cancer program, regarded among peers to be at the forefront of not just discovery, but clinical care.

Simmons Cancer Center has recruited and nurtured an unusually deep bench of lung cancer physician-scientists, who are urgently generating new research findings and translating them for practical application, and of clinical innovators, who are developing and delivering safer and more effective therapies. This dynamic lung cancer team is captained by a trio of physicians—Drs. Joan Schiller, Hak Choy, and Kemp Kernstine—who themselves are pacesetters in their respective fields of medical oncology, radiation oncology, and thoracic surgery. Besides providing the latest high-quality care to patients and extensive support to physicians in the community, a key priority of the lung cancer program is ensuring that an array of clinical trials is available, expanding the range of treatment options for people desperately in need of new solutions.

Vanquishing a foe as formidable as lung cancer will require novel scientific strategies encompassing multiple disciplines of research and care. As described in this book, Simmons Cancer Center has achieved such innovations—potential game-changers—and has incorporated them into a clinical infrastructure designed at every step to provide lung cancer patients the best of treatment, and their best chance of beating the odds.

Close-up view of renowned artist Dale Chihuly's blown-glass sculpture that is on display in the lobby of the Seay Biomedical Building at Simmons Cancer Center.

A multidisciplinary approach to care

It takes a village to provide comprehensive lung cancer care.

For patients at UT Southwestern, that village is populated with lung cancer specialists in pulmonary medicine, medical and radiation oncology, thoracic surgery, radiology, and pathology, as well as oncology nurses and practitioners in a wide range of supportive services. Those specialists are supported by the infrastructure of the university and Simmons Cancer Center, which fosters frequent and in-depth collaboration and promotes seamless delivery of care.

Conferring on complex cases

Lung cancer is a tumor type that often is treated by multiple approaches—surgery, radiation, chemotherapy, targeted therapy. The trick is to get all the doctors in the same room at the same time to determine which patient requires what treatment—and when.

UT Southwestern's full range of lung cancer expertise is brought to bear weekly on the most complex cases at the Thoracic Oncology Tumor Board. The Friday afternoon conference regularly includes about 40 clinicians, basic and translational scientists, residents and fellows, data and clinical trial managers, and others involved in patient care or clinical research. The goal is to reach an evidence-based consensus on the best avenues for an individual's care, says radiation oncologist Dr. Puneeth Iyengar, co-leader of the Cancer Center's lung cancer disease-oriented team (DOT).

"The tumor board may have four or five physicians from each discipline, so we really get a consensus across the DOT on the difficult cases," he says. Usually, three to five cases, and sometimes more, are discussed each week.

Cases can be submitted for consideration without charge by oncologists in the community as well as by UT Southwestern physicians. "This is a hugely valuable service," notes thoracic surgeon Dr. Kemp Kernstine. "We look over each other's shoulders, we criticize, we use the literature, we use guidelines and meta-analyses to make sure each of the treatment pathways is appropriate to that patient. Almost every patient has some wrinkle, a little something that's different."

Typically, eight or more pathologists attend each tumor board meeting, he says, which is essential to understanding the outcomes of immunohistochemistry studies and molecular profiling done on each tumor and what they imply for diagnosis and prognosis. "Things were very simple before," Dr. Kernstine says. "Now lung cancer is broken up into many different cell types and molecular subsets and evaluating the behavior on the pathology slides. So getting the educated opinion of a lung cancer pathologist is a very important aspect of sending patients to UT Southwestern." (*See "One family's lung cancer legacy" on page 30.*)

At the end of each tumor conference, a document is created for each case that summarizes the discussion and conclusions that are reached. On campus, that information is shared with all of the patient's providers through the Medical Center's electronic medical record, which is also used to submit cases for discussion. And the deliberations, minus information about the patient's identity, can be accessed on the Medical Center's intranet.

Lung cancer program leaders hope to expand tumor conference access to other institutions' physicians who wish to observe a discussion by allowing them to sign on and watch the de-identified deliberations or request a case review and provide relevant patient records via the Internet—and perhaps even participate from remote sites.

The convenience of one-stop care

Lung cancer patients at UT Southwestern also benefit from the Cancer Center's Thoracic Multidisciplinary Clinic. With the convenience of just one visit, "patients can be evaluated by pulmonologists, medical oncologists, radiation oncologists, and surgeons," Dr. Iyengar says. The ability of those physicians to confer immediately onsite, he adds, facilitates the prompt development of a multidisciplinary treatment plan.

Dr. Kernstine cites a recent patient whose PET scan suggested metastatic disease. A radiologist reviewed the scan then and there and concluded with a high degree of certainty that the cancer had metastasized.

"This is all within about an hour of the patient's arrival," Dr. Kernstine says. "Then we were able to consult with medical oncology, who was right there—the patient didn't have to leave the room. And a clinical trials person came down and was able to give the patient a series of appropriate trial opportunities." Such immediate follow-up allows patients to receive the care they need sooner, without enduring anxiety-filled gaps worrying about what might come next.

Because the patient spoke Spanish, an interpreter was on hand to help, Dr. Kernstine adds, and all needed documents were provided in Spanish.

The Cancer Center's comprehensive, multidisciplinary approach ensures cutting-edge care is available to all patients in the region, which includes a large, diverse, urban-to-rural population.

"That," says Dr. Kernstine, "is what a cancer center is all about."

Efficient, compassionate support at all stages of treatment

Collaboration among UT Southwestern's specialists is supported by the integrated Epic electronic medical record (EMR), which allows providers to access all test results and other information about a patient's care in any university hospital or clinic without delay. "We can all read what the others are writing about and doing—it's just a single page away," says interventional pulmonologist Dr. H. Thomas Chiu.

The EMR improves efficiency, adds medical oncologist Dr. David Gerber. "It decreases the amount of time until results are available, and it prevents unnecessary repeat testing. If all physicians have access to a result, then only one of us needs to draw a blood test."

That system is further enhanced by a tool called Care Everywhere, which facilitates secure sharing of patient records outside UT Southwestern. And for patients, the MyChart health portal, part of the EMR, allows direct communication with health providers and clinical staff, as well as prescription renewals, appointment scheduling, and access to results of lab tests and radiological studies. Patients' MyChart use grew fivefold each year over a recent six-year period, with overall logins increasing more than tenfold, Dr. Gerber says.

Patients at the Cancer Center also have access to specialists who assist with many issues that arise during and after cancer treatment. Oncology supportive services help patients and families with disease- or treatment-related side effects, as well as other physical, emotional, social, or spiritual concerns, says Dr. Jeff Kendall, Clinical Leader of Oncology Supportive Services at Simmons Cancer Center.

Dietitians are available to guide patients who are managing eating challenges amid treatment. Psychologists and social workers help patients and families adjust to the changes a cancer diagnosis brings and ensure needed resources are available. Chaplains provide spiritual support. And integrative care such as music therapy is available to improve well-being and aid with stress management. "Many cancer programs don't have the specialists to deal with these problems," Dr. Kendall says.

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Confronting Lung Cancer from All Angles

Smoking cessation

UT Southwestern's Simmons Cancer Center smoking cessation educators, all of whom are American Lung Association– and American Cancer Society–certified, provide free individual and group educational sessions, while a cessation clinic offers pharmaceutical support.

Screening & diagnosis

Patients at risk for lung cancer can be referred where appropriate for low-dose CT screening at UT Southwestern; funding assistance is available.

Bronchoscopy, endobronchial ultrasound (EBUS), electromagnetic navigational bronchoscopy (ENB), endoesophageal ultrasound (EUS), and surgical and CT-guided biopsy are performed by highly specialized physicians, with cytopathologists providing rapid on-site evaluation of samples.

Thoracic surgery

UT Southwestern is an international leader in offering lung-cancer patients minimally invasive surgical approaches—video-assisted thoracic surgery (VATS) or robotic VATS.

Multidisciplinary Tumor Board

Specialists in pulmonary medicine, medical oncology, radiation oncology, thoracic surgery, and pathology, along with nurses, basic and translational scientists, clinical research coordinators, and others, gather weekly to review care and discuss evidence-based strategies for individual patients.

Pathology

Histopathologic, cytogenetic, and molecular genetic analyses are performed on all indicated lung tumors to guide therapy decisions using the most advanced targeted treatments.

UT Southwestern Clinical Center at Richardson/Plano

Patients can see a UT Southwestern medical oncologist, receive chemotherapy, and have labs drawn at the Simmons Cancer Center clinic near UT Dallas.

Medical oncology

World-renowned experts in lung cancer provide advanced care using not only established chemotherapeutic and targeted agents but, where appropriate, additional options through clinical trials.

Cancer Answer Line

Simmons Cancer Center's free Cancer Answer Line (1-888-980-6050) fields questions from community physicians, patients, family members, and others, offers education and resources, and assists with patient referrals.

Urgent care

Patients who need additional help managing their cancer or treatment side effects can be referred to Simmons Cancer Center's Urgent Care Clinic Monday through Friday, 1 p.m. to 5 p.m.

William P. Clements Jr. University Hospital

The new, state-of-the-art university hospital has an entire floor devoted to cancer care (page 38); UT Southwestern physicians also provide care at Parkland Health and Hospital System and the Dallas VA Medical Center.

Radiotherapy

Highly specialized radiation oncologists and an array of the latest treatment technologies deliver precise care; groundbreaking work by UT Southwestern radiation oncologists in stereotactic ablative radiotherapy (SABR)—also known as stereotactic body radiotherapy (SBRT)—have revolutionized treatment for some patients and revealed the science behind that therapy.

Oncology support services

Patients receive advanced supportive care from a broad array of providers, including psychologists, chaplains, social workers, dietitians, and others.

Other thoracic malignancies

Besides care for non-small cell and small cell lung cancers, UT Southwestern offers the same range of care for bronchial carcinoids, thymic malignancies, mesothelioma, and other thoracic malignancies.

Thoracic Multidisciplinary Clinic

This cross-disciplinary clinic allows patients to see multiple specialists at one location during one visit, fostering an integrated approach to treatment, which may involve surgery, radiation therapy, and a systemic treatment such as chemotherapy or a targeted therapy.

Clinical trials

Simmons Cancer Center's lung cancer disease-oriented team (DOT) has a robust lung cancer clinical trials program for patients with disease at any stage, cell type, and condition, enabling patients to receive drugs that might not be available elsewhere.

Cancer genetics

For lung cancer patients who are nonsmokers with a family history of the disease, genetic testing for clinical inherited mutations such as in the EGFR gene, as described by UT Southwestern researchers, may be appropriate, as well as full-genome evaluation to search for other heritable mutations that may increase disease risk.

Moncrief Cancer Institute

A new Simmons Cancer Center clinic, opened in early 2015 at Moncrief Cancer Institute in Fort Worth, expands care options at that site for patients in and around Tarrant County; Moncrief also offers smoking cessation classes and wellness and survivorship care.

Interventional pulmonology

Patients receive alleviation of airway obstruction from cancer through tumor ablation and excision with electrosurgery and cryotherapy, balloon dilation, and endobronchial stent placement; alleviation of shortness of breath from fluid around the lungs through ultrasound-guided thoracentesis and placement of intrapleural catheters.

AN ENGINE OF DISCOVERY

Nearly 25 years ago, longtime collaborators Adi Gazdar, M.D. (left), and John Minna, M.D., arrived at UT Southwestern from the National Cancer Institute. Their early focus on the biology of lung cancer put UT Southwestern and Simmons Cancer Center at the forefront of lung cancer research's molecular revolution.

BIG SCIENCE

Decades of dedication

For a quarter-century, UT Southwestern has been blazing the path for the lung cancer treatments of tomorrow, as well as the care of today.

It started with the arrival at UT Southwestern in 1991 of longtime collaborators Drs. John Minna and Adi Gazdar, formerly of the National Cancer Institute (NCI). The two have carefully curated lung cancer cell lines since the 1970s—a collection of about 300 that now is the world's largest. Those cell lines are regularly tapped to develop and test new therapies not just by investigators at UT Southwestern's Simmons Cancer Center but by thousands of researchers around the globe.

Each line, derived from a different patient's cancer, is indexed to a tumor sample plus information on how the person was treated and other clinical data. "In the past year, we have the complete genome sequence of most of these lines, which makes them much more valuable," Dr. Minna says.

The early, intense focus on the biology of lung cancer put UT Southwestern at the forefront internationally of lung cancer research's molecular revolution. It also laid the foundation for the university's research award in 1996, in collaboration with the University of Texas MD Anderson Cancer Center, of a highly competitive Specialized Program of Research Excellence (SPORE) grant from the NCI. The grant, with annual funding totaling $2.5 million, leverages the talents of some of the world's top lung cancer scientists, along with progress in genomics, to advance the dream of personalized medicine—not just through discovery, but with innovation that makes that discovery practicable.

"The SPORE has to move research into the clinic, or if there are things that happen in the clinic, take them back to the lab," says Dr. Minna, the program's principal investigator. "This is one of the few places in the world where the whole package is here—the clinical, surgical, medical, and radiation oncology expertise, the mechanisms to get the specimens into the lab and study them, and then the comprehensive approach that involves biology and genetic and chemical analysis of the tumors."

The comprehensive scientific and clinical infrastructure that supports the SPORE, along with other expertise and resources deployed across UT Southwestern, have provided a framework for innovative lung cancer research and care throughout Simmons Cancer Center, including:

- work pinpointing new genetic markers that might help identify the most aggressive lung tumors (page 17 insert);
- novel studies of cancer metabolism to decipher mechanisms of lung cancer cell growth (page 25);
- development of a multigene test to predict which surgical patients stand to benefit most from chemotherapy (page 31 insert);
- identification of an inherited gene mutation that boosts risk of lung cancer in nonsmokers (page 30);
- a focus on how to treat cachexia more effectively, and sooner (page 35 insert);
- studies of attitudes surrounding lung cancer diagnosis and treatment (page 19); and
- clinical trials that complement discovery science at UT Southwestern and bring new therapies to patients, such as trials of the antifungal drug itraconazole (page 25 insert) and of the monoclonal antibody bavituximab (page 34).

Size, scope, longevity

The University of Texas SPORE, now in its 18th year, is the largest thoracic oncology effort in the U.S. Only a handful of other institutions nationwide are similarly recognized for excellence in lung cancer research.

Among their achievements, scientists working in the SPORE have discovered alterations between the normal-to-malignant DNA tissue of lung cancer patients that may yield new therapeutic avenues; elucidated differences between individuals that make some more susceptible to lung cancer or more likely to survive, or that indicate greater risk of toxicities during treatment; described the role of cancer "stem cells" in lung cancer recurrence; and shed light on potential ways to block cancer growth, invasion, and metastasis in patients.

The SPORE has four main research arms:

- One, co-led by Dr. Minna and Dr. John Heymach of MD Anderson and in collaboration with UT Southwestern's Dr. Luc Girard, focuses on analyzing lung tumors for genetic vulnerabilities and selecting therapies based on the findings.

"When we started, we were talking about whether we could analyze one or two tumors and know what that meant for patients in terms of prognosis and specific treatment," Dr. Minna says. "Now we've analyzed more than 1,000. It's taken all this time to assemble the tools to do these analyses on tumors, to develop preclinical models to test this outside patients' bodies, and to have analyzed a large enough number of tumors to know this was the right approach."

The approach is now being implemented at the bedside, with drugs already on the market or in clinical studies being matched with patients' molecular profiles.

- A second SPORE project, led by Dr. Xifeng Wu of MD Anderson, involves epidemiological studies that are finding genetic markers indicating individual differences, including who is at greatest risk of developing lung cancer.

- A third project, co-led by UT Southwestern's Dr. Pier Paolo Scaglioni and MD Anderson's Dr. Jonathan Kurie, is developing new molecularly targeted therapies aimed at metastatic lung cancer and at sensitizing tumors to radiation. The project has linked particular microRNAs, or bits of genetic material, to highly metastatic versus nonmetastatic tumors.

- The fourth arm, led by UT Southwestern's Drs. Jerry Shay and Joan Schiller, leverages the vast expertise developed by Dr. Shay and colleagues in telomerase, an enzyme related to cell immortality, to develop therapies to kill cancer stem cells, hobbling a tumor's ability to regenerate. Researchers recently completed a phase II study of the telomerase inhibitor imetelstat as maintenance therapy for patients with advanced non-small cell lung cancer.

The SPORE also has three supporting arms: an administrative core led by Dr. Minna and SPORE co-principal investigator Dr. Jack Roth of MD Anderson; a pathology core overseeing specimens and clinical annotation, led by Dr. Gazdar and Dr. Ignacio Wistuba of MD Anderson; and a bioinformatics-biostatistics core, led by Dr. Yang Xie, that is managing the flood of data related to the project and that has developed a massive database available to researchers worldwide. The database, called Lung Cancer Explorer, contains genome-wide mRNA expression and clinical data for nearly 5,500 lung cancer patients' tissue samples.

Well-connected

Much as UT Southwestern scientists are lung cancer leaders, UT Southwestern leaders are lung cancer scientists—with a slate of department chairs, Cancer Center principals, and institution luminaries focused on the disease. As a research powerhouse, the lung cancer program is plugged in with investigators around the world and with resources across Texas and the U.S.

In one large project, funded by the Cancer Prevention and Research Institute of Texas (CPRIT), UT Southwestern scientists are evaluating many facets of radiotherapy, the primary treatment in more than half of lung cancer patients. Led by Radiation Oncology Chair Dr. Hak Choy in collaboration with Dr. Chul Ahn, the project seeks to propel technology to improve cancer control and reduce toxicity for patients with early-stage or locally advanced tumors. A key goal is to export these advances via training programs throughout the state.

Another research collaboration funded by CPRIT applies the unique cancer-fighting properties of stereotactic ablative radiotherapy (SABR), which delivers high-dose radiation in fewer visits than with traditional radiation therapy, to lung tumors located centrally in the chest, where radiation sufficient to treat cancer can be risky for nearby organs. The research is led by radiation oncologist Dr. Robert Timmerman and involves Drs. Ralph Mason, Rolf Brekken, Debu Saha, and Dr. Ahn.

Two arms of the project focus on overcoming radiation therapy resistance caused by low oxygen concentrations in the tumor, and the impact of using the antibody bavituximab—a treatment developed at UT Southwestern—to specifically sensitize tumors to radiation, allowing the cancers to be treated effectively with lower, more tolerable doses.

Meanwhile, in work funded by NASA, UT Southwestern researchers, including Drs. Minna, Shay, and Xie, and Drs. Michael Story and David Chen, are investigating how the additional radiation exposure that occurs during spaceflight increases lung cancer risk and how lung cancers respond to radiation. "We know that some are very sensitive and some resistant, and we have a molecular profile that looks like it identifies those," Dr. Minna says.

The research, also of interest to the NCI, should elucidate how radiation exposure from procedures such as CT scanning affects lung cancer risk, including in patients undergoing repeated low-dose scans for cancer.

UT Southwestern scientists also are among the leaders of the national Lung Cancer Mutation Consortium (LCMC), a high-profile alliance of 16 top academic cancer centers and hospitals across the U.S.

Deepak Nijhawan, M.D., Ph.D., (left) and Steven McKnight, Ph.D., are members of a research team identifying new biological markers linked to different families of lung cancers.

From left: Mahboubeh Papari, Boning Gao, Ph.D., Victor Stastny, John Minna, M.D., and Adi Gazdar, M.D., are among scientists working to advance new therapies from discovery to drug development.

that is helping to lead the charge nationally to personalize lung cancer treatment—and providing direct benefit to Simmons Cancer Center's lung cancer patients.

Institutions in the consortium are collaborating to match 1,000 lung cancer patients each year to therapies based on genetic mutations in each individual's tumors. "The key goals," says Dr. Schiller, UT Southwestern's principal investigator for the LCMC, "are to learn all the types of mutations that occur—and how frequent they are—in non-small cell lung cancer, and to determine through clinical trials whether patients given drugs targeting those mutations will fare better than with standard treatments."

UT Southwestern is also a Cancer Target Discovery and Development (CTD2) center, part of a network of sites honing and leveraging massive amounts of genomics data to advance precision medicine.

Less formal collaborations also abound. Dr. Minna estimates that at least half of UT Southwestern's published research in lung cancer involves other institutions. "In many cases we provide resources as part of the national scientific fabric, but we have a very high amount of inter-institutional collaboration."

Gene-by-gene quest

Collaboration is also a hallmark within the Cancer Center of a sweeping, multimillion-dollar lung cancer drug discovery effort funded by CPRIT and the NCI's CTD2 Network.

To lay a foundation for the drug discovery work, UT Southwestern scientists have been pioneering new ways to classify non-small cell lung cancers functionally based on their vulnerabilities. As lung tissue develops from normal to cancerous, hundreds of mutations in genetic coding can arise, says project investigator Dr. Michael White—and they can differ widely from tumor to tumor. But only a few of those mutations matter. By figuring out which genes appear significant, the researchers have been able to group lung cancer cell lines into families, with cell lines in the same families having similar vulnerabilities and sensitivities to certain chemical compounds.

A team with diverse talents—including Dr. Minna, Dr. White, Dr. Michael Roth, and Dr. Xie; Chair of Biochemistry Dr. Steven McKnight; and Drs. Bruce Posner, Deepak Nijhawan, John MacMillan, Joseph Ready, and Noelle Williams—is pursuing the quest for new therapies from discovery to drug development. The researchers are identifying new biological markers linked to potential vulnerabilities in the different families of lung cancers, pinpointing the vulnerabilities themselves along with potential biological and chemical therapies that can exploit them, and learning how to predict the cases in which the new potential therapies are likely to work. Team members are also developing promising chemicals into therapeutic compounds that are more potent, tolerable, and accessible in the body, and creating cutting-edge mouse models of lung cancer in which the compounds can be tested.

The effort is enormous, knocking out some 25,000 human genes one by one and testing the effects of a quarter-million chemical compounds, plus thousands more natural products, on more than 100 lung cancer cell lines. So far, the team has identified approximately 100-150 gene products and 100-200 new chemical compounds that can hit lung cancer targets while sparing normal epithelial cells.

Dr. Minna says some of these potential therapeutic targets seem very common in other tumor types. "People who have smoked have a lot of mutations, so lung cancer is a testing ground to find targets that could apply in many other tumors. We're just beginning to explore that."

New frontiers in tailoring therapy

Simmons Cancer Center scientists are also taking a systematic approach to understanding how cells' nuclear hormone receptors work in concert to influence genes that affect the development and growth of lung, as well as breast, cancers. Chair of Pharmacology Dr. David Mangelsdorf is leading a CPRIT grant of more than $7.4 million that unites UT Southwestern with Baylor College of Medicine and MD Anderson in the effort. The work includes UT Southwestern investigators Drs. Minna, Xie, Ralf Kittler, and Scaglioni.

Together, the researchers are exploring how the body's 48 nuclear hormone receptors, along with more than 100 coregulators, can be activated or suppressed by hormone therapies, many of which are already on the market as cancer medicines.

"The whole idea is to be able to come up with a way to individualize and tailor treatment based on a nuclear hormone receptor expression and activity profile," says Dr. Mangelsdorf, who envisions the strategy as complementary to other, non-hormonal treatments. "We want to come up with something that will be clinically useful."

DETECTING AND PREVENTING A DEADLY DISEASE

Lung cancer expert Joan Schiller, M.D., Deputy Director of Simmons Cancer Center, heads a comprehensive program that offers the latest advanced technology for lung-cancer screening and diagnosis, as well as a full range of follow-up care tailored to meet individual patient needs.

SCREENING AND DIAGNOSIS:

AT THE RIGHT TIME & PLACE

LUNG CANCER SCREENING

The U.S. Preventive Services Task Force recommends annual screening with low-dose computed tomography for asymptomatic patients who:

- Are between 55 and 80 years old;
- Have a 30-pack-year history of smoking*; and
- Now smoke, or quit within the past 15 years.

Screening should be discontinued when the patient:

- Has not smoked for 15 years; or
- Has developed a health problem likely to significantly limit life expectancy or ability/willingness to undergo curative lung surgery.

*Pack-year history is calculated by multiplying the number of packs of cigarettes a person smoked per day by the number of years the person has smoked.

Source: uspreventiveservicestaskforce.org/uspstf/uspslung.htm

DIAGNOSING LUNG CANCER

Low-risk lesions:

- Regular CT monitoring

Moderate- to high-risk lesions:

- Bronchoscopy and endobronchial ultrasound (EBUS) for lesions accessible in or by the airway
- Electromagnetic navigational bronchoscopy (ENB) for lesions not directly in the airway
- CT-guided biopsy, for more peripheral lesions
- Surgical biopsy, when appropriate
- Rapid on-site evaluation of samples

Low-dose CT clinical tool is boosting survival rates

Low-dose computed tomography (LDCT) screening for lung cancer represents a vital new opportunity to more frequently catch tumors early, when they often can be cured with surgery.

Increased early detection alone could make a difference in survival rates, says Dr. Joan Schiller, Deputy Director of Simmons Cancer Center. Results of the National Lung Screening Trial, published in 2011, found that participants had a 20 percent lower risk of dying of lung cancer if they were screened with low-dose helical CT scans rather than chest X-rays. Before that, Dr. Schiller says, "We didn't have any proven screening method. Now we do."

At UT Southwestern, the LDCT screening program is led by Dr. Muhanned Abu-Hijleh, who is one of the interventional pulmonary and critical care physicians at the Pulmonary Specialty Clinic, serving patients with suspected pulmonary malignancies and pulmonary nodules. Screening is available to anyone in the targeted population (see screening guidelines at left), even to those who can't afford to pay. Vouchers are provided by the Roger Williams Fund for CT Screenings for Lung Cancer. The fund aims to spare as many people as possible from the devastation of a diagnosis of advanced lung cancer by promoting early detection.

Roger Williams was a prominent Dallas trial lawyer who died of lung cancer in 2013. "His family wants screening to be barrier-free—if you think this is an issue for you, just do it," says oncology-certified nurse Maria Grabowski, Program Manager for Patient Education and Community Outreach. "Peace of mind or early detection is priceless. Because of the Williams fund, this opportunity is now available to everyone."

At UT Southwestern, patients also benefit from cutting-edge technology and faculty expertise. "We have the latest-generation multidetector CT scanners and are continually adding the newest flagship scanners from major vendors," says Dr. Suhny Abbara, Chief of Cardiothoracic Imaging. Meanwhile, UT Southwestern radiologists are meticulous about radiation dose (a typical dose is about 1.2 to 1.5 mSV for LDCT, compared with 6 mSV or more for a standard chest CT). "We minimize the doses to as low as reasonably achievable clinically," Dr. Abbara says, "and we do research to further push the limits."

The targeted population for LDCT screening has been carefully defined to ensure benefits outweigh any harm, adds lung cancer specialist Dr. David Gerber. "When you compare it to breast, prostate, colon, or cervical cancer screening, the number needed to screen to save a life is best for lung cancer," he says. "This reflects the lethality of lung cancer and the high risk of the targeted population."

Any center providing screening should offer a full range of follow-up care, he notes. "Screening needs to be done at a place that can guide patients through all the subsequent processes, counsel patients on what a radiographic abnormality may mean, and have an aggressive, comprehensive smoking cessation program," tailored to meet individual needs—all services available at Simmons Cancer Center.

Radiologist Lori Watumull, M.D., prepares to perform a CT-guided biopsy. "It's important we understand lung cancer's various imaging features (and) the multiple ways to obtain a tissue diagnosis" to help achieve the best possible outcome for patients, she says.

The team and technology behind the diagnosis

At UT Southwestern, teamwork begins even before a patient is ever told, "You have lung cancer."

When imaging reveals a suspicious nodule, patients referred to UT Southwestern for follow-up have the benefit of a highly specialized team of interventional pulmonologists, radiologists, and pathologists, all working together to ensure fast and accurate diagnosis by the least invasive means possible.

The team also must obtain enough of a sample so UT Southwestern physicians and scientists—leaders globally in the molecular analysis of lung tumors—can glean important clues about which cancer treatments might work best.

For patients whose lesions look suspicious, the goal is to move quickly and safely to diagnosis and staging, says Dr. Hsienchang Thomas Chiu. Dr. Chiu and his colleague Dr. Abu-Hijleh are a fairly rare breed in their field: Both are interventional pulmonologists specializing in minimally invasive techniques for advanced diagnosis and staging.

Those techniques include linear endobronchial ultrasound (EBUS), which visualizes body tissues that then can be sampled by instruments passed through the bronchoscope. EBUS is used to access central sites.

Electromagnetic navigational bronchoscopy (ENB) is deployed for harder-to-reach lesions. ENB uses CT scan data to build a virtual reality representation of the lung. Then, as the patient lies on a plate that generates an electromagnetic field, the bronchoscope is tracked within the field and an airway map is generated. A computer combines that map with virtual reality to guide the probe.

Dr. Chiu often is referred patients whose previous biopsies didn't collect relevant tissue—even when cancer is evident on scans—or who were told erroneously that the tumor is too small to biopsy. "We can deal with these challenging cases," he says.

To investigate very peripheral lesions, a radiologist is enlisted to perform a CT-guided biopsy. While the procedure is not without risk—most commonly lung collapse—"if it's done in the hospital, we are prepared to deal with any potential complications," says radiologist Dr. Lori Watumull. "It's a safer environment, especially for high-risk patients."

Meanwhile, cytopathologists with expertise in lung cancer are always on hand to provide rapid on-site evaluation as samples are collected. "They can tell us on the spot, are we actually getting cancer cells?" Dr. Chiu says. Also, adds Dr. Watumull, they can ensure a sample isn't composed of necrotic tumor tissue, or, if the lesion is an infectious site, ensure enough tissue is gathered for culture and antibiotic sensitivity determination.

"We work together as a multidisciplinary team," she says. "It's important we understand lung cancer's various imaging features, the multiple ways to obtain a tissue diagnosis, and the various treatment alternatives—the whole process—to obtain the best possible outcome for the patient."

Extinguishing smoking—one patient at a time

For smokers aiming to kick the habit, UT Southwestern's Simmons Cancer Center won't quit until they do.

Yet some patients referred to the center's smoking cessation resource just aren't ready. In that case, program educators—all of whom are American Lung Association–certified in smoking cessation—can act as a telephone resource to help patients prepare.

This resource also helps lung cancer patients get smoke-free before surgery. "When we get that referral, we stay close," says oncology-certified nurse Maria Grabowski, Program Manager for Patient Education and Community Outreach. At no cost, educators will help the patient set a quit date and offer telephone or in-person motivational and educational sessions as well as regular check-ins.

The cessation resource has a medical director, Dr. David Balis, and an advanced practice nurse from the lung cancer team, Sharon Hoskin, who are highly experienced in pharmaceutical support for smokers trying to quit. That team makes varenicline or bupropion available and provides the close management advised for patients using varenicline.

Also available to the public is a weekly class, the Lung Association's Freedom from Smoking course, whose only cost is $35 for the companion book. Classes meet on campus at noon on Tuesdays. Participants can range from people struggling with quitting to those who are smoke-free but tempted to resume. Patients ready to quit but who miss the course's start receive catch-up tutoring. Class participants also have access to the rest of the resource's services and may return to classes anytime in the future.

Referrals come from within UT Southwestern and from the community. Smokers are also encouraged to explore other resources aimed at screening and early detection of lung problems, including UT Southwestern's low-dose CT lung cancer screening program.

Some smokers are so relieved that their screening revealed no lung tumors that they are then raring to quit, Ms. Grabowski says. "They are grateful. They feel as if they can get out alive."

Muhanned Abu-Hiljeh, M.D. (left), and his colleague Hsienchang Thomas Chiu, M.D., are a rare breed in their field: Both are interventional pulmonologists who specialize in minimally invasive techniques for advanced diagnosis and staging.

The O'Donnell Grove surrounds Simmons Cancer Center, providing a scenic and peaceful environment for patients, their families, and Simmons physicians and scientists.

The pain of stigma, the embrace of family, the complexity of care

Shame or guilt, anger, depression, defensiveness, confusion, or even stark misconceptions can lurk below the surface of a lung cancer diagnosis.

At Simmons Cancer Center, researchers are probing such psychosocial concerns to better understand their impact on lung cancer patients and their care. Work led by psychologist Dr. Heidi Hamann is exploring the experience of lung cancer stigma, which burdens patients with feelings of judgment as they repeatedly are asked whether they are smokers—and, if so, are confronted with people's assumption that their disease is therefore their fault.

"Patients need as much support from friends, family, and medical providers as they can get," Dr. Hamann says. "If they feel like they are constantly having to answer questions about whether they smoked and what that means, they may not feel they are getting that full support."

Her research showed that even lung cancer patients who did not have a smoking history felt the weight of stigma. "When they would tell someone they had lung cancer, they would have to start by saying, 'But I never smoked,'" Dr. Hamann says. "People know others will react to them in a certain way unless they say this."

Based on feedback from individuals and focus groups, Dr. Hamann and her colleagues have been developing a questionnaire as a tool to gauge stigma's impact. When patients internalize lung cancer stigma, guilt and regret may cause them to isolate themselves and to avoid screening, medical appointments, or discussing health concerns with professionals, Dr. Hamann says.

Identifying such patients can prompt an intervention that helps them reframe their thinking, recognize smoking as an addiction, and focus on moving forward. Dr. Hamann works closely with Dr. Jeff Kendall and the Simmons Cancer Center Supportive Services team to help translate these research findings into clinical practice.

Meanwhile, UT Southwestern medical anthropologist Dr. Simon Craddock Lee is shedding light on social interaction and decision making among African-American lung cancer patients, their caregivers, and the health care system. Lung cancer takes an especially heavy toll on African-Americans, who have a higher risk of getting the disease, are diagnosed with more advanced cases, and are more likely to delay care after diagnosis.

Over two years, Dr. Lee and his colleaguessurveyed 100 African-American patients receiving care at the county safety-net hospital, Parkland, then conducted multiple in-home follow-up interviews with patients and their primary caregiver to better understand the role of family in their treatment experience.

Generally, the patients had caregivers and close family who were highly engaged, as well as strong networks of extended family. "Everyone worries that lower socioeconomic status patients may lack social support; that may not be an issue here," Dr. Lee says.

His findings also undercut another concern: that care for medically underserved or minority patients may be hindered by a lack of trust in physicians. Patients in Dr. Lee's study liked and respected their doctors.

But there were communication challenges between caregivers and patients who were uneasy about their understanding of the disease and its treatment and who struggled to convey that uncertainty to their treatment team. They were concerned about doctors using big words or talking too quickly, Dr. Lee says, and they needed help understanding, for instance, what stage III cancer means.

"Patients would ask me, 'How many stages are there?' So they're lacking some basic information about how the disease progresses and what the implications are," he says.

Also, most of the patients did not perceive conversations with clinicians as discussions of treatment options but instead felt that decisions about care rest with their clinical team.

"Trying to explain to patients about decisions they need to make often doesn't make sense to these patients. They are interested in understanding what's happening to them, what the doctor is going to do to them, and what this means is coming next," Dr. Lee says.

The research also highlighted the importance of correcting misconceptions, he says, such as the notion that surgery can cause a cancer to spread. Otherwise, "patients predisposed to think cutting is bad are relieved when they are not referred to surgery. They don't understand that can mean their cancer is more advanced."

Although the research focused on African-Americans, most findings were not race-specific, Dr. Lee notes. "I think a lot of the issues in this cohort are likely generalizable to other low-socioeconomic status patients, whose lives can be particularly complicated by a cancer diagnosis."

CONTINUUM OF LUNG CANCER TREATMENT

Medical oncologist David Gerber, M.D. (left), and radiation oncologist Puneeth Iyengar, M.D., Ph.D., embody the breadth of expertise offered to patients by Simmons Cancer Center specialists—expertise that enables effective treatment of lung cancer at every phase of the disease, from early stage to locally advanced to late stage.

EARLY-STAGE LUNG CANCER

TREATMENT APPROACHES

Surgery:

- Video-assisted thoracic surgery (VATS)
- Robotic VATS
- Open thoracotomy

Radiotherapy:

- Stereotactic ablative radiotherapy (SABR)
- Adjuvant radiotherapy, including brachytherapy
- Adjuvant (Postoperative) Chemotherapy

Clinical Trials

Minimally invasive techniques, dedicated surgeons characterize surgical treatments

The most advanced minimally invasive surgical techniques, used routinely at UT Southwestern to resect early-stage lung cancers, are sparing patients much of the pain and debility that can accompany open thoracotomy.

Dr. Kemp Kernstine, Chief of UT Southwestern's Division of Thoracic Surgery, has been on the leading edge of this paradigm shift in lung cancer resection. In 1992, Dr. Kernstine and a colleague performed one of the earliest video-assisted lobectomies, a minimally invasive procedure, in the Northeast. He's done hundreds of video-assisted thoracic surgeries (VATS) since and 10 years later became an early developer of robotic lobectomy techniques.

"With VATS, there were aspects of efficiency and detail that could be even better, so when robotics came along, it just made sense," he says.

Patients undergoing robotic VATS spend less time in surgery than with open thoracotomy, while blood loss and infection risk potentially are reduced. Patients are typically home in three days, back to work in a couple of weeks, and often off pain medication within about a week, Dr. Kernstine says.

At many institutions, lung cancers are resected by cardiothoracic surgeons whose caseload is dominated by heart procedures, says medical oncologist Dr. Jonathan Dowell, who specializes in lung cancer and mesothelioma. But patients at UT Southwestern benefit from the vast experience of dedicated thoracic surgeons—Dr. Kernstine and Dr. Scott Reznik. "That's a key difference," Dr. Dowell says.

The thoracic surgery team performs about 150 surgeries for thoracic malignancies each year at UT Southwestern, about 100 more at Parkland Memorial Hospital, and 100 at the Dallas VA Medical Center.

At UT Southwestern, roughly 85 percent of thoracic surgical patients have a minimally invasive procedure—thoracoscopic, robotic, or a combination—even if their disease is locally advanced. By contrast, nationwide only about half of thoracic surgeons in a recent survey were performing lobectomies using VATS or robotic VATS—and among them, only about one-fifth used VATS in 80 percent or more of cases (Cao, *Chest*, 2014).

Of surgeons in the survey who never performed a VATS lobectomy, many cited a lack of opportunities to learn the procedure. Dr. Kernstine is spearheading efforts at UT Southwestern to change that.

"We really perfected the details of the robotic procedure and are now teaching it regularly to our trainees," he says. "They are removing lobes in one-third the time it would take to do an open procedure, learning how to make it an efficient and extraordinarily safe process." Dr. Kernstine also goes to other hospitals, and even abroad, to train surgeons, while many come to UT Southwestern to observe and learn.

Patients with early-stage cancers also benefit from UT Southwestern's academic research environment. Their cases frequently are presented at Simmons Cancer Center's multidisciplinary lung tumor conference (see page 3), at which a range of lung cancer experts develop individualized treatment strategies. "Often there are questions, if it's a marginally resectable tumor, about whether the patient should receive chemotherapy and/or radiation before surgery to improve the likelihood of a successful resection," Dr. Dowell says. Resected tumor tissue is

Kemp Kernstine, M.D., Ph.D., Chief of UT Southwestern's Division of Thoracic Surgery, is one of the world's foremost authorities on video-assisted thoracic surgeries (VATS), having performed hundreds of the minimally invasive procedures. At UT Southwestern, about 85 percent of thoracic surgery patients have a minimally invasive procedure—even if their disease is locally advanced.

subjected to a rigorous molecular analysis to inform further treatment decisions, and with patients' consent the tissue is also used for research.

Important research questions include the optimal use of molecularly targeted therapies in early-stage lung cancer, notes medical oncologist Dr. David Gerber. A new, five-year study that Dr. Gerber co-chairs, called ALCHEMIST, aims to help. Up to 8,000 patients nationwide will be enrolled in the trial, in which resected lung tumor tissue will be checked for dozens of molecular alterations, with targeted therapies used in certain cases. Other research aims to determine whether patients can benefit from new therapies given before surgery.

"What we need to remember," Dr. Gerber says, "is that even stage I lung cancer has survival rates that could be markedly improved."

Radiotherapy: Leading-edge tools to supplant—and supplement—surgery

Pioneering radiotherapy research at Simmons Cancer Center has opened the door to a potential cure for early-stage lung cancer patients too frail to undergo surgery. Such patients might have COPD or heart or renal issues that simply make surgery too risky.

Four specialist radiation therapy physicians in the Department of Radiation Oncology focus on lung cancer, a level of expertise rare in most centers. "They are innovators," Department Chair Dr. Hak Choy says of his colleagues, noting that the research on inoperable patients, using stereotactic ablative radiotherapy (SABR), has established UT Southwestern as the global expert in the field.

Each year, stage I non-small cell lung cancer is diagnosed in about 25,000 U.S. patients, and more than 5,000 of them are medically inoperable, says radiation oncologist Dr. Robert Timmerman. At the three-year mark, Dr. Timmerman and his colleagues found that SABR (also known as SBRT) eliminated the primary tumor in 98 percent of such patients and roughly doubled survival rates, to about 60 percent, compared with the previous usual care. "That changed the standard of care for those patients," he says.

Now, after seven years of follow-up, high rates of tumor control have persisted, and worries about a surge of late toxic events have proved unfounded. "What we're proud of is the fact that SABR is now used worldwide," Dr. Timmerman says, adding that UT Southwestern has by far the most experience with the therapy (he estimates he personally has treated around 1,000 patients). "We've trained hundreds of physicians, physicists, and dosimetrists across the U.S. and around the world."

A key question soon to be addressed is whether—in borderline operable, early-stage lung cancer patients—SABR is equivalent to or better than surgery with respect to tumor control, survival, and toxicity. "We think SABR will be quite competitive, but we've never had a head-to-head study with surgery to address these questions in such a patient population," says radiation oncologist Dr. Puneeth Iyengar. UT Southwestern researchers hope to lead a nationwide, randomized phase III trial enrolling about 600 such patients to answer that question.

Meanwhile, along with chemotherapy, radiotherapy remains an important treatment for patients whose cancers are revealed after surgery to be more extensive than pre-surgical evaluation indicated. And to further help prevent recurrence, UT Southwestern is poised to begin offering intraoperative brachytherapy, where the tumor bed is treated with special applicators or radioactive seeds at the time of surgery. Another technique is endobronchial brachytherapy, used sometimes to treat the surgical margin after a large lobar resection or pneumonectomy, says brachytherapy specialist Dr. Michael Folkert.

As for the future, the department's radiation oncologists are exploring the power of SABR in metastatic lung cancer (see page 35). And they are aiming to develop SABR and other radiotherapy procedures using protons instead of photons—lowering dose to healthy tissues—once a new proton therapy center opens in 2017. Research by UT Southwestern radiation oncologist Dr. Ken Westover and others has shown that protons can deliver SABR to lung cancer patients who are even more frail than those who typically receive the therapy. "If a patient has very poor lung function, if the tumor is in a tricky location, or if patients have sensitive implantable devices like a pacemaker, protons can give you a very sharp dose gradient, allowing you to treat these otherwise untreatable patients," he says.

The university already is on the leading edge in its technical ability to precisely target tumors while sparing normal tissue. Most radiation oncology facilities have just one or two of the multimillion-dollar machines used to treat cancer; UT Southwestern has a toolbox of nine, all with the latest imaging capabilities, and can choose the optimal one for each individual case.

"We reinvest our resources to continually update to the latest technology for patient care," Dr. Choy says. "That's our drug; that's our knife."

Patients benefit from the vast experience of UT Southwestern's thoracic surgeons, who, as a team, have perfected the details of robotic procedures and are now teaching the art to other surgeons, at home and abroad.

ADVANCED IMAGING RESEARCH CENTER:

Providing a clearer view to lung cancer's pathways and metabolic process

Advanced imaging technology, a quarter-century of foundational radiological studies, and extensive resources focused on lung cancer and metabolism are bearing fruit in innovative new research at UT Southwestern.

The new, multidisciplinary research may reveal whether specific metabolic traits of lung cancer cells are related to their propensity to metastasize. It also might help researchers devise better diagnostic imaging methods or more quickly determine with noninvasive scans whether a lung cancer is responding to a particular therapy, says Dr. Craig Malloy of the Advanced Imaging Research Center (AIRC) at UT Southwestern.

Crucial elements of the research are high-strength MRI magnets, among the only such facilities in the Southwest, and the expertise of AIRC Director Dr. Dean Sherry and Medical Director Dr. Malloy. The new work exploits 13-carbon—a stable natural isotope—as a tracer to help figure out how cancer cells rearrange normal metabolic pathways to produce energy that fuels cell growth.

"Our whole careers have been a partnership in developing these stable isotope methods, understanding how to use 13-carbon nuclear magnetic resonance (NMR) and how to apply it to biological systems," Dr. Malloy says.

Molecules that are 13-C-labeled are not radioactive, which enables their safe and routine use in clinical experiments. By administering glucose heavily enriched with 13-carbon, researchers can learn key details about the cancer's metabolic activity.

The work focusing on non-small cell lung cancer is spearheaded by medical geneticist Dr. Ralph DeBerardinis, who designed the experiments, and thoracic surgeon Dr. Kemp Kernstine. Patients participating in the study are infused with the enriched glucose just before surgery to remove their lung tumors. Upon excision, the tumors are quickly frozen and sent to Dr. DeBerardinis' lab. There, using NMR and gas chromatography–mass spectrometry, the research team can carefully trace the activity of tumors' core energy-producing metabolic pathways and contrast this with metabolic activity in healthy lung tissue.

"A reprogramming of metabolic activity allows cancer cells to survive and grow abnormally," Dr. DeBerardinis says. "If we can determine which metabolic pathways specifically stimulate tumor cell growth, then it may be possible to treat cancer by inhibiting those pathways."

The team will deploy complementary techniques to obtain "snapshots" capturing the quantities of hundreds of individual metabolites in many pathways at once. The research is also incorporating genetic and other data from each tumor to create a comprehensive portrait of lung cancer metabolism.

In work spearheaded by the Department of Radiology's Vice Chair of Research, Dr. Robert Lenkinski, investigators hope to correlate their data from the surgical samples with information about tumor variations such as oxygen levels and blood supply that can be gleaned noninvasively and without any radiation danger, using cutting-edge magnetic resonance (MR) approaches.

Imaging lung cancer is particularly tricky because as the patient breathes, the lung and tumor are moving. "In Radiology, the development and implementation of advanced imaging has led to a program utilizing advanced MRI fusion techniques that very few people can do," Dr. Lenkinski says.

MRI fusion uses multiple MR techniques to characterize different features of a tumor, then layers the images for a more complete picture of the cancer, "an approach that has never previously been applied to lung cancer in humans," he says. "Using that imaging, we can see heterogeneity in the tumors and guide tissue procurement," helping project investigators select the most useful tissue for the metabolism experiments.

That capability builds off previous research by Dr. Lenkinski; Chair of Radiology Dr. Neil Rofsky (who is also Director of Translational Research at the AIRC); Division of MRI Chief Dr. Ivan Pedrosa; and Assistant Professor Dr. Daniel Costa. Their work, which has devised innovative MR approaches to help diagnose, stage, and treat various cancers, began about six years ago when all four were at Harvard and has been carried forward at UT Southwestern.

One key advance was developing sophisticated methods to speed up acquisition of the images, making it possible to do multiple studies on the same patient. Along with Deputy Cancer Center Director Dr. Joan Schiller, the AIRC and Radiology "felt that optimizing the imaging so it could be used clinically would change the standard of care," Dr. Rofsky says. "It was one of the projects we identified at UT Southwestern where we could make a difference."

In the metabolism research, preliminary data has already yielded insights, Dr. Kernstine says, such as whether lung tumors compensate for abnormal cell metabolism and gain the fuel to proliferate by increased blood flow. That doesn't appear to be the case, he says.

He notes that current patients typically have a CT scan of the chest, then a PET scan, and often bronchoscopy. "What if we had a single study that would provide all this information at once and tell us more than these current studies? It would give us an idea of tumor health—and perhaps we could give small doses of chemotherapy to patients and see whether it altered the tumor's function. Then we'd know it works."

LOCALLY ADVANCED LUNG CANCER

TREATMENT APPROACHES

Multimodal therapy is typical, including

Surgery:

- Tumor resection for cancers up to and including stage IIIA, and in some special situations IIIB cases

Chemotherapy:

- Before, after, or along with radiation therapy
- Before or after surgery in patients with resectable tumors

Radiotherapy:

- In conjunction with chemotherapy
- In patients with unresectable tumors who are not candidates for chemotherapy
- After resection and chemotherapy in patients found to have stage III cancer at the time of surgery
- For palliation

Clinical Trials

Coordination, cohesion mark treatment for middle-stage lung cancers

Treatments for locally advanced lung malignancies run the gamut of cancer care. So does the lung cancer expertise at Simmons Cancer Center.

Locally advanced lung cancer represents a heterogeneous disease requiring complex staging and treatment procedures. Although there is general agreement that patients should be treated with both local and systemic therapy, whether that entails surgery and chemotherapy, radiation and chemotherapy, or all three modalities requires detailed multidisciplinary discussion.

"We know a single treatment modality is not enough, but there is not clear consensus on which combination of surgery, chemotherapy, and radiation is best. In some cases, all three may be appropriate," says medical oncologist Dr. David Gerber.

At UT Southwestern, where such complex cases are regularly discussed at the Thoracic Oncology Tumor Board (see page 3), interventional pulmonologists, radiation oncologists, medical oncologists, and thoracic surgeons all provide input.

Being able to identify the optimal treatments for each patient, and making that care as seamless as possible, is what makes UT Southwestern's multidisciplinary expertise in lung cancer important, says Chair of Radiation Oncology Dr. Hak Choy. "Coordination is essential," he says. "Here, radiation oncologists, medical oncologists, surgeons, and pulmonologists are a cohesive practice, literally under the same roof—and we work together to make decisions."

Still, with lung cancer survival rates stubbornly low, the devil is in the details: How can radiation therapy in the locally advanced setting deliver better outcomes and with fewer side effects? Which surgical approaches offer the best chance of cure and have the fewest possible complications? And what new medicines, or new treatment combinations, may work better for these patients?

Seeking better answers

At UT Southwestern, a robust clinical trials program in lung cancer is aiming to answer such questions. It's not just for the sake of science or for patients far in the future. People currently in treatment—including those across lung cancer stages—can benefit.

Patients in cancer trials generally receive the current standard of care, or that standard plus the experimental therapy. "Studies have shown that a person is likely to do better on a clinical trial even if the drug being tested turns out not to be effective, just because the patient is getting so much attention," says Deputy Cancer Center Director Dr. Joan Schiller, a medical oncologist. "In a clinical trial you have a much bigger cancer care team, and they are all looking at you under a microscope, so to speak."

UT Southwestern recently received federal funding to become a National Clinical Trials Network Lead Academic Participating Site—one of 30 hubs for clinical cancer research, especially large, multi-institution trials sponsored by national cooperative groups. "Through this program, patients receiving care at UT Southwestern will have unfettered access to high-quality clinical trials sponsored by the NCI," says Chair of Internal Medicine Dr. David Johnson, a lung cancer clinical researcher.

Department Chair Hak Choy, M.D. (right), is one of four UT Southwestern radiation oncologists who specialize in treating lung cancer. Among them is Robert Timmerman, M.D. (left), who has led research into the use of stereotactic ablative radiotherapy to treat the disease.

Such trials are key in bringing new therapies to the clinic. "The current approach to lung cancer treatment is largely a product of well-conducted, cooperative trials, often of an intergroup nature," Dr. Johnson says.

While clinical trials are offered by other cancer treatment centers in the community, few have the number and variety that UT Southwestern does. Most of those sites lack the depth and breadth of research that UT Southwestern offers, Dr. Schiller says. And studies involving multiple disciplines are fairly uncommon outside an academic environment, adds Dr. Choy. "They take a lot of coordination and are difficult to do."

Maximizing synergies

But multidisciplinary studies are crucial in locally advanced lung cancer, where scientists are ever striving for improved treatment combinations.

One new strategy would incorporate immunotherapy. "When you give radiation to a cancer you may make the body's immune system more aware of the cancer by causing the cancer to release substances in the blood that might not have been there on their own," Dr. Gerber says.

Other efforts focus on some of the latest targeted therapies, whose potential role in locally advanced lung cancer is not clear. A study open at UT Southwestern, part of a national cooperative group trial, is testing the effectiveness of adding erlotinib or crizotinib to standard chemoradiation, depending on genetic characteristics of each patient's tumor.

Simmons Cancer Center researchers are also leading a national trial testing a newer version of an older treatment. That study aims to see whether nab-paclitaxel, a different formulation of the chemotherapy drug paclitaxel, is more effective in a chemo-radiation regimen.

Meanwhile, the integration of advanced imaging technology into radiotherapy—which allows more precise treatment delivery while better sparing normal tissue—has facilitated research into whether hypofractionated radiation can improve cancer control and survival, be more convenient for patients, and perhaps cost less. With hypofractionated radiation, the same total dose is delivered but at higher doses per treatment, with fewer visits to the radiation therapy center.

The approach is of growing interest in patients with locally advanced lung cancers who are too ill to tolerate the addition of chemotherapy, says radiation oncologist Dr. Puneeth Iyengar. A study of such patients, with stage II or III or recurrent non-small cell lung cancer, is underway at UT Southwestern. "The hypofractionated radiation may be able to overcome the loss of benefit provided by concurrent chemotherapy," Dr. Iyengar says.

With a varied and ever-changing slate of lung cancer trials, UT Southwestern is pushing the envelope of available treatment options. Dr. Schiller urges patients and their doctors to consider a trial early in the course of cancer care.

"In clinical trials we're introducing what we hope will be more effective treatments, and we want to introduce them early on, when someone is newly diagnosed." That's because the first treatment is the one that's most important for patient outcomes, Dr. Schiller says. "A clinical trial is absolutely not a last step. It should be a first step."

Experienced, specialized lung cancer pathologists such as Dwight Oliver, M.D., work with treating teams to determine the precise biology of each patient's cancer. A cancer's histology is critical in determining the most appropriate therapy.

Pathologists: Shining a light on lung cancer

UT Southwestern pathologists work at the cutting edge of lung cancer science for individual patients and for all patients everywhere, transforming how researchers and clinicians understand and treat the disease and providing Cancer Center physicians the most complete picture to affect a cure.

During biopsy and surgery, experienced, specialized lung cancer pathologists are onsite to ensure quality tumor tissue is acquired for analysis and to save portions for future analysis. For each case, they work with the treating team to determine the precise biology of that patient's cancer.

A cancer's histology is critical in determining therapy. "Knowledge of the precise histology of non-small cell lung cancer may help guide both selection—or exclusion—of therapy and may be an indicator to perform molecular testing for specific druggable targets," notes Professor of Pathology Dr. Adi Gazdar.

Conventional drugs are more effective when used in some histological types of lung cancer—small cell lung cancer, for example—while some specific medicines are contraindicated due to serious complications in certain histologies, such as angiogenesis inhibitors in squamous carcinoma, says Associate Professor of Pathology Dr. Dwight Oliver.

In advanced lung adenocarcinoma, molecular analysis is performed because targeted therapies are now available for many of these tumors. At UT Southwestern, testing starts with preanalytic microscopic review and tumor microdissection to remove normal tissue and enrich for malignant cells, which helps to ensure a sufficient volume of cancerous cells are harvested for mutation analysis.

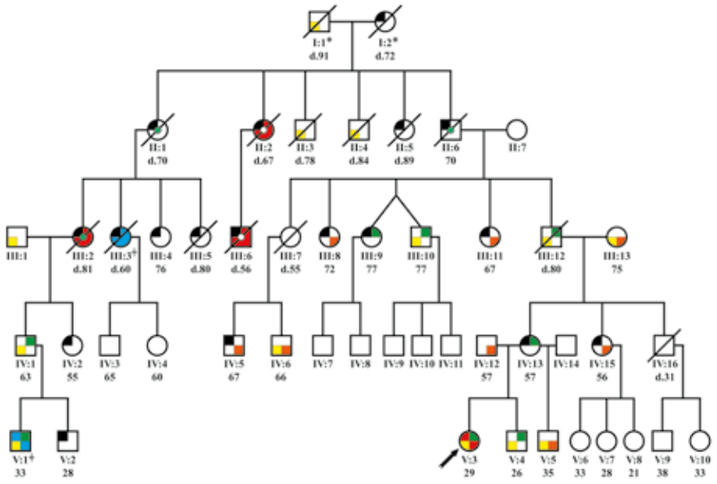
Molecular testing is available at UT Southwestern for any patient or physician requesting services. It is performed onsite with the latest technology, including DNA sequencing and Sequenom mass-spectrometry-based genotyping, which allows molecular pathologists to hunt for many more mutations with less DNA than earlier technologies.

UT Southwestern's Molecular Diagnostics Laboratory is accredited by the College of American Pathologists (CAP) and is classified as a high-complexity lab, according to the Clinical Laboratory Improvements Amendment of 1988 (CLIA). The Medical Center's full-service Cytogenetics and Immunohistochemistry laboratories, directed by Dr. Prasad Koduru and Dr. Jose Torrealba, respectively, are also CAP-accredited and CLIA-certified.

As lung cancer's molecular mysteries unfold, so does a need for new assays that can be applied in the clinic. UT Southwestern pathologists are constantly developing molecular pathology resources and processes to ensure that newly characterized types of lung cancer are analyzed by means certifiable under CLIA.

Sometimes patients whose tumors have undergone earlier molecular testing are later referred to Simmons Cancer Center for further work. "We're a tertiary cancer center," Dr. Oliver says, "so often patients come here who have failed therapies on the outside, and we can do additional mutation testing, looking for targetable mutations that have not been tested for by other labs." In all, the activity of more than a dozen genes can be examined with molecular, cytogenetic, or immunohistochemical testing at UT Southwestern, including *EGFR, KRAS, BRAF, AKT, MEK, NRAS, PI3K, HER2/ERBB2, ROS1, RET, ALK, MET,* and *PTEN*.

Cancer Center pathologists might also re-examine select lung cancers after treatment. "Sometimes the patients are on these targeted therapies and their tumors become resistant," Dr. Oliver says, "and in those cases we'll do additional mutation analysis."



Five generations of a family tree

- Never smoker
- Smoker
- T790M germline mutation positive
- T790M germline mutation negative
- Lung Cancer
- Cancer‡
- Assumed Carrier
- Obligate Carrier

One family's lung cancer legacy

As a leading center for lung cancer care, UT Southwestern had all the pieces in place to discover why a 29-year-old woman with scant smoking history developed lung cancer—and to identify relatives who also were at high risk.

Cancer Center Deputy Director Dr. Joan Schiller, the patient's physician, launched a genetic investigation after the patient mentioned in passing that she'd had two great aunts, also nonsmokers, who had died of lung cancer. The patient's tumor revealed two mutations in the *EGFR* gene; blood samples showed that one, a T790M mutation that usually isn't present in untreated tumors, was actually inherited.

Clinical Cancer Genetics Assistant Director Linda Robinson and other experts from UT Southwestern tracked down relatives, interviewed them, performed blood tests for the T790M mutation, and mapped out a family tree (above) that ultimately covered five generations. The team found seven relatives, including a fourth cousin, a descendant of one of the aunts, who had the mutation. Those who tested positive for it face a higher risk of developing lung cancer—even more so than heavy smokers—and are now undergoing regular lung screening with low-dose CT.

"What we worked out for the first time was if you had this mutation you were at a greatly increased risk of lung cancer, but it was much more so if you were a never smoker and if you were a woman," notes pathologist Dr. Adi Gazdar, the study's senior author.

Little research has been done into the hereditary components of lung cancer, Ms. Robinson notes, in part because the focus has been on smoking, which causes an overwhelming number of cases. "The amount of testing we did on this one family pretty much doubled in the medical literature what's known about this gene mutation," she says. The findings indicated about 30 percent of people with the mutation get lung cancer—and it accounts for about 1 percent of all non-small cell lung cancers.

"The big message for primary care providers is the importance of a family history," Ms. Robinson says. "It can totally change how we manage these patients."

For many patients with lung cancer, a clinical trial should be the first step—instead of a last resort, notes Joan Schiller, M.D., Deputy Director of Simmons Cancer Center. Clinical trials offer patients access to what may be more effective treatment not yet available to the general public.

LATE-STAGE LUNG CANCER

TREATMENT APPROACHES

Chemotherapy:

- Combination chemotherapy
- Chemotherapy plus monoclonal antibody treatment
- Single-agent chemotherapy

Targeted drugs:

- For patients with tumors harboring anomalies such as EGFR mutation or ALK rearrangement

Maintenance therapy

Radiotherapy:

- External beam radiation for localized symptoms or some metastases
- Endobronchial brachytherapy, primarily to ease symptoms
- Brachytherapy administered through the skin to treat metastases (primarily hepatic; also renal, adrenal, and lung)
- Stereotactic ablative radiotherapy (SABR) targeting metastases

Surgery:

- In select cases with controlled brain, adrenal, and other carefully considered metastases
- Pleurodesis (elimination of the cavity around the lungs) for some cases with recurrent pleural fluid

Pulmonary interventions:

- Electrosurgery or electrocautery to remove, or cryotherapy to destroy, airway obstruction
- Stent placement to keep airway open
- Pleural catheter placement for some cases with recurrent pleural fluid

Clinical Trials

The changing face of late-stage lung cancer treatment

Promising new treatment approaches—including ones developed at UT Southwestern—are steadily improving care for patients with metastatic lung cancer.

Medical therapies—chemotherapy, targeted drugs, and biological treatments—are pivotal in slowing the cancer's growth throughout the body. Although new advances to treat lung cancer are still sorely needed, medical therapies have improved markedly in the past 20 years, says lung cancer specialist Dr. Joan Schiller, Deputy Director of Simmons Cancer Center. The latest chemotherapies are more effective and have fewer ill effects, while other medicines, like today's anti-nausea drugs, make treatment more tolerable.

"It's not your grandmother's chemotherapy in terms of hair loss, in terms of nausea, in terms of fatigue," Dr. Schiller says.

Molecular profiling—identifying genetic features of a tumor that help drive its growth—has also changed the face of lung cancer care. "We're making strides all the time," Dr. Schiller says, noting that drugs targeting those molecular features are oral therapies, simple for patients to take, with minimal side effects.

Dr. David Gerber, co-leader of the Cancer Center's lung cancer disease-oriented team, estimates that about 25 percent of non-small cell lung cancer patients have tumors with molecular profiles that respond to currently available "targeted" therapies.

The most common such molecular anomaly, occurring in up to 15 percent of non-small cell lung cancers in the U.S., are *EGFR* gene mutations, typically found in people who smoked a little or not at all. Another anomaly occurs in the *ALK* gene and is found in about 5 percent of non-small cell lung cancers.

"Three to five years ago we had one class of drugs for each of these clinical scenarios. Now we have several, including second- and third-generation *EGFR* inhibitors and second-generation *ALK*-targeting drugs," Dr. Gerber says.

Taken together, other, rarer molecular features of lung cancer—which individually may account for only 1 to 3 percent of cases—can also make a substantial mark on care. "These less common subtypes also provide promising opportunities that we are currently investigating," Dr. Gerber says, citing one subset, involving an abnormality in the molecule *ROS1*; patients with this type of lung cancer appear to respond to *ALK* inhibitors. People whose lung tumors bear a *BRAF* mutation, or have a *HER2* mutation, also may benefit from specific targeted therapies.

Testing for these rare molecular subtypes may not be common outside of an academic medical center setting, Dr. Gerber says. But because UT Southwestern belongs to the national Lung Cancer Mutation Consortium, patients' cancers can undergo extensive molecular profiling as part of a clinical trial—meaning what could cost thousands of dollars is provided free of charge to Simmons Cancer Center patients. "Depending on the results of this molecular testing, there are associated treatment studies that allow patients access to the newest targeted therapies," Dr. Gerber says.

Typically, UT Southwestern has around two dozen lung cancer trials open. That sets Simmons Cancer Center apart from many other treatment centers, which don't have large volumes of lung cancer patients, says lung cancer specialist Dr. Jonathan Dowell. "We have a very large portfolio of clinical trials for essentially every stage of disease, specifically advanced disease, including first-line, second-line, and beyond, as well as for many different molecular subtypes of lung

Medical oncologist David Gerber, M.D., co-leader of the lung cancer disease-oriented team, estimates that about 25 percent of non-small cell lung cancer patients have tumors with molecular profiles that respond to currently available "targeted" therapies.

UT Southwestern offers clinical trials for every stage of lung cancer—many of them for metastatic disease—and for a variety of molecular subtypes of lung cancer.

cancer that we've identified," he says. "At a smaller center it's not practical to open trials for a subset of patients who represent only a few percent of lung cancers. But here we can do that because we will see enough of those patients."

Bench to bedside

Also taking the spotlight in the fight against metastatic lung cancer are biological therapies—such as the man-made antibodies cetuximab, which targets tumors with *EGFR* mutations, and bevacizumab, which interferes with the growth of tumor-fueling blood vessels.

Meanwhile, a promising new antibody called bavituximab, developed at UT Southwestern, is undergoing phase III testing as a second-line treatment in late-stage non-small cell lung cancers. That study will include more than 500 patients on three continents. The antibody has shown early promise when combined with conventional chemotherapy (paclitaxel and carboplatin) as a first-line treatment in patients with locally advanced or metastatic non-small cell lung cancer, Dr. Gerber says.

Bavituximab was developed by the late Dr. Phil Thorpe, a professor of pharmacology, with work continuing under collaborator and Associate Professor of Surgery Dr. Rolf Brekken. Research has found that bavituximab overcomes the immune system's tolerance of a cancer, allowing patients to develop an anti-tumor immune response, and can also inhibit development of tumor blood vessels.

Using serial biopsies to look for immune cell infiltration of the tumor, investigators are striving to understand better in patients how those immune effects may evolve over time—as well as to elucidate the drug's impact on tumor blood vessels.

Tailored care

A range of other care may be offered to patients with metastatic lung cancer, depending on details of their cases. In rare cases with only a single site of metastasis, surgical resection of both the metastatic site and the primary lung tumor may provide long-term disease control, says thoracic surgeon Dr. Kemp Kernstine.

UT Southwestern's interventional pulmonologists are also available to help patients breathe easier. A pleural catheter can be implanted to drain chronic pleural fluid buildup outside the lungs. A stent can be placed to prop an airway open if a tumor is encroaching. And techniques such as electrocautery or electrosurgery can be deployed to burn away tumor tissue, or cryotherapy to freeze it away, says interventional pulmonologist Dr. Hsien-chang Thomas Chiu. Patients are referred to the pulmonary medicine team by oncologists in the community as well as at UT Southwestern.

Radiotherapy can ease symptoms such as pain, bleeding, and swallowing problems. And a type of radiotherapy called endobronchial brachytherapy is now available to patients at UT Southwestern, says radiation oncologist Dr. Michael Folkert. Brachytherapy is administered via a catheter placed through the mouth, typically to treat patients who are bleeding in the airways, or to prevent a tumor from re-obstructing an airway after stenting. Additionally, percutaneous approaches, where radiation sources are placed directly into tumors via needles inserted through the skin, will soon be available for treating metastases to the liver, adrenal glands, and possibly the kidneys or lungs.

Slowing the cancer's course

Another type of radiotherapy—which shoots highly focused beams of radiation from multiple angles at a tumor—is forestalling progression of metastatic lung cancers. UT Southwestern radiation oncologists have been leaders in developing the treatment, stereotactic ablative radiotherapy (SABR, also known as stereotactic body radiation therapy), in lung and other cancers.

In a phase II study, radiation and medical oncologists at Simmons Cancer Center and the University of Colorado treated 24 patients who had metastatic lung cancer and for whom other treatments had failed. Each patient was diagnosed with no more than six metastatic sites, other than the brain.

Doctors administered a standard drug therapy, the *EGFR* inhibitor erlotinib, and treated the tumors with limited courses of SABR, says UT Southwestern radiation oncologist Dr. Robert Timmerman. Instead of an expected three months, patients' median time until progression totaled 14-plus months.

"This is a game-changer," says Dr. Puneeth Iyengar, co-leader of the lung disease-oriented team. "Historically, once patients had stage IV lung cancer, doctors gave up trying to target areas of gross disease."

None of the patients tested for an *EGFR* mutation actually had one, suggesting the therapeutic difference came from the SABR, he says.

The researchers are exploring how the treatment might spark the immune system to act against the cancer. "We used to think lung cancer is not immunogenic enough," Dr. Timmerman says. "It turns out lung cancer does have immune antigens that can be exploited. They've just been hidden inside the cells."

At UT Southwestern, SABR is now being incorporated into stage IV lung cancer care, Dr. Iyengar says. "Our goal is to extend survival, to make this a chronic illness."

Large-scale interest in small cell lung cancer

While non-small cell lung cancer is by far the most common form of lung cancer, 10 to 15 percent of lung cancers are the small cell type, a form of the disease that is seen almost solely in people who have smoked. Small cell lung cancer is named for the small appearance of the malignant cells under a microscope.

Because small cell lung cancer is very aggressive, it is only rarely detected in the early stages when surgery could be beneficial, says thoracic surgeon Dr. Kemp Kernstine. As with other lung cancers, when small cell cancer is caught very early, the most advanced minimally invasive surgical techniques, video-assisted thoracic surgery (VATS) and robotic VATS, may be used.

Chemotherapy and radiation therapy can both lengthen survival in patients with limited or extensive disease. Dr. Hak Choy, Chair of Radiation Oncology, notes that prophylactic cranial irradiation is administered in an effort to prevent growth of cancer that has spread undetected to the brain.

UT Southwestern has a longstanding research interest in small cell lung cancer, notes medical oncologist Dr. David Gerber. "Currently, we have an ongoing effort where we're taking blood from small cell patients and trying to identify the cancer cells in the blood, and then growing them in the laboratory to learn more about the patients' tumors," he says.

UT Southwestern has several trials underway for small cell lung cancer, looking at new ways to deliver radiation as well as new medicines. Recent or current trials include:

- **A PHASE III,** national cooperative group trial comparing three different radiotherapy regimens, which vary in dose, frequency, and duration. The multicenter study will be conducted in patients with limited small cell lung cancer who are also receiving chemotherapy with cisplatin or carboplatin, plus etoposide.

- **A PHASE II,** national cooperative group study testing prophylactic cranial radiation alone versus that plus additional radiation aimed at treating any remaining cancer elsewhere in the body. The trial is for patients with extensive disease after they receive chemotherapy.

- **A PHASE I/II** study testing the addition of veliparib, a type of drug known as a PARP inhibitor, to cisplatin and etoposide chemotherapy in small cell patients with extensive disease.

Caring for a community

As the only National Cancer Institute–designated cancer center in the North Texas region, UT Southwestern's Simmons Cancer Center is committed to sharing its expertise and improving the quality of lung cancer care for this area of the country.

That community includes nearly 6.8 million people in the Dallas-Fort Worth region—the nation's fourth-largest metropolitan area—as well as residents of dozens of nearby counties. The Cancer Center's reach extends into Oklahoma, Arkansas, and Louisiana, none of which have cancer centers that are NCI-designated, a hallmark of institutions that meet stringent criteria for state-of-the-art research and care.

A key part of Simmons Cancer Center's mission is implemented one cancer case at a time. Oncology professionals at the Center regularly confer with and support referring physicians to ensure communication, evidence-based care, and consensus with a patient's full treatment team, including the primary care doctors. In addition, practitioners in the community are invited to submit complex lung cancer cases, free of charge, to the Cancer Center's Thoracic Oncology Tumor Board (page 3), a weekly conference of about 40 experts from the

full range of disciplines devoted to lung cancer care. After an evidence-based review, those experts create a document summarizing their discussion and recommendations, which is given to the patient's referring physician.

The Cancer Center also maintains a speakers' bureau, which arranges for cancer professionals to share their expertise with community groups. And Cancer Center physicians frequently give presentations to physicians' organizations about new developments in their specialties.

For Simmons Cancer Center patients, care and support are available at satellite sites, including the UT Southwestern Clinical Center at Richardson/Plano, at 3030 Waterview Parkway in Richardson. There, patients can receive care from a medical oncologist, have laboratory tests performed, and receive chemotherapy.

In addition, UT Southwestern's Moncrief Cancer Institute, at 400 W. Magnolia Ave. in Fort Worth, offers a comprehensive Community Survivorship Program that provides multidisciplinary support for patients and survivors to improve their quality of life during and after treatment. Among Moncrief's ongoing services is a comprehensive smoking/tobacco cessation program, open to all cancer survivors at the Institute and in the community. The Institute also collaborates with population scientists at UT Southwestern to study implementation of guidelines from the National Lung Screening Trial, particularly in rural counties. Moncrief also houses a new Simmons Cancer Center clinic, expanding services to include chemotherapy and cancer imaging.

Finally, patients, their families, and others affected by cancer can receive assistance from Simmons Cancer Center's Cancer Answer Line, a free and confidential phone service. The Answer Line offers guidance and referrals to UT Southwestern care and fields questions about diagnoses, testing, treatment, and more.

William P. Clements Jr. University Hospital

A new home for the future of medicine

The new William P. Clements Jr. University Hospital at UT Southwestern, in the Medical District of Dallas, brings together the knowledge, expertise, research, and innovation of a world-class medical institution into one remarkable facility—with the patient at the center of it all.

Redefining the future of care, today.

Inspired by your needs, focused on your care

It's a hospital unlike any other in North America. Conceived and designed with the needs of patients and their families in mind. Connecting them like never before. Keeping them safe and comfortable. Ensuring that compassionate care is never more than a few steps away.

Clements University Hospital's oncology unit has 64 beds and is staffed by oncology-certified nurses and transitional coordinators. The patient/nurse ratio is 5:1 or better. Here's more of what you'll find in the new hospital:

- 12 floors
- 1.3 million square feet
- 460 single-patient rooms
- 40 emergency treatment rooms
- 24 surgical suites
- 12 interventional suites
- 72 adult ICU rooms
- 30 neonatal ICU rooms
- 16 labor and delivery rooms
- 6 endoscopy suites
- 4 CT scan, 2 MRI, and 6 X-ray suites
- 2 nuclear medicine rooms

CLINICAL RESEARCH

Simmons Cancer Center's vast portfolio of lung cancer research includes projects focused on:

Assaults on *KRAS*. Researchers are finding new ways to neutralize the impact of the *KRAS* gene mutation, a notorious molecular villain in lung as well as other cancers.

Much like *EGFR* mutations and *ALK* rearrangements, *KRAS* mutations drive lung cancer development and growth. However, *KRAS* mutations, frequently seen in smokers, are more common—representing about 25 percent of lung adenocarcinomas, compared with 10 percent for *EGFR* and just 5 percent for *ALK*.

As part of an initiative to advance genomics-guided medicine, the laboratory of Professor of Cell Biology Dr. Mike White is carrying out massively parallel chemical toxicity screens in a group of molecularly and clinically annotated lung tumor cell lines. The efforts are defining new mechanistic subtypes of oncogenic *KRAS*-driven cancers, together with drug leads that specifically target those subtypes.

The initiative is just one of several at Simmons Cancer Center that are addressing the unique challenge of *KRAS*-driven cancers. "*KRAS* for decades has been considered undruggable," notes lung cancer specialist Dr. David Gerber.

Yet there may be more than one way to drug the "undruggable." For instance, one compound now in clinical trials at UT Southwestern takes aim at a *KRAS* accomplice—a downstream enzyme, called focal adhesion kinase (FAK), that impacts tumor growth at the behest of *KRAS*.

Research led by Associate Professor of Internal Medicine Dr. Pier Paolo Scaglioni has shown in a mouse model of human lung cancer that inhibiting FAK can effectively treat tumors with *KRAS* mutations and prolong survival. He and other Cancer Center scientists are striving to enhance the effectiveness of FAK inhibitors and also are testing in the lab whether the drugs work in lung cancers that do not carry *KRAS* mutations.

Based on that work, Drs. Scaglioni and Gerber have developed a trial testing defactinib (VS-6063), an oral FAK inhibitor, in patients with *KRAS*-mutant cancers. The trial, involving about 10 centers across the U.S., is nearing the end of phase II testing.

Meanwhile, the laboratory of radiation oncologist and lung cancer specialist Dr. Kenneth Westover has synthesized a molecule that directly inactivates the *KRAS* protein. X-ray crystallography and mass spectrometry showed that the molecule, SML-8-73-1, interferes selectively and irreversibly with *KRAS* molecules carrying the G12C mutation, a hallmark of tobacco-associated lung cancer. The researchers are now chemically tweaking the molecule to make it more drug-like, to facilitate its study in living cancer cells and in animals.

"It's the first step in a long journey," Dr. Westover says.

Targeting neuroendocrine tumors. Cancer Center scientists are also tackling new challenges in lung neuroendocrine tumors—a category that includes small cell, carcinoid, and large cell neuroendocrine cancers of the lung. Pulmonary neuroendocrine tumors, for which no targeted "personalized," treatment is yet available, account for about 40,000 new U.S. lung cancer cases each year.

Pioneering research led by Professor of Pharmacology Dr. Melanie Cobb, collaborating with Professor of Neuroscience Dr. Jane Johnson, is revealing that many neuroendocrine cancers in the lung and elsewhere are dependent on two related proteins that govern gene transcription. The proteins, ASCL1 and NeuroD1, are important in normal development but can go haywire and promote tumor growth.

The research effort has found that each transcription factor can influence at least 1,000 genes downstream and has cataloged how those genes differ in normal versus tumor tissue. The findings are helping to reveal which downstream genes might be targeted successfully with drugs to halt tumor growth.

Opening up clinical trials. Clinical trials can't speed new knowledge to the bedside if they can't accrue patients, and quickly. And trials can't help individual patients who aren't permitted to participate.

To address these concerns, Cancer Center researchers have shined a spotlight on exclusion criteria for lung cancer clinical trials.

"Well under 5 percent of adult cancer patients are accrued to clinical trials," notes Dr. Gerber, "and a major limiting factor is stringent eligibility criteria."

In one study of more than 50 lung cancer clinical trials, Dr. Gerber and colleagues found that about 80 percent of trials automatically excluded patients who had a previous cancer—even though the prior cancer seemed unlikely to interfere with the study treatment, conduct of the trial, or interpretation of the outcomes. For example, "you have patients who three years ago had prostate cancer surgery who can't go on a clinical trial," Dr. Gerber says.

In all, up to 18 percent of potential trial patients—perhaps more than 200 people in some studies—were excluded from the lung cancer studies, the research found.

Exclusion of patients with a cancer history is likely only to increase over time. "In the past 30 years, the number of cancer survivors in the U.S. has grown fourfold," Dr. Gerber notes. Including more cancer survivors, he says, could lead to faster trials that better reflect the real-world population of lung cancer patients.

Newer work by the research team, which includes UT Southwestern's Dr. Ethan Halm and Dr. Sandi Pruitt, studied more than 100,000 patients older than 65 who were diagnosed with stage IV lung cancer from 1992 to 2009. Almost 15 percent had a prior cancer, typically within five years of the lung cancer diagnoses, and about three-quarters of the prior cancers were diagnosed at stages I, II, or III.

Regardless of its type, stage, or timing, a previous cancer did not adversely impact survival in the advanced lung cancer patients, the study found. Lung cancer patients with previous cancers should therefore be considered candidates for clinical trials seeking new therapies, the researchers say.

A mechanism for metastasis. Research rooted at UT Southwestern is shedding new light on metastases, the major cause of death from cancer.

Collaborating with colleagues in China, Chief of Pulmonary and Critical Care Medicine Dr. Lance Terada, along with Cancer Center lung cancer researchers Dr. John Minna and Dr. Luc Girard, have characterized a protein—a transcription factor called Aiolos—that is important in the spread of cancer cells. Aiolos is frequently overexpressed in lung cancers and is a marker of poor prognosis.

Although the protein is also produced by normal blood cells, Aiolos is repurposed in cancer cells to allow them to circulate in the bloodstream and metastasize.

Aiolos promotes metastasis by interfering with normal adhesion that anchors tissue cells to their environment and by repressing another protein, p66Shc, that normally quashes metastatic activity.

"Cellular behaviors that are largely responsible for cancer mortality are poorly understood," notes Dr. Terada. "Our study reveals a central mechanism by which cancer cells acquire blood cell characteristics to gain metastatic ability."

Understanding this metastasis mechanism opens a door to finding new medicines to rein in tumors, Drs. Terada and Minna say.

Cessation motivation. Simmons Cancer Center members Dr. Darla Kendzor and Dr. Michael Businelle are testing ways to help safety-net and homeless patients break their smoking addiction.

People living in poverty are less likely to quit smoking than people of greater means, even though both groups try to quit about as frequently, note Drs. Businelle and Kendzor, faculty at the University of Texas School of Public Health Dallas Regional Campus. "Although the prevalence of smoking has declined to 18 percent among U.S. adults," Dr. Kendzor says, "nearly 30 percent of those living below the poverty threshold and over 70 percent of those who are homeless continue to smoke."

In one of their recent studies at the Parkland Hospital Tobacco Cessation Clinic, patients who were randomized to receive standard care plus small weekly financial incentives were twice as likely to remain abstinent four and 12 weeks later, compared with patients who received standard care alone. The cost of the incentives averaged $63 per participant. Given that the first year of lung cancer treatment costs about $70,000, preventing a single case of lung cancer would cover the cost of at least five years of the financial incentives program.

In another Parkland-based smoking cessation study, the team is testing whether delivering messages via smartphone can help patients quit smoking and avoid relapse. The messages are tailored in real-time based upon patients' responses to select questions.

The researchers have also recently evaluated the effects of offering a small financial incentive for smoking cessation among clients at The Bridge homeless recovery center in Dallas. Weekly incentives during the first month after quitting—costing an average of $42 per participant—markedly increased abstinence rates at four weeks.

Earlier work by the team shed light on the difficulties that homeless shelter residents face when trying to quit, leading to a smoking ban in a large area of the shelter campus. "Homeless adults are less likely to quit smoking partially due to a shelter culture that is permissive of smoking and results in exposure to over 40 other smokers each day," Dr. Businelle says. Residents' support for the no-smoking area was high, and tests of exhaled carbon monoxide indicated that smoking may have declined after the change was implemented.

LUNG CANCER DISEASE-ORIENTED TEAM FACULTY

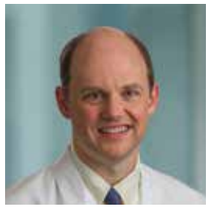
Cardiovascular and Thoracic Surgery – Thoracic Surgery

Kemp Kernstine, M.D., Ph.D.
Professor and Chair
Robert Tucker Hayes Foundation Distinguished Chair in Cardiothoracic Surgery

Scott Reznik, M.D.
Associate Professor

Internal Medicine – Hematology/Oncology

Joan Schiller, M.D.
Deputy Director, Harold C. Simmons Comprehensive Cancer Center; Professor and Chief
Andrea L. Simmons Distinguished Chair in Cancer Research



Jonathan E. Dowell, M.D.
Associate Professor

David Gerber, M.D.
Associate Professor

Randy Hughes, M.D.
Associate Professor

Saad Khan, M.D.
Assistant Professor

Lorraine Pelosof, M.D., Ph.D.
Assistant Professor

Internal Medicine – Pulmonology

Muhanned Abu-Hijleh, M.D.
Associate Professor

Hsienchang Thomas Chiu, M.D.
Assistant Professor

Radiation Oncology

Hak Choy, M.D.
Professor and Chair
Nancy B. & Jake L. Hamon Distinguished Chair in Therapeutic Oncology Research

Robert Timmerman, M.D.
Professor and Vice Chair
Effie Marie Cain Distinguished Chair in Cancer Therapy Research

Puneeth Iyengar, M.D., Ph.D.
Assistant Professor

Ken Westover, M.D., Ph.D.
Assistant Professor

Lori Watumull, M.D.
Clinical Professor

Not Pictured

Internal Medicine

James Kim, M.D., Ph.D.
Assistant Professor

Pathology

Dwight Oliver, M.D.
Associate Professor

Radiology

Kirk Jordan, M.D.
Associate Professor

Michael Landay, M.D.
Professor

PEER-REVIEWED RESEARCH

Cancer Center members with peer-reviewed lung cancer research

Neal Alto, Ph.D., "Using Microbial Pathogens to Probe Weaknesses in Human Lung Cancer" (CPRIT - RP130515) $199,472; June 2013 – May 2015.

David Boothman, Ph.D., "Use of Beta-lapachone for Lung Cancer Chemotherapy" (National Cancer Institute - 5 R01 CA102792-12) $1,675,700; July 2013 – April 2018.

Rolf Brekken, Ph.D., "Radiation-Guided Vascular Targeting of Lung Cancer" (CPRIT - RP120670) $1,353,233; September 2012 – August 2017.

Michael Businelle, Ph.D., "Socioeconomic Disparities in Smoking Cessation: Identifying the Mechanisms", (American Cancer Society - MRSG-12-114-01-CPPB) $717,000; July 2012 – June 2017.

David Chen, Ph.D., & Aroumougame Asaithamby, Ph.D., "Risk Estimates and Mechanisms of Lung Cancer Pathogenesis after Space Radiation – Project 3: Human Organotypic (3D) Genomic Instability Model of HZE Particle-Induced Lung Carcinogenesis" (NASA - NNX11AC54G-04) $952,060; January 2011 – December 2015.

Hak Choy, M.D., "Technology Directed Advances in Radiation Therapy of Lung Cancer" (CPRIT - RP110562) $595,713; July 2011 – June 2016.

Melanie Cobb, Ph.D., "Dependence of Small Cell Lung Cancer on the Basic Helix-Loop-Helix Transcription" (CPRIT - RP140143) $900,000; August 2014 – August 2017.

Ralph DeBerardinis, M.D., Ph.D., "The Metabolic Phenome of Human Lung Cancer" (CPRIT - RP130272) $665,559; June 2013 – May 2016.

Ralph DeBerardinis, M.D., Ph.D., & Kemp Kernstine, M.D., Ph.D. (Co-PIs), "Translational Studies in Lung Cancer Metabolism: Creating New Paradigms in Diagnosis and Therapy (V Foundation for Cancer Research- Translational Research Award) $600,000; November 2013 – October 2016.

Adi Gazdar, M.D., "Development of Targeted Therapy for SMARCA4 Mutant Containing Non-Small Cell Lung Cancers (Uniting Against Lung Cancer - Impact Award) $200,000; March 2013 – March 2015.

David Gerber, M.D., "Phase 0 Trial of Itraconazole for Early-Stage Non-Small Cell Lung Cancer" (US Department of Defense - W81XWH-14-1-0540) $588,552; September 2014 – September 2017.

Sandra Hofmann, M.D., Ph.D., "Role of DHHC Protein Palmitoyltransferases in Non-Small Cell Lung Cancer" (National Cancer Institute - 1 R21 CA185840-01) $380,408; April 2014 – March 2016.

Darla Kendzor, Ph.D., "Small Financial Incentives to Promote Smoking Abstinence in Safety Net Hospital Patients", (National Cancer Institute - 1 R01 CA197314) $1,724,570; July 2015 – June 2020.

James Kim, M.D., Ph.D., "Targeting of Cancer Stem Cells and Their Microenvironment in Early Stage Mutant K-ras Lung Cancer" (US Department of Defense - W81XWH-14-1-0338-01) $381,588; September 2014 – September 2016.

Simon Craddock Lee, Ph.D., "Inter-Personal Framework for Lung Cancer Decision-Making in African Americans" (National Cancer Institute - 5 R03 CA159706-02) $158,875; March 2012 – February 2015.

John MacMillan, Ph.D., "Natural Product for Treatment of Non-Small Cell Lung Cancer" (CPRIT - RP140152) $772,368; August 2014 – August 2017.

David Mangelsdorf, Ph.D., "Development of Nuclear Receptors and CoRegulators as Diagnostic and Therapeutic Targets in Breast and Lung Cancers" (CPRIT - RP120732) $289,715; September 2012 – August 2017.

Ralph Mason, Ph.D., "Exploiting Radiobiology of Stereotactic Ablative Radiotherapy for Lung Cancer - Effects of Hypoxia" (CPRIT - RP120670) $1,298,237; September 2012 – August 2017.

Steven McKnight, Ph.D., "Discovery of New Drugs for Treatment of Lung Cancer" (CPRIT - RP110708) $658,755; July 2011 – June 2016.

John Minna, M.D., "Lung Cancer SPORE – Project 1: Molecular Signatures for Individualizing Lung Cancer Therapy" (2 P50 CA070907-16A1) $2,171,525; September 2014 – August 2019.

John Minna, M.D., "Characterization of Nuclear Receptor and Co-Regulator Expression and Function in Lung Cancers" (CPRIT - RP120732) $2,057,582; September 2012 – August 2017.

John Minna, M.D., "Discovery of New Drugs for Treatment of Lung Cancer - Molecular Biomarker Identification" (CPRIT - RP110708) $1,972,269; July 2011 – June 2016.

John Minna, M.D.; John MacMillan, Ph.D.; Michael Roth, Ph.D.; & Michael White, Ph.D. (Co-PIs), "Lung Cancer Oncogenotype-Selective Drug Target Discovery (National Cancer Institute - 5 U01 CA176284-02) $2,116,175; May 2013 – April 2017.

Deepak Nijhawan, M.D., Ph.D., "Using Chemistry to Identify New Targets in Lung Cancer (Damon Runyon Cancer Research Foundation - CIA 68-13-02) $450,000; July 2013 – June 2016.

Pier Paolo Scaglioni, M.D., "Lung Cancer SPORE – Project 3: Preclinical Development and Clinical Testing of MEK and PI3K Targeted Therapy for KRAS-mutant NSCLC as a Method of Radiosensitization and Metastasis Inhibition" (2 P50 CA070907-16A1) $1,367,300; September 2014 – August 2019.

Pier Paolo Scaglioni, M.D., "Identification of Critical Components of the K-RAS Network in Lung Cancer", (American Cancer Society - RSG-13-068-01-TBG-03) $720,000; January 2013 – December 2016.

Pier Paolo Scaglioni, M.D., "Characterization and Drug Targeting of PML Tumor Suppressor in Lung Cancer (National Cancer Institute – 5 R01 CA137195-05) $1,628,875; June 2009 – May 2015.

Jerry Shay, Ph.D., "Risk Estimates and Mechanisms of Lung Cancer Pathogenesis after Space Radiation – Project 2: Mouse Models of Lung Cancer after HZE Particle Irradiation" (NASA - NNX11AC54G-04) $1,802,120; January 2011 – December 2015.

Jerry Shay, Ph.D., and Joan Schiller, M.D., "Lung Cancer SPORE – Project 4: Therapeutic Targeting of Telomerase in Lung Cancer Stem Cells" (2 P50 CA070907-16A1) $1,245,320; September 2014 – August 2019.

Michael Story, Ph.D.; Adi Gazdar, M.D.; & John Minna, M.D., "Risk Estimates and Mechanisms of Lung Cancer Pathogenesis after Space Radiation – Project 1: HZE Particle Exposure and the Risk for Human Lung Carcinogenesis" (NASA - NNX11AC54G-04) $1,895,045; January 2011 – December 2015.

Robert Timmerman, M.D., "Exploiting Radiobiology of Stereotactic Ablative Radiotherapy for Lung Cancer" (CPRIT - RP120670) $310,602; September 2012 – August 2017.

Robert Timmerman, M.D., "Technology Directed Advances in Radiation Therapy of Lung Cancer - State of TX Advanced Radiation Therapy (START) Trials" (CPRIT - RP110562) $2,356,538; July 2011 – June 2016.

Michael White, Ph.D., "Discovery of New Drugs for Treatment of Lung Cancer - Compound Target Identification" (CPRIT - RP110708) $2,845,411; July 2011 – June 2016.

Guanghua (Andy) Xiao, Ph.D., "Integrative Analysis to Identify Therapeutic Targets for Lung Cancer" (National Cancer Institute - 5 R01 CA172211-02) $1,649,625; September 2013 – September 2018.

Yang Xie, Ph.D., "Predicting Adjuvant Chemotherapy Response in Lung Cancer (National Cancer Institute - 5 R01 CA152301-05) $1,533,722; September 2010 – February 2015.

Yang Xie, Ph.D.; Adi Gazdar, M.D.; & John Minna, M.D., "Risk Estimates and Mechanisms of Lung Cancer Pathogenesis after Space Radiation – Project 4: Integrating Biomarkers for Mechanistic Understanding of Lung Cancer Pathogenesis and Risk Assessment after HZE Particle Irradiation" (NASA - NNX-11AC54G-04) $1,397,815; January 2011 – December 2015.

PUBLICATIONS

Peer-Reviewed Publications — 2014-2015

1. Kendzor DE, Businelle MS, Poonawalla IB, Cuate EL, Kesh A, Rois DM, Ma P, Balis DS. Financial incentive for abstinence among socioeconomically disadvantaged individuals in smoking cessation treatment. *Am J Public Health 2015 Jun;105(6):1198-205.*

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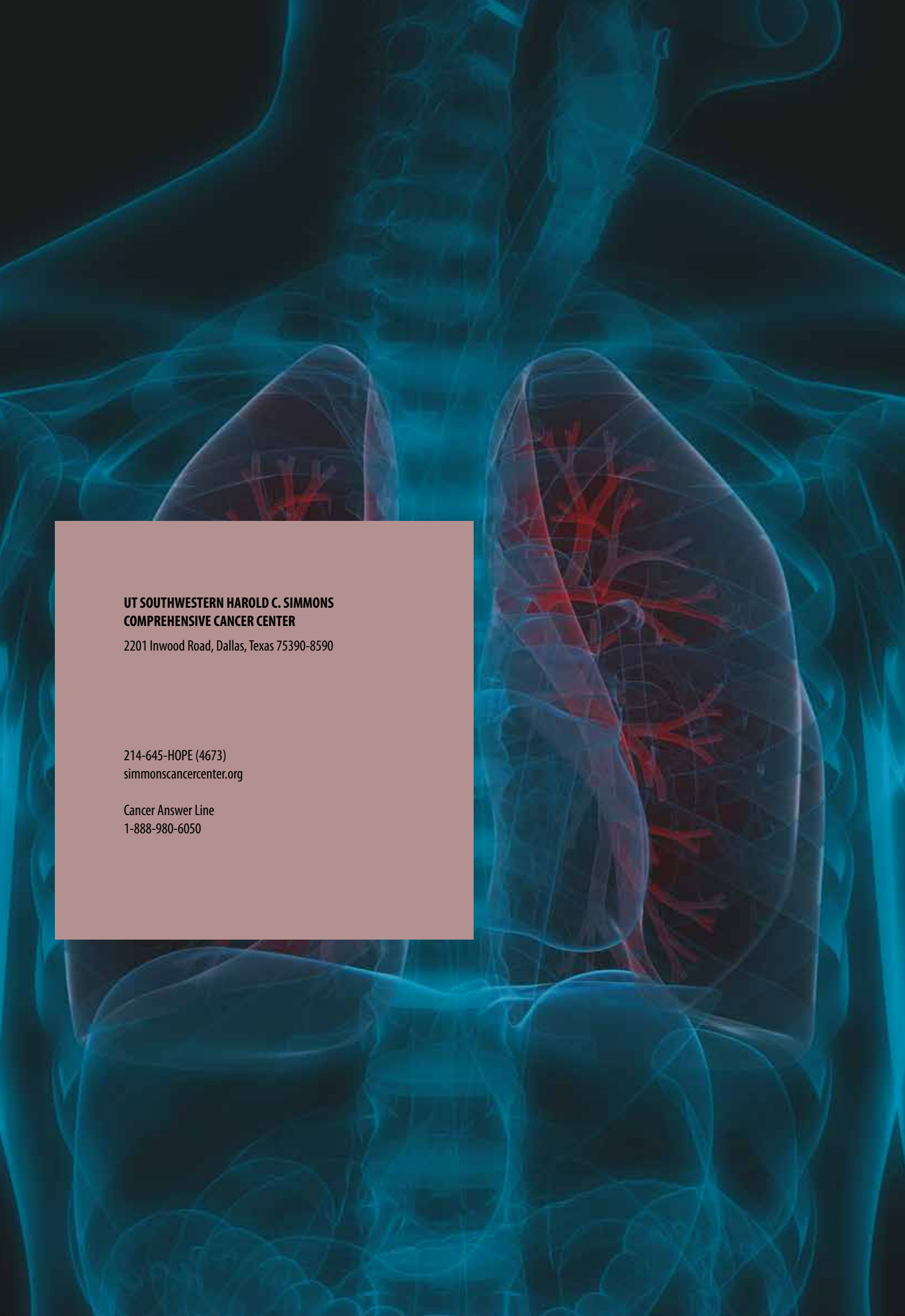

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