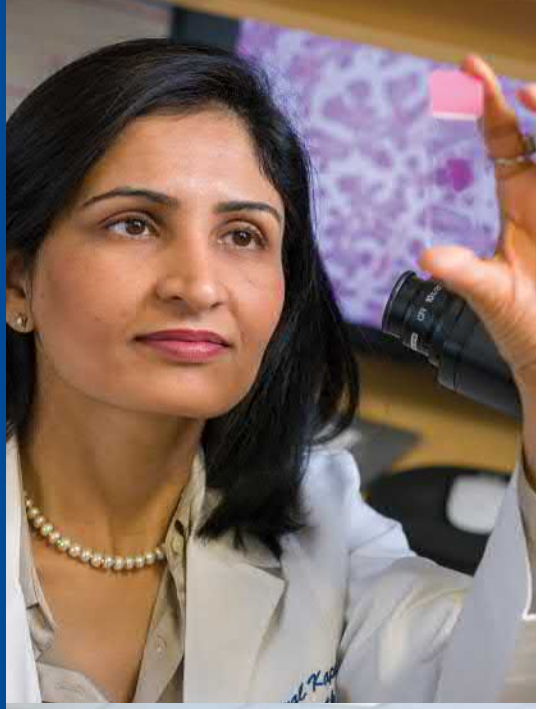


UT Southwestern
Simmons Cancer Center

Breakthroughs in Kidney Cancer

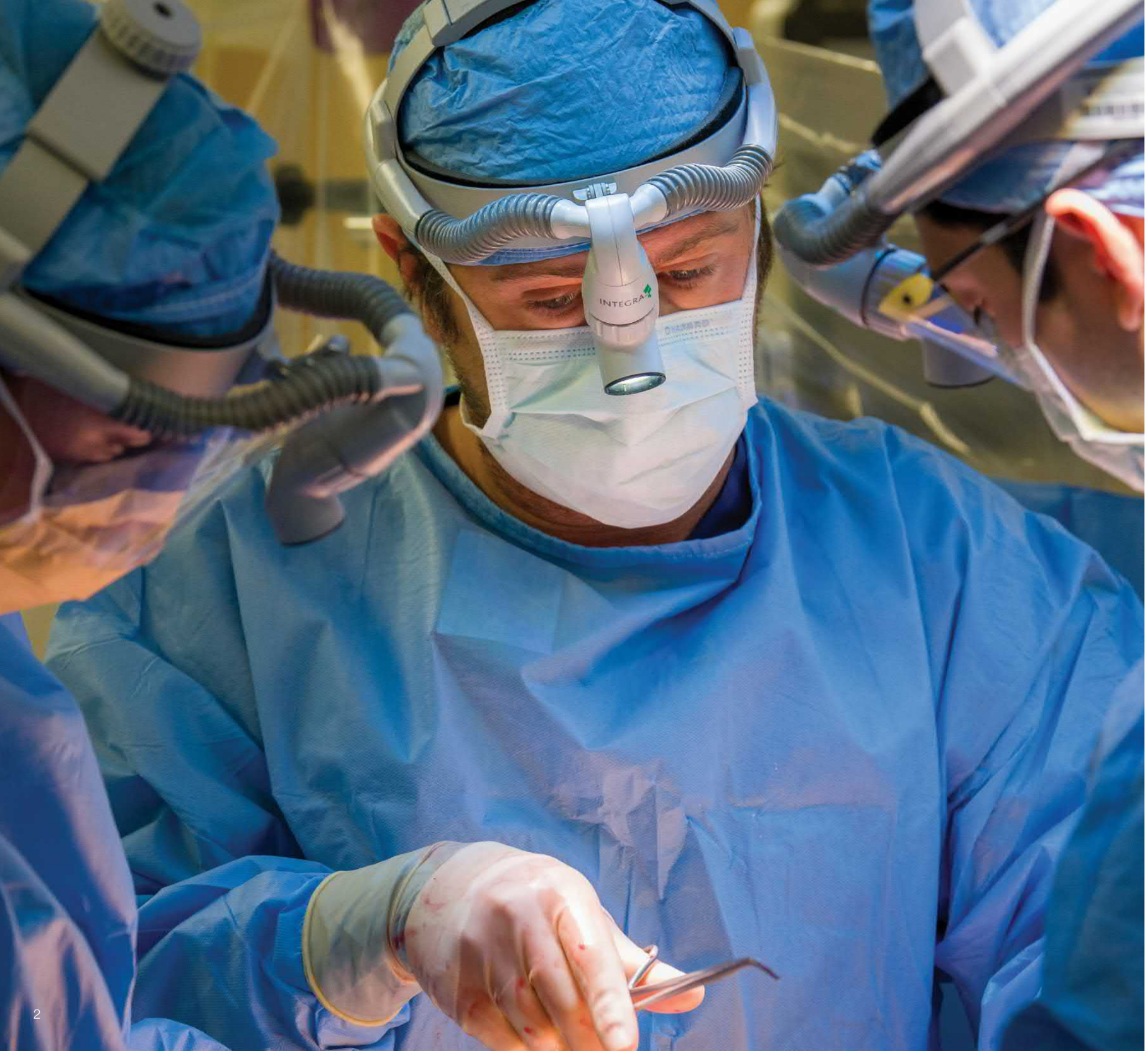


Table of Contents

From the Cancer Center Director

In Pursuit of Breakthroughs

In 2019, kidney cancer killed an estimated 14,000 people in the U.S., including more than 1,200 in Texas. Fighting this disease is an all-hands-on-deck priority.

A leader nationally and globally, the Kidney Cancer Program at the Simmons Comprehensive Cancer Center is an inspirational example of how to sort out and fight this disease. Scientists in laboratories across UT Southwestern probe the most fundamental questions of how kidney cancer starts and then spreads. Oncologists in our clinical facilities identify and apply the most effective surgical, medical, and radiotherapy approaches. Professionals on our support staff tend to a wide range of other needs that patients have during their cancer journey and treatment. In addition, our program is blessed with guidance and resources generously given by former and current patients, as well as other advocates.

Together, these factors fuel the program's relentless pursuit of breakthroughs that are yielding better outcomes for kidney cancer patients in Dallas-Fort Worth, throughout Texas, and across the U.S. In this report, we describe:

- The wide-ranging expertise and superior patient outcomes of our Kidney Cancer Program, one of just two in the country to be recognized and funded as a Specialized Program of Research Excellence (SPORE) by the National Cancer Institute.
- The many ways that Simmons Cancer Center's physician-scientists are addressing the diverse treatment challenges that fall under the umbrella of "kidney cancer."
- How unique scientific resources at UT Southwestern are driving research progress.

This broad array of forces allows us to provide our patients comprehensive, attentive, and highly advanced care for their disease – and to envision a future for our community in which lethal kidney cancer has been eradicated.

Sincerely,

Carlos L. Arteaga, M.D.
Director, Harold C. Simmons Comprehensive Cancer Center
UT Southwestern Medical Center

"At the Kidney Cancer Program, we are committed to delivering superb care to patients, advancing the field through discovery and innovation, and training the next generation of physicians and scientists."

James Brugarolas, M.D., Ph.D.
Director, Kidney Cancer Program

"As mayor, I was proud when the Kidney Cancer Program received the SPORE Award in 2016. Not only did it put UT Southwestern Medical Center in the class of leading cancer research institutions, it also continues to show what we are doing with science and patient care in Dallas. As we build cities, the medical community is essential. We need to attract the greatest scientists, doctors, and healthcare workers to this place we call home, and we are doing that. On behalf of all our residents, especially those with kidney cancer and their family members, I thank the doctors and the team at UT Southwestern."

Mike Rawlings
Mayor of Dallas (2011-2019); Vice Chairman and Founding Partner, CIC Partners LP; Former CEO of Pizza Hut

"The UT Southwestern Kidney Cancer Program is a national jewel right here in Dallas. Because of its capabilities, UT Southwestern has become a global destination for kidney cancer research and treatment."

Andy Geisse
Kidney Cancer Program Business Advisory Committee Member; Operating Partner, Bessemer Venture Partners; former CEO of AT&T Business Solutions

"I have never seen a program so engaged and so focused on not only exceptional research, but also extraordinary patient care. This focus comes from the top, and as Director of the Kidney Cancer Program, Dr. Brugarolas inspires his team of stellar researchers and clinicians to provide excellence in everything they do. Most importantly, they care – about patients, their families, and about finding effective treatments and potentially a cure for this devastating disease."

Carole Baas, Ph.D.
Patient Advocate

After seven years battling metastatic kidney cancer, **Merlinda Chelette**, a pioneer of the **Patient Advocacy Program**, passed away in 2019. This report is dedicated to her memory and the countless patients fighting the disease.

We unite pioneering research and care.

The mission of UT Southwestern Medical Center’s Kidney Cancer Program is to bring together the strengths of UT Southwestern in both basic research and clinical medicine to reduce kidney cancer incidence and mortality. Program investigators are focused on understanding the fundamental biology of kidney cancer evolution and developing new clinical interventions and treatments. Anchored within our pursuit of groundbreaking research is our goal to provide world-class care.

Just as each cancer journey is unique, so is each patient’s experience. We are committed to delivering quality, expert, and compassionate care, keeping patients and their families at the heart of what we do.

We invite you to join us as we pursue what is yet to come.

Program Highlights

1. With more than 120 physician and research faculty, possibly the largest kidney cancer program in the world.[1]
2. Survival rates triple the national benchmarks for stage 4 kidney cancer patients and are higher across stages.[2]
3. One of only two kidney cancer programs to receive a Specialized Program of Research Excellence (SPORE) Award from the National Cancer Institute.[3]
4. Only program to develop a new drug for kidney cancer going from gene discovery to clinical trials.[4]
5. One of two programs in the U.S. developing immunotherapies with a Nobel Prize winner for immunology research.[5]
6. Developed first classification of kidney cancer based on gene mutations, paving the way for tailored treatments.[6]
7. Broadest and most innovative radiation oncology program for kidney cancer.[7]
8. One of the first to develop kidney tumor ablation in the U.S.[8]
9. Top 10 robotic kidney surgery program in the U.S. and largest in North Texas.[9]

[1] As of January 2020, the Kidney Cancer Program comprised more than 30 dedicated physicians, over 90 collaborating physicians, and more than 100 investigators distributed across 19 research tracks. [2] Analysis from UTSW Quality Improvement Office compared to national SEER data. [3] NIH Kidney Cancer SPORE Program. [4] Discovered gene encoding HIF-2α and developed an inhibitor, PT2385/PT2977, now in clinical trials. [5] Two scientists have been awarded a Nobel Prize for Immunology Research in the United States in the last 20 years, Dr. Bruce Beutler at UT Southwestern Medical Center, and Dr. James Allison at University of Texas MD Anderson Cancer Center. [6] UT Southwestern investigators reported: (i) discovery that the BAP1 gene is mutated in 15% of clear cell renal cell carcinomas, the most common type of kidney cancer; (ii) mutations in BAP1 tend to be mutually exclusive with mutations in PBRM1; (iii) BAP1-deficient tumors are of high grade, whereas PBRM1-deficient tumors are of low grade; (iv) BAP1-deficient tumors are associated with poor survival whereas survival for patients with PBRM1-deficient tumors is better; and (v) BAP1 and PBRM1 genes control cancer aggressiveness (Peña-Llopis, *Nat Genet*, 2012; Joseph, *J Urol*, 2016; Peña-Llopis, *Cancer Res*, 2013; Gu, *Cancer Discov*, 2017). [7] Largest reported experience of stereotactic body radiation therapy (SBRT) beyond the brain (Wang, *Int J Radiat Oncol Biol Phys*, 2017) and first to report its deployment for oligoprogression as well as tumor extensions into large veins (tumor thrombi) (Straka, *J Clin Oncol*, 2013; Hannan, *Cancer Biol Ther*, 2015). Search of national clinical trials registry (clinicaltrials.gov) with the terms "Kidney Cancer" and "Stereotactic" (December 1, 2018) shows no other programs with similar breadth and number of active clinical trials. [8] Ogan, *Urology*, 2002. [9] DFW County Hospital District Database, 2016; Solucient Database, 2014.

A Robust Foundation

The Kidney Cancer Program is located at the Harold C. Simmons Cancer Center, one of 51 National Cancer Institute-designated comprehensive cancer centers in the U.S. and one of only three in Texas. It is the only comprehensive cancer center in North Texas.

UT Southwestern ranked No. 1 in the world by the prestigious *Nature Index (2020)*

UT Southwestern is one of the nation's preeminent academic medical centers with an esteemed faculty of physicians and scientists that includes:

- **4 Nobel Laureates**
- **24 members of the National Academy of Sciences**
- **16 members of the National Academy of Medicine**
- **13 Howard Hughes Medical Institute Investigators**

2006

Dr. James Brugarolas, founding Director of the Kidney Cancer Program, is recruited from the Dana-Farber Cancer Institute/Harvard Cancer Center to UT Southwestern.

2010

Peloton Therapeutics is co-founded by Dr. Steve McKnight, Chair of the Biochemistry Department at UT Southwestern, to develop a first-in-class drug targeting the HIF-2α protein.

2011

Immunologist Dr. Bruce Beutler is awarded the Nobel Prize.

2013

Dallas Mayor Mike Rawlings inaugurates the Kidney Cancer Program.

2016

The Kidney Cancer Program becomes the second in the U.S. to earn the prestigious Specialized Program of Research Excellence (SPORE) Award from the National Cancer Institute.

2017

An analysis by the UT Southwestern Office of Quality Improvement shows improved survival across stages compared to national rates.

2018

Biochemist Dr. Zhijian "James" Chen is selected for the Breakthrough Prize in Life Sciences and develops a new immunotherapy drug designed to activate the STING pathway.

2019

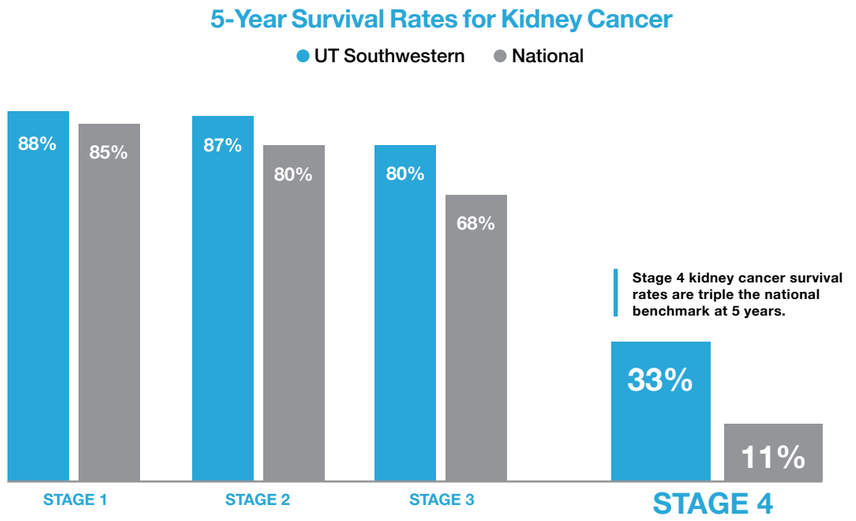
At the forefront of ushering new technologies into practice for treating advanced kidney cancer, UT Southwestern pioneers a groundbreaking radiation strategy for controlling metastatic disease. In recognition of its many innovations and achievements, the Kidney Cancer Program earns the Leaders in Clinical Excellence Program Development Award for advanced patient care.

2020

Recognizing North Texas companies, entrepreneurs, and leaders redefining their industries, the Kidney Cancer Program is a finalist for *D Magazine* & *D CEO*'s Innovation in Healthcare Award.

Improving Survival Rates

UT Southwestern ranks higher than the national average for patient survival across all stages of kidney cancer, most prominently for stage 4 patients, for whom survival rates are three times the national benchmark.



Analysis from UT Southwestern Quality Improvement Office compared to national SEER data.

Leading the Way

A leader in cancer research, UT Southwestern has been revolutionizing kidney cancer care with groundbreaking discoveries, innovative surgical techniques, and novel cancer treatments.

The key to improved survival?

Volume. Consistently across medicine, large centers tending to many patients outperform smaller ones. UT Southwestern treats hundreds of new kidney cancer patients each year.

Access. Access to drugs in expertly vetted clinical trials.

Teamwork. Urologists, medical oncologists, and radiation oncologists work together to develop treatment plans tailored to each patient's individual needs.

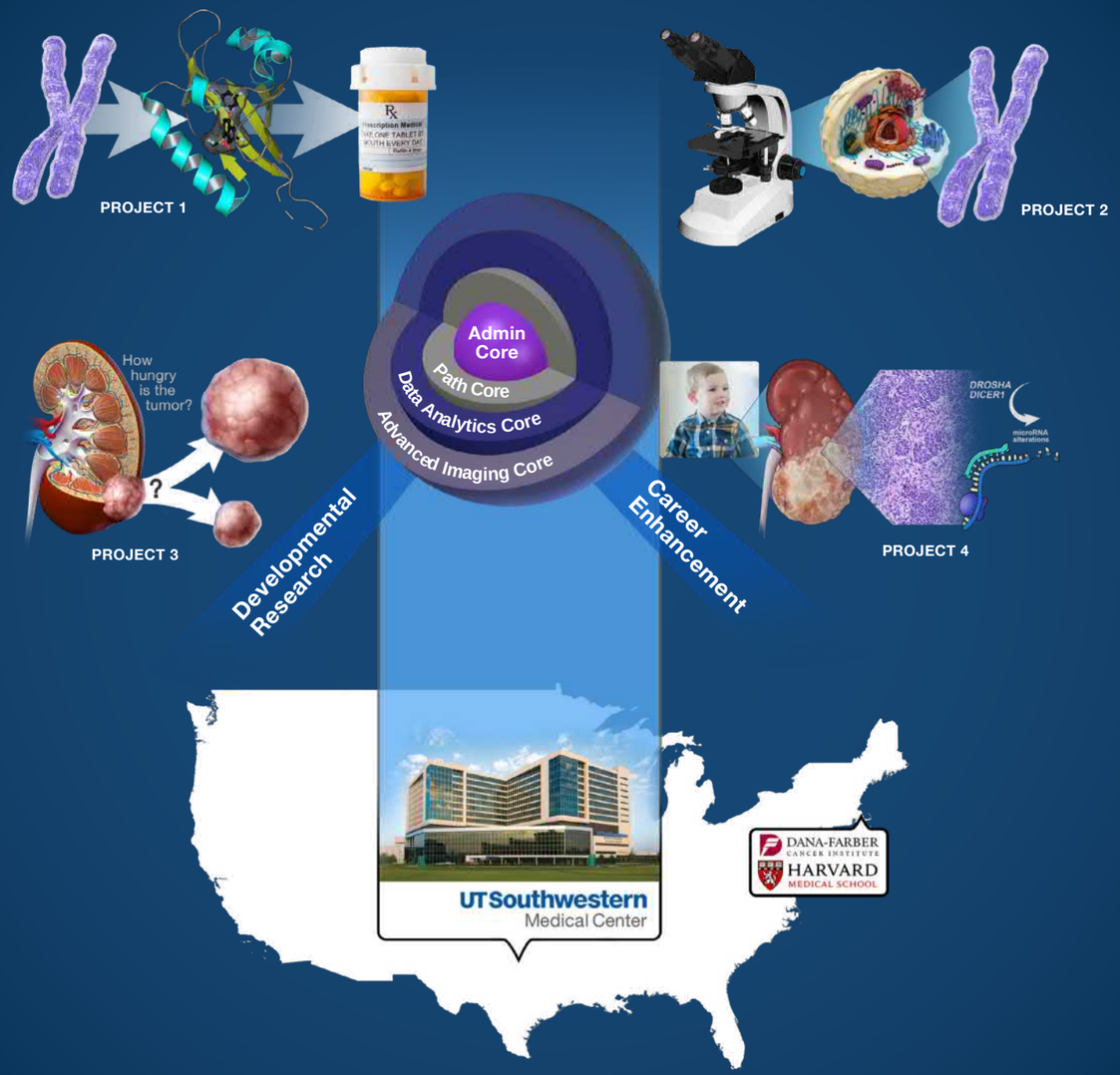
Collaboration. Kidney cancer can travel to any organ in the body. By working with neurosurgeons, orthopedic surgeons, and other specialists at UT Southwestern, patients benefit from comprehensive specialized care.

"I was in shock when I found out I had kidney cancer. I asked my doctor where the best program was in the U.S. and he sent me to UT Southwestern – and he was correct. Great doctors and results that beat the national averages at every stage."

Bill Huber
Stage 3 kidney cancer survivor; Kidney Cancer Program Business Advisory Committee Chair; Former AT&T Executive

Pioneering Research

Recognized by the National Cancer Institute with a SPORE Award



Leveraging breakthrough research, discovery, and technological innovation at UT Southwestern, the Kidney Cancer Program is one of two programs in the U.S. recognized by the National Cancer Institute as a Specialized Program of Research Excellence in kidney cancer, earning the prestigious SPORE Award.

In 1992, the National Cancer Institute (NCI) established the Specialized Program of Research Excellence (SPORE). A cornerstone of NCI's efforts to promote collaborative, interdisciplinary translational research, SPORE awards are designed to enable the rapid movement of fundamental scientific findings into clinical settings. Highly prized and selectively awarded, they typically focus on a specific area of cancer, such as breast, lung, or kidney cancer.

Among the 63 SPORE awards in the U.S., two focus on kidney cancer – one at the Simmons Cancer Center and the other at the Dana-Farber Cancer Institute/Harvard Cancer Center (Boston).

National Cancer Institute Specialized Program of Research Excellence Award (SPORE)

Award term: 2016-2021 | Amount: $11 million
Principal Investigator: James Brugarolas, M.D., Ph.D.

Projects

1 Evaluation of a promising first-in-class drug that blocks the HIF-2α protein, arguably the main driver of kidney cancer.

James Brugarolas, M.D., Ph.D.
Kevin Courtney, M.D., Ph.D.
Ivan Pedrosa, M.D., Ph.D.

2 Understanding how BAP1 loss causes aggressive kidney cancer with development of counteracting therapeutic strategies.

Payal Kapur, M.D.
Thomas Carroll, Ph.D.
Yonghao Yu, Ph.D.

3 Predicting aggressiveness in small kidney tumors by understanding their higher need for nutrients.

Ralph DeBerardinis, M.D., Ph.D.
Ivan Pedrosa, M.D., Ph.D.
Vitaly Margulis, M.D.

4 Defining a new subtype of childhood kidney cancer and developing tailored therapies.

James Amatruda, M.D., Ph.D.
Joshua Mendell, M.D., Ph.D.

Administration Core

Organizing hub of the SPORE.

James Brugarolas, M.D., Ph.D.
Arthur Sagalowsky, M.D.
Renée McKay, Ph.D.

Pathology Core

Integrating genetics, biology, and new technologies to identify and define distinct subtypes.

Payal Kapur, M.D.
Dinesh Rakheja, M.D.

Data Analytics Core

Pioneering new technologies designed to leverage artificial intelligence.

Yang Xie, Ph.D.
Tao Wang, Ph.D.

Advanced Imaging Core

Developing and applying new technologies to characterize kidney cancer and its variants noninvasively.

Ivan Pedrosa, M.D., Ph.D.
Robert Lenkinski, Ph.D.

Developmental Research Program

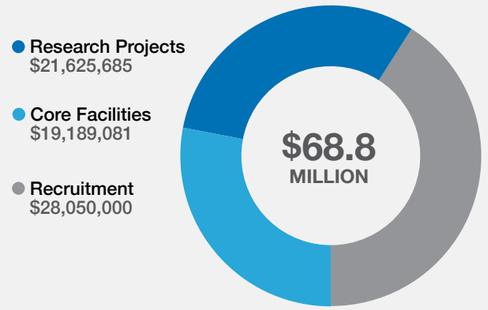
Seed funding supporting innovation in translation.

Career Enhancement Program

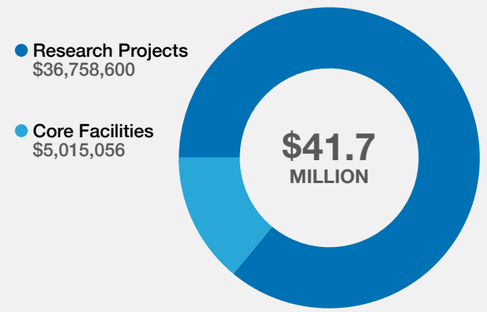
Seed funding to develop the next generation of kidney cancer researchers.

The SPORE award builds upon discoveries fueled by competitive kidney cancer research funding from the Cancer Prevention and Research Institute of Texas and the National Institutes of Health.*

Cancer Prevention and Research Institute of Texas (CPRIT) Awards



National Institutes of Health (NIH) Awards



***Apportioned amounts from 2013 (when Kidney Cancer Program was founded) through 2019**

Patient Snapshot

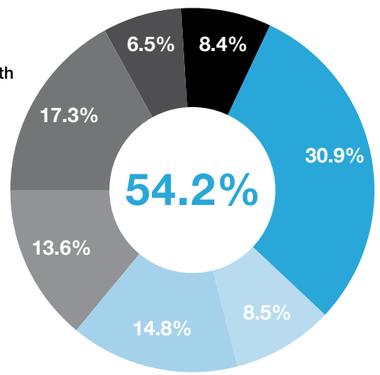
A leading referral center, the Kidney Cancer Program serves patients from across Texas, the country, and beyond.

3,608 Kidney cancer patients*

Serving over half of all patients in North Texas.**

UT SOUTHWESTERN AFFILIATES:

- UT Southwestern (30.9%)
- Parkland (8.5%)
- Texas Health Resources (14.8%)
- Medical City Healthcare (13.6%)
- Baylor Scott & White Health (17.3%)
- Methodist Health System (6.5%)
- All other (8.4%)



More than 50 percent of patients in the Dallas-Fort Worth Metroplex seek care for kidney cancer at UT Southwestern and its health network, which includes partnerships with Parkland Hospital and Texas Health Resources.

*Currently active kidney cancer patients

**2019 figures, Dallas-Fort Worth Hospital Council

From Queensland, Australia, to Dallas, Texas

Darren Nolan, from Queensland, Australia, was diagnosed with stage 4 kidney cancer at the beginning of 2018. After seeing his own father succumb to kidney cancer several years prior, Nolan embarked on a global search in pursuit of the most effective treatment.

"I needed to deal with it the best way that I possibly could," Nolan says. "For me, education is paramount. If you're not educated about the options and available treatments, you're not doing yourself the greatest favor."

After learning of UT Southwestern from a patient care blog, Nolan reached out from the Southern Hemisphere and contacted the Kidney Cancer Program.

Nolan traveled nearly 9,000 miles to Dallas for a consultation – a decision he doesn't regret.

During his three days in Dallas, Nolan met with kidney cancer experts in medical oncology, urology, and radiation oncology.

"I feel very fortunate to be able to get a second opinion," he says. "UT Southwestern has an awesome reputation – that's the reason I came here."

Getting a Second Opinion

Dallas: 214-645-8300

Fort Worth: 817-882-2700

Email: KCP@utsw.edu

Referrals can be made by phone or at utswmed.org/physician-resources/refer-or-transfer-a-patient

Building Community

Educational and social events hosted throughout the year bring patients, caregivers, advocates, and supporters together to build a sense of community.

"My mother was a kidney cancer patient of Dr. Brugarolas, one that did not make it past five years. During her treatment, I realized two things: 1) the lack of knowledge about the disease, and 2) the exceptional patient-centric approach of UT Southwestern. Because of that, I am a tremendous supporter of the Kidney Cancer Program."

Mike Rawlings, Mayor of Dallas (2011-2019)

Connect with Us

facebook.com/kidneycancerprogram

twitter.com/KCPUTSW

UTSWMed.org/kcpyoutube

Outreach & Advocacy

The Kidney Cancer Program at UT Southwestern is a world-class destination for cancer treatment. But that's only part of the story. Along with advancing discoveries and health for patients, we want to be known as a resource for information, advocacy, and support services for patients and their families.

Community Outreach

Education and awareness are integral parts of our mission. We routinely host tailored programs and special events that bring together patients, physicians, and community thought leaders to discuss the most prevalent issues related to medical innovation, treatment, and patient access to quality care.

Patient Advocacy

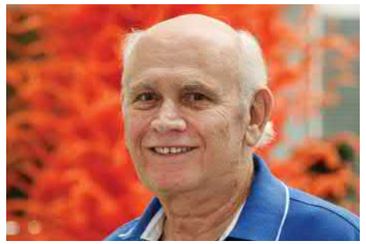
Our team of Patient Advocates serves a vital role as a liaison between the Kidney Cancer Program and the community, raising awareness about the disease, helping fellow patients navigate the kidney cancer landscape, and assisting program leadership in its mission to provide outstanding and holistic patient care.

Support Services

UT Southwestern offers numerous support services for kidney cancer patients and families, from rehabilitation specialists and registered dietitians to clinical psychologists, patient care coordinators, and financial counselors.

Patient Advocates

Carole Baas, Ph.D., was educated as a biomedical engineer and is passionate about connecting patients and members of the scientific community. A breast cancer survivor herself, she is active in cancer-related patient advocacy groups affiliated with the National Cancer Institute.



Larry Carlson was a stage 4 kidney cancer patient when he came to UT Southwestern. He was enrolled in the RADVAX trial and had a tremendous response. He now volunteers in the clinic, helping to support other patients by offering a hopeful outlook.

Jürgen von Hövell, B.B.A., has supported his wife through her battles with kidney cancer. He knows that strengthening the fighting spirit can be a factor. Thankful to UT Southwestern for the ongoing care and treatment of her disease, he volunteers his time giving hope to other patients and caregivers.

Brenda Stinson, B.S.Ed., was diagnosed in 2016 with stage 1 kidney cancer and had surgery after a period of surveillance. She embraces the opportunity to lend an ear and a hand to others grappling with their own cancer diagnoses.

Sophia Moschos, M.Ed., lost her husband, Tom, to renal cancer in 2012. With firsthand knowledge of the challenges that both patients and their caregivers face, she is deeply committed, in her husband's memory, to helping others navigate their cancer journeys.

Anthony L. Towler, B.Sc., learned in 2011 that he had large tumors, later identified as clear cell RCC, in both kidneys. Opting against surgery and a lifetime of dialysis, he receives ongoing care for stage 4 disease and is unwavering in aiding other patients in the clinic.

To find out more, please visit
www.utsouthwestern.edu/departments/kidney-cancer/patient-council

COPING WITH A CANCER DIAGNOSIS

BY ANTHONY TOWLER

"The diagnosis of any cancer can be a traumatic event that can challenge a patient's most fundamental beliefs about life, themselves, and their future. It may even leave them feeling overwhelmed and powerless. Cancer treatment itself is an unfamiliar and sometimes frightening experience with many uncomfortable side effects.

These challenges do not always present themselves to the same extent and complexity in all patients and their families. However, for a majority of patients, in order to cope with these experiences in living with cancer, the body, mind, and soul have to be nurtured. This 'holistic' approach within the clinical setting may require the advice and direction by the doctor to heal the body, as well as psychological counseling and social assistance from a social worker to ease the mind, and spiritual advice from a chaplain to soothe the soul. These facets are held together with input from the volunteers and Patient Advocates who are patients and caregivers themselves and who help close the circle for total care."

Partnerships That Fuel the Fight

The Kidney Cancer Program's unique approach to multidisciplinary treatment is made possible not only by our commitment, but by the compassion of all those who join the fight.

Partnerships across Texas and beyond have propelled significant fundraising initiatives. The contributions born out of these partnerships give us the ability to improve the way we confront kidney cancer at every level.

With the collective support of an engaged community, we're able to focus on providing the best possible experience for those we serve – today and in the future.

Merlinda Chelette of Arlington, Texas
A stage 4 renal cancer patient and advocate, Merlinda was a cornerstone of the program. Diagnosed with metastatic kidney cancer in 2012, she was an ardent proponent of funding for kidney cancer research and a driving force behind the Kidney Cancer Program's inaugural fundraising event in 2017, the first Dallas Rock the Cure fundraiser, which she co-chaired with Anita Bird, whose husband, Joe, was a kidney cancer patient. The event raised more than $100,000. Merlinda succumbed to kidney cancer in 2019, but lives on in the memory of the many patients whose lives she touched as well as the members of the Kidney Cancer Program who were her second family.

Kathy Liu of San Diego
Kathy started Joey's Wings Foundation in 2014 in memory of her son, a funny and sweet 5th grader who loved science, music, art, and origami. Joey's life was taken by a rare and aggressive form of kidney cancer – translocation renal cell carcinoma (tRCC). Through a variety of events, including an annual 5K run in Plano, the foundation has raised more than $150,000 to advance research in tRCC at UT Southwestern. The seed funding provided by Joey's Wings was instrumental in securing $1.1 million from CPRIT (Cancer Prevention and Research Institute of Texas) to advance tRCC research.

Judy Green of Kemp, Texas
Judy lost her husband, Tom, to renal cell carcinoma in 2012. Each spring, she and her family (daughter, Cris, and son-in-law, David Cary, and son, Mike, and daughter-in-law, Denise Green) have honored his memory by organizing and running the Tom Green Memorial Benefit Golf Tournament. The event, which draws 70 to 80 golfers each year, has raised over $100,000 for kidney cancer research.

Frank & Brenda Stinson of Dallas
Frank and Brenda have been avid supporters of the UT Southwestern Kidney Cancer Program since Brenda was diagnosed with kidney cancer in 2016. The Stinsons have been a major sponsor at every Kidney Cancer Program event and received the 2018 Rock Star Award.

Ralph & Brenda Knapp of Virginia Beach
Ralph and Brenda founded the Kidney Cancer Coalition to raise funds for a novel kidney cancer clinical trial. That trial (NCT03065179), headed by Dr. Hans Hammers, Co-Leader of the Kidney Cancer Program, is testing stereotactic ablative radiotherapy combined with two immunotherapies, nivolumab and ipilimumab. Ralph Knapp, diagnosed with metastatic kidney cancer in 2014, was one of the first patients to receive this therapy, which was shown to be successful. Seeking ways to make the treatment available to others, he and his wife organized the first Rock the Cure fundraising event in Virginia Beach, raising more than $300,000 to support the study. A second $100,000 gift went to support immunotherapy research being conducted by Dr. Hammers.

IN THIS TOGETHER

The Kidney Cancer Program is supported by community members, businesses, and grantors that make our work possible. These vital connections are what set our program apart, bolstering our mission and enabling us to maintain our personalized approach to each patient's experience.

VOLUNTEER
Join us in providing compassionate support to patients and caregivers.

PARTNER
Host events in your community to raise awareness and funds in the fight against kidney cancer.

DONATE
Every donation impacts the lives of patients by supporting research, treatments, and programs that make the entire continuum of care possible. Through the collective impact of donations, tributes, and endowed gifts, your support makes a difference!

Give or Get Involved

To support the Kidney Cancer Program, please visit
www.utsouthwestern.edu/departments/kidney-cancer/support

Internationally Recognized Clinical Leaders

James Amatruda, M.D., Ph.D.
Chair, Germ Cell Tumor and Rare Tumor Committees of the National Children's Oncology Group

James Brugarolas, M.D., Ph.D.
Inaugural Chair, Programmatic Panel of the Congressionally directed Kidney Cancer Research Program. Member, Renal Task Force of the Genitourinary Steering Committee for the National Cancer Institute's Clinical Trials Enterprise

Jeffrey Cadeddu, M.D.
Member of the American Association of Genitourinary Surgeons, American Urological Association, and author of guidelines for the management of renal masses

Kevin Courtney, M.D., Ph.D.
Member, Genitourinary Committee of the National ECOG-ACRIN cancer research group

Hans Hammers, M.D., Ph.D.
Member, Renal Task Force of the Genitourinary Steering Committee for the National Cancer Institute's Clinical Trials Enterprise

Raquibul Hannan, M.D., Ph.D.
Member, Renal Task Force of the Genitourinary Steering Committee for the National Cancer Institute's Clinical Trials Enterprise

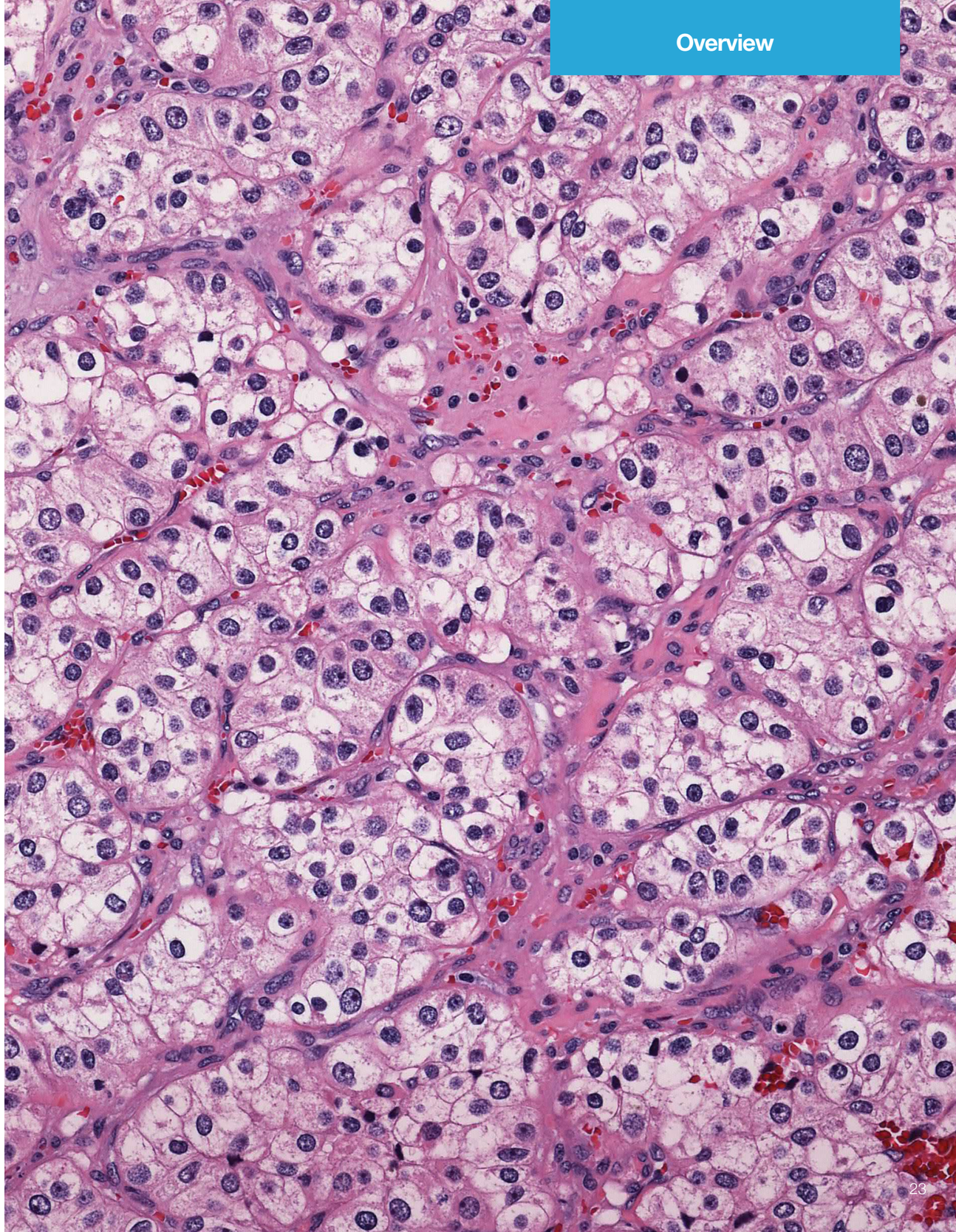
Payal Kapur, M.D.
Member, Renal Task Force of the Genitourinary Steering Committee for the National Cancer Institute's Clinical Trials Enterprise

Vitaly Margulis, M.D.
Member, European panel setting forth guidelines on management of tumors of the upper urinary tract

Ivan Pedrosa, M.D., Ph.D.
Member, Renal Task Force of the Genitourinary Steering Committee for the National Cancer Institute's Clinical Trials Enterprise, the Genitourinary Committee of the National ECOG-ACRIN cancer research group, and the Renal Cell Carcinoma Disease Focused Panel of the Society of Abdominal Radiology

Arthur Sagalowsky, M.D.
Member, American Association of Genitourinary Surgeons

Robert Timmerman, M.D.
Member, American Society for Therapeutic Radiology and Oncology, National Principal Investigator for the Radiation Therapy Oncology Group, Society for Neuro-Oncology



Kidney Cancer at a Glance

In most patients, kidney cancer is diagnosed incidentally, often during an imaging test for another illness.

Types of Kidney Cancer

Renal Cell Carcinoma (RCC)
- 90% of adult kidney cancer

Urothelial Carcinoma
- 5-10% of adult kidney cancer

Most common RCC subtypes
- Clear Cell (ccRCC) – 70%
- Papillary (pRCC) – 15%
- Chromophobe (chRCC) – 5%

Most common pediatric kidney cancer
- Wilms Tumors – 90%

Symptoms

Blood in urine

Low back pain or pressure on one side

Lump on the lower back

Swelling around a testicle or in legs that develops quickly

Loss of appetite or weight

Unexplained low-grade fevers or night sweats

Tiredness

Anemia

Stages

Kidney cancers are categorized by stages:

1. Tumor less than 7 cm (2.7 in) and confined to the kidney
2. Tumor greater than 7 cm (2.7 in) and still confined to the kidney
3. Tumor growing into surrounding tissue or spread to nearby lymph nodes
4. Tumor growing beyond the kidney or spread to distant lymph nodes or other sites

Approximate new cases of kidney/renal pelvis cancer per year*

73,820 U.S. | **6,280** TEXAS

Annual deaths due to kidney/renal pelvis cancer*

14,770 U.S. | **1,220** TEXAS

People living with renal cancers in the United States‡‡

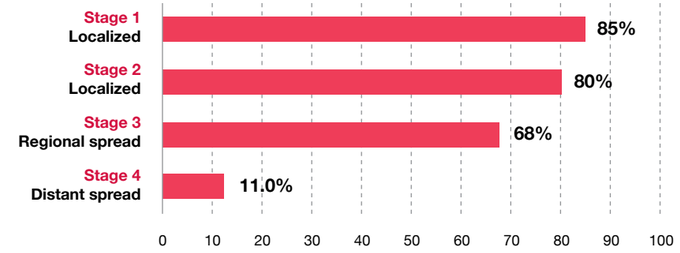
533,204

Average years of life lost when kidney cancer is the cause of death**

15.5

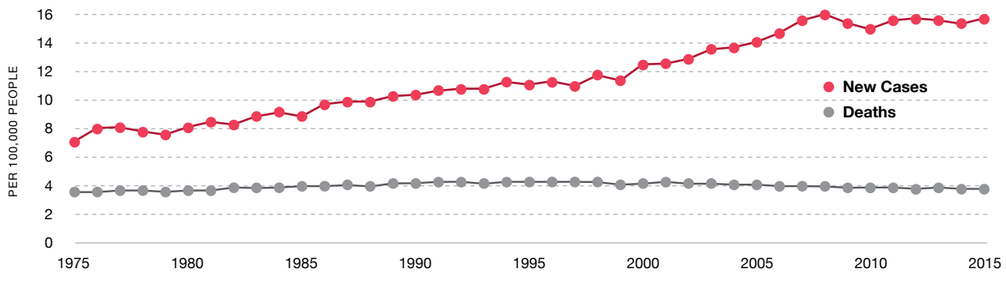
5-Year Survival Rate§

Early detection is key to improved survival rates



U.S. Kidney Cancer Trends | 1975-2015

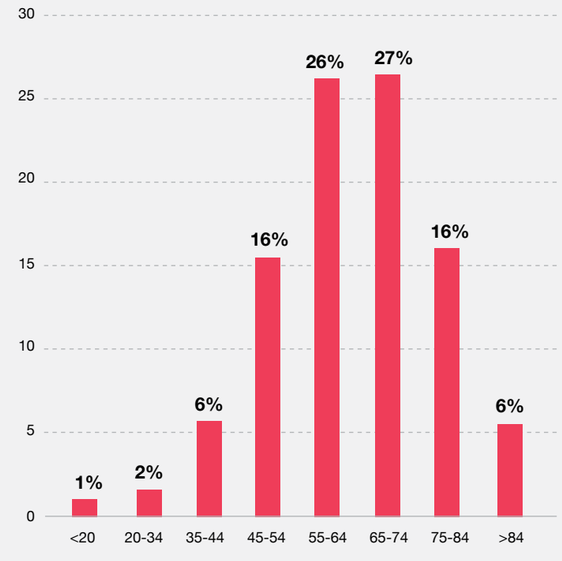
Per 100,000 people, age-adjusted



Source: National Institute of Cancer Surveillance, Epidemiology, and End Results (SEER) Program – SEER 9

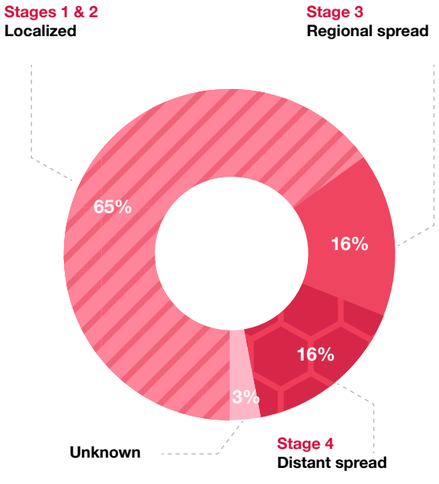
Age at Diagnosis§

More than 80% of renal cancer diagnoses occur after age 50



Extent of Disease§

At diagnosis, a majority of renal cancers have not yet spread beyond the kidney



Sources: American Cancer Society; National Cancer Institute; Texas Department of State Health Services/Texas Cancer Registry; National Institute of Cancer Surveillance, Epidemiology, and End Results (SEER). *Estimates for 2019; **Figure for 2016; ‡‡Estimate for 2016; §SEER 18.

Bold Innovation

From the genetics to the clinic, from small tumors to tumors that invade and metastasize, the award-winning UT Southwestern Kidney Cancer Program is redefining patient care by developing innovative surgical techniques, radiation approaches, and new medications.

Redefining Research & Care

At Simmons Cancer Center, kidney cancer leaders harness the latest discoveries and innovation, translating breakthroughs into new approaches that benefit patients.

Innovations for Small Kidney Tumors

Some kidney tumors grow slowly and won't cause problems. The question is, which ones?

Among newly found kidney tumors, nearly half are small renal masses – measuring less than 1.5 inches (or 4 cm). These cancers are often detected by happenstance on scans to evaluate other conditions.

In many cases, this presents a dilemma: Is the mass a benign tumor, a cancer that urgently requires surgery, or a cancer that can simply be watched?

To determine how dangerous a cancer may be, a sample of the tumor can be obtained through a biopsy. However, sometimes biopsies are not informative or simply cannot be performed because the location of the tumor makes them unsafe.

Dr. Ivan Pedrosa, Chief of MRI, reviewing a case.

Physician-scientists at UT Southwestern have developed a new approach that can evaluate kidney tumors and spare patients the biopsy.

Breakthrough: New MRI technology bypasses need for biopsies

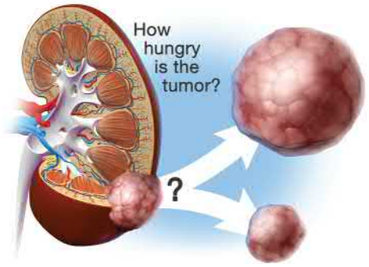
Using a state-of-the-art technique, mpMRI (multiparametric magnetic resonance imaging), Drs. Ivan Pedrosa and Jeffrey Cadeddu have developed a protocol to predict whether a small tumor is a clear cell renal cell carcinoma (ccRCC), an aggressive type.

The study involved more than 100 patients with small kidney tumors who underwent a mpMRI before they had surgery. Seven expert radiologists reviewed the images. By comparison to microscopic analyses after tumors had been removed, the radiologists correctly predicted whether a tumor was RCC (renal cell cancer) 80 percent of the time. An MRI-based formula has now been incorporated into clinical practice at the Kidney Cancer Program to help doctors determine whether a tumor is clear cell RCC. (Canvasser et al., *J Urol,* 2017; Kay et al., *Radiology,* 2018)

Challenge: Which Small Tumors Require Intervention?

Of course, those that grow. But to know whether a tumor is growing, its behavior needs to be observed over time, which means patients have to wait until time goes by and additional scans are obtained. Research at the Kidney Cancer Program is changing the playing field. Investigators have developed tools to determine today how tumors will behave.

With SPORE funding, urological surgeons Drs. Cadeddu and Margulis have teamed up with biochemist Dr. Ralph DeBerardinis and medical oncologist Dr. Kevin Courtney to find the answer. Their approach: to determine which tumors are "hungry." Rapidly growing tumors need to "beef up" with extra nutrients to fuel their growth. By measuring the tumor's nutrient intake, doctors believe they will be able to predict which tumors are aggressive and should be removed. Using avant-garde techniques such as stable isotope infusions and NMR spectroscopy, available at just a few centers around the world, the team studies tumor metabolism – how the tumor processes nutrients to fuel its growth. (Zhang et al., *JCI Insight,* 2017; Courtney et al., *Cell Metab,* 2018)



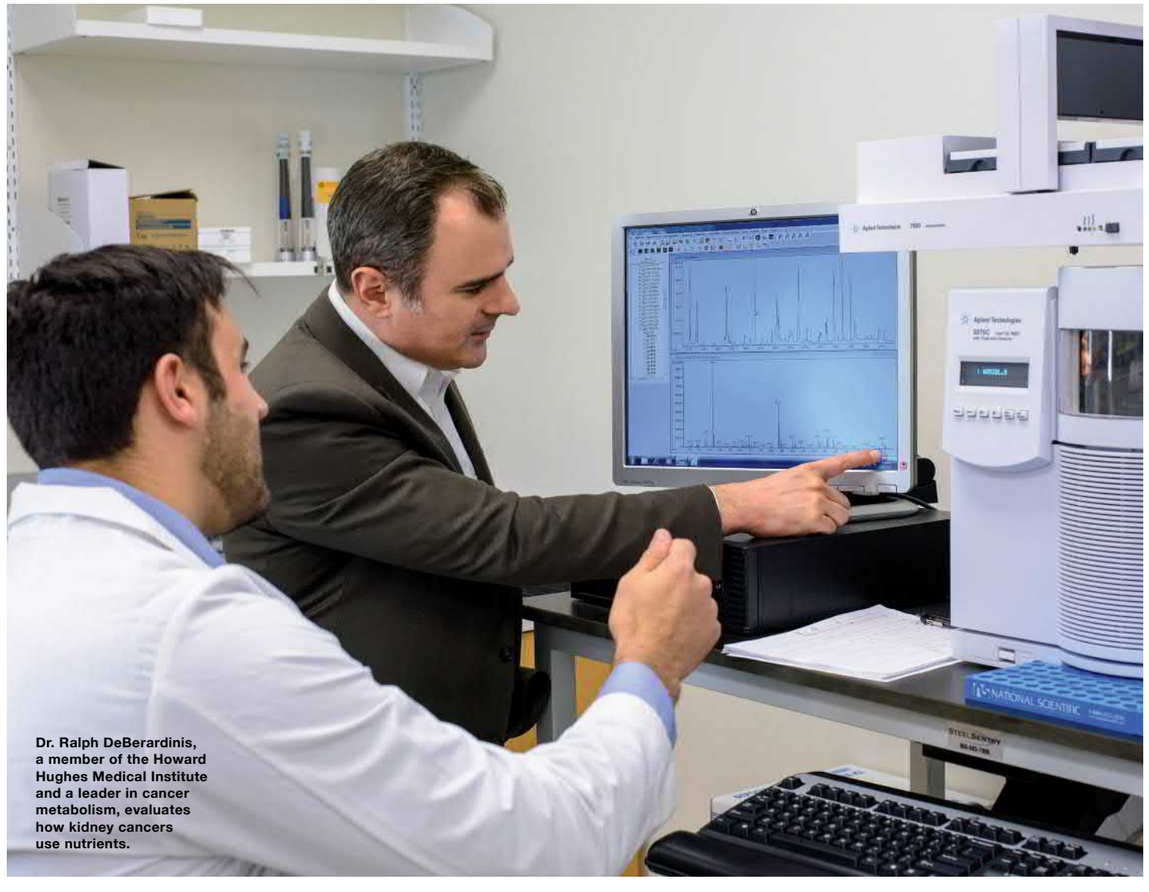
To assess tumor aggressiveness and predict future behavior, a team of investigators with support from the SPORE is measuring nutrient intake by tumors.

First Ablation Program in Texas

When tumors require intervention, radiofrequency ablation is one option.

In 2000, UT Southwestern urologist Dr. Cadeddu was the first in Texas (and one of the first in the U.S.) to perform an ablation for kidney cancer. Today, after having treated more than 400 patients, the kidney tumor ablation program has become the most experienced in the region.

At UT Southwestern, some 30 to 40 kidney cancer patients are treated with RFA (radiofrequency ablation) per year. Guided by ultrasound or CT scans, surgeons insert a long, thin probe through the skin. The probe applies high-energy radio waves to



Dr. Ralph DeBerardinis, a member of the Howard Hughes Medical Institute and a leader in cancer metabolism, evaluates how kidney cancers use nutrients.

Dr. Jeffrey Cadeddu leading a robotic surgery, one of the areas in which UT Southwestern is blazing a trail.

the cancer, heating and destroying tumor cells. It is an outpatient procedure and patients recover quickly. (Olweny et al., *Eur Urol,* 2012; Ma et al., *BJU Int,* 2014)

Leaders in Robotic Surgery

Surgical volume improves patient outcomes. At UT Southwestern, kidney cancer patients benefit from a large, experienced, pacesetting program.

With the largest, most experienced kidney surgery program in North Texas, and one of the top robotic kidney surgery programs in the nation, UT Southwestern has a versatile team of fellowship-trained urologists proficient in the latest surgical approaches. Robot-assisted surgeries and traditional "open" procedures are both performed in state-of-the-art operating rooms at William P. Clements Jr. University Hospital. Operational since 2014, the hospital offers the benefits of the latest technologies.

More than 300 patients undergo nephrectomy (removal of a kidney) or partial nephrectomy each year. Most surgeries are performed laparoscopically, meaning through small incisions about a half-inch long. Miniature video cameras aid these procedures by letting surgeons peer inside the body. Laparoscopic techniques generally result in reduced pain and scarring, and faster recovery times.

Some two-thirds of kidney cancer surgeries are aided by robots. These robots enable more agile and precise maneuverings. For example, robotic surgery facilitates partial nephrectomies, highly intricate procedures that remove only the tumor rather than the whole kidney.

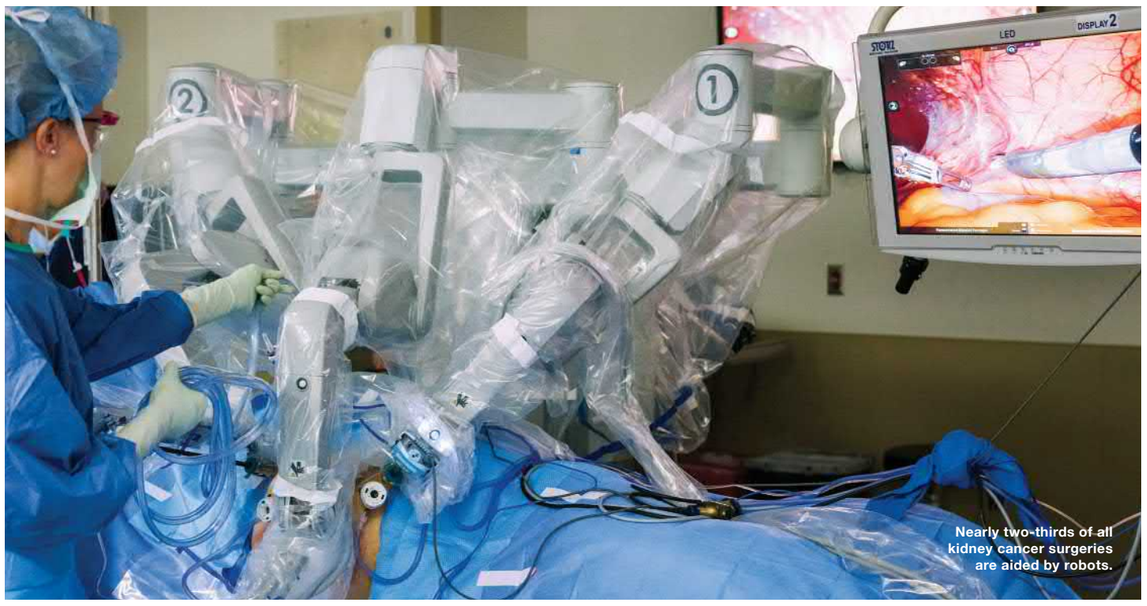
In 2007, Dr. Cadeddu became the first U.S. surgeon to remove a kidney using LESS (laparoendoscopic single-site surgery), which uses a single incision at the navel. This procedure leaves virtually no scar. (Krabbe et al., *Semin Intervent Radiol,* 2014; Raman et al., *Eur Urol,* 2009)

Shining a Light So No Tumor Cells Are Left Behind

With support from the SPORE, Jeffrey Cadeddu, M.D., Jinming Gao, Ph.D., and Gang Huang, Ph.D., have partnered to generate dyes that distinguish tumor cells from normal cells. The team has developed nanoparticles that change depending on the environment, based on changes in the acidity (pH) of tumors. When these nanoparticles encounter tumors, they emit fluorescent light that the surgeon can see with a special detector. This ensures that surgeons have the opportunity to remove all the tumor cells.

Controlling Small Tumors without Surgery

A clinical trial (NCT02141919) led by radiation oncologist Dr. Raquibul Hannan is evaluating the treatment of small renal masses with radiation, as an alternative to RFA or surgery. While conventional radiation does not work well for kidney cancer, improved outcomes are observed with modern forms of radiation, such as SBRT (stereotactic body radiation therapy). By projecting highly focused beams of radiation shot from many angles onto a tumor, lethal doses can be administered. The procedure is noninvasive and can treat tumors otherwise difficult to access.



Nearly two-thirds of all kidney cancer surgeries are aided by robots.

Dr. Vitaly Margulis, an expert surgeon, in the operating room.

Kidney Cancer Program surgeons perform more than three times as many surgeries as any other hospital in the region.

Tackling Large Tumors

Masters of Complex Surgeries

Intricate kidney cancer operations are commonly performed at Simmons Comprehensive Cancer Center. Kidney Cancer Program surgeons perform more than three times as many surgeries as any other hospital in the area. Experience gained from the volume and complexity of procedures makes a difference in the operating room. These complex surgeries are done at William P. Clements Jr. University Hospital, recognized as the best hospital in Dallas by *U.S. News & World Report* and recipient of the national Rising Star Award from Vizient for improved quality and safety.

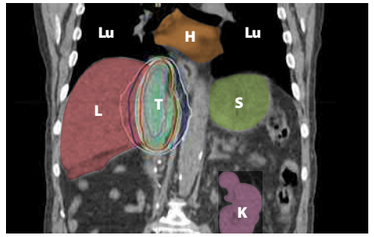
Among the most complex procedures is the removal of kidney tumors invading through the renal vein into the IVC (inferior vena cava), the main conduit of blood from the body back into the heart. Traveling within the vena cava, a tumor can extend into the heart. Along the way, it can block liver blood drainage, a life-threatening complication. Further, pieces of the tumor may break off, travel through the heart, lodging themselves in small lung arteries, causing deadly pulmonary embolisms and lung infarcts.

Complex procedures to treat kidney tumors invading major veins involve expert urologists such as Drs. Margulis and Sagalowsky, who team up for this surgery with cardiothoracic surgeons, such as Dr. Wait. When necessary, patients are temporarily placed on a heart-lung machine, which takes over the functions of the heart and lungs during the surgery.

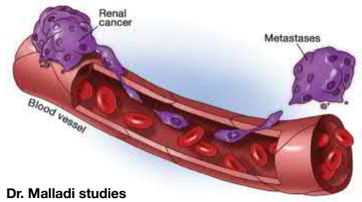
These challenging operations are routine for Kidney Cancer Program specialists, who have found a 30 percent reduction in complications between 2006 and 2012 with expert teams and advanced surgical techniques.

Efforts are also directed to identify factors that can predict for complications. Leading a national team including MD Anderson Cancer Center and Mayo Clinic, UT Southwestern urologists recently determined that tumors that develop blood clots were associated with worse outcomes. (Haddad et al., *Urol Oncol,* 2015; Gayed et al., *BMC Urol,* 2016; Hutchinson et al., *Urology,* 2018)

UT Southwestern Urology ranks No. 3 in the U.S., based on academic contributions. (Kutikov et al., *Eur Urol*, 2012)



Radiation plan to treat a kidney tumor inside the vena cava (T). The upper edge of the tumor is within an inch of the heart (H). (K), left kidney; (L), liver; (Lu), Lung; (S), stomach.



Dr. Malladi studies how kidney cancer causes metastases.

First in the World: Deploying Stereotactic Radiotherapy to Target Tumor Invasion

UT Southwestern urologists are teaming up with radiation oncologists to break new ground in the treatment of tumor extensions into the IVC. A multidisciplinary team, featuring radiation oncologists Drs. Hannan and Timmerman, urologists Drs. Margulis and Sagalowsky, and medical oncologist Dr. Brugarolas, reported for the first time the deployment of SBRT (Stereotactic Body Radiation Therapy) for treating tumors invading the vena cava.

The team is now conducting a phase 2 clinical trial (NCT02473536) using SBRT before surgery to treat IVC tumors, which they hope will reduce the chances of cancer spreading. Because the cancer is already inside a blood vessel, live cells may be shed during surgery that could create new tumors elsewhere. Many patients undergoing this treatment eventually develop metastatic disease, notes Dr. Hannan, who leads the trial along with Dr. Margulis.

Researchers hope that treating the tumor inside the vein with SBRT just before surgery will kill the tumor cells and reduce the risk of cancer spreading. Their trial was selected for oral presentation at the Late Breaking Abstract session of the American Urological Association Annual Meeting in San Francisco in 2018. It is "an example of the innovation and team approach that characterizes the Kidney Cancer Program," says Dr. Brugarolas. (Hannan et al., *Cancer Biol Ther*, 2015; Freifeld et al., *Kidney Cancer*, 2019)

How Do Cancer Cells Invade, Travel, and Spread?

With funding from the SPORE, Srinivas Malladi, Ph.D., who trained with Joan Massagué, Ph.D., biologist and current Director of the Sloan Kettering Institute at Memorial Sloan Kettering Cancer Center, joined UT Southwestern in 2017 and is applying his expertise in tumor invasion to kidney cancer. Dr. Malladi is using samples from patients with IVC tumor extensions to understand how tumors get inside blood vessels and travel to other organs. He is evaluating how cells once part of the original tumor stealthily survive in the blood, later giving rise to metastases. One approach he has taken, in partnership with Dr. Brugarolas and Somasekar Seshagiri, Ph.D., longtime molecular biologist with Genentech®, involves using next-generation sequencing technologies.

Dr. Raquibul Hannan, Co-Leader of radiation oncology, discussing a case with medical oncologist Dr. Kevin Courtney and urological surgeon Dr. Yair Lotan.

A Radiotherapy 'Boost'

Radiation is also being used in another context. Radiation oncologist Dr. Michael Folkert has established a program to assist surgeons with complex cases in which the tumor infiltrates nearby structures, from where they may be difficult to remove. The approach uses IORT (intraoperative radiation therapy). IORT delivers high doses of radiation to these areas during surgery. Surgeons directly expose the area of concern, which is then treated with radiation. Radiation can treat areas up to 5 millimeters deep. Adjacent normal tissues, such as bowel or stomach, are moved out of the way, or even shielded with lead. The procedure typically takes 30 minutes. It requires, however, a shielded operating room, where radiotherapy can be safely delivered. UT Southwestern is the only center in North Texas to offer IORT.

UT Southwestern is the only center in North Texas to offer IORT.

Borrowing from Immunotherapy to Lower Recurrence

Stage 3 tumors (T3), such as those invading the IVC, or stage 4 tumors (T4) invading beyond the kidney have recurrence rates as high as 80 percent. To reduce recurrence, investigators in the Kidney Cancer Program have opened three major phase 3 trials (each involving more than 200 centers) testing the following immune-checkpoint inhibitors.

- Atezolizumab. Sponsor: Genentech®/Roche. UT Southwestern principal investigator: Dr. Brugarolas (NCT03024996).
- Nivolumab. Sponsor: National Cancer Institute. UT Southwestern principal investigator: Dr. Margulis (NCT03055013).
- Pembrolizumab. Sponsor: Merck. UT Southwestern principal investigator: Dr. Hammers (NCT03142334).

TEAMING UP FOR SUCCESS

The Kidney Cancer Program gathers experts from various disciplines to collaborate on challenging cases, developing tailored strategies for treatment. These teams include urologic surgeons, medical and radiation oncologists, pathologists, radiologists, and, depending on the circumstances of each patient's cancer, cardiothoracic surgeons, neurosurgeons, orthopedic surgeons, liver surgeons, and other physicians.

Challenging cases that most benefit from this approach are:

- Kidney cancer invading adjacent organs (such as the liver or pancreas), or into the vena cava
- Multiple tumors, tumors in both kidneys, or a tumor in a patient with just one kidney
- Tumors already metastatic

The program's interdisciplinary teamwork – along with its comprehensive infrastructure, vast experience, and cutting-edge approaches – gives hope to patients who may have few options elsewhere.

One goal is to make these forums available to physicians in the community, who are then able to obtain expert input about their patients via teleconference.

Case review at a multidisciplinary conference.

The latest CyberKnife® technology to deliver focused and ablative radiation for kidney cancer metastasis.

When Kidney Cancer Spreads

Surveillance for Slow-growing Kidney Cancers

Some kidney cancers grow slowly even after they have spread. Physicians familiar with the disease learn to recognize them and may recommend active surveillance – a careful monitoring program. In appropriate instances, delaying treatment can spare patients debilitating side effects and the expense of cancer drugs.

Challenge: Pinpointing Indolent Tumors

Researchers are investigating why some kidney cancers grow slowly after spreading. In a partnership with Dr. Brian Rini, former Director of the Genitourinary Program at Cleveland Clinic Cancer Center and now Clinical Trials Chief at Vanderbilt-Ingram Cancer Center, Dr. Brugarolas and colleagues are performing genomic analyses on tumors from patients with slowly growing tumors. These patients participated in a prospective clinical trial of active surveillance led by Dr. Rini and analyses of their tumors may help identify similar patients who may be good candidates for active surveillance. (Rini et al., *Lancet Oncol*, 2016)

AIMING STEREOTACTIC RADIATION TO TARGET LIMITED SPREAD

UT Southwestern investigators have developed a program to treat kidney cancer with limited spread using SBRT. This approach lets physicians target individual metastases with highly focused radiation, sparing patients drug therapy and its side effects. These tumors are known as oligometastatic, which comes from the Greek “oligos,” meaning “few.”

A clinical trial ongoing at UTSW seeks to better understand how patients benefit from this approach. (Wang et al., *Int J Radiat Oncol Biol Phys*, 2017; Zhang et al., *Int J Radiat Oncol Biol Phys*, 2019)

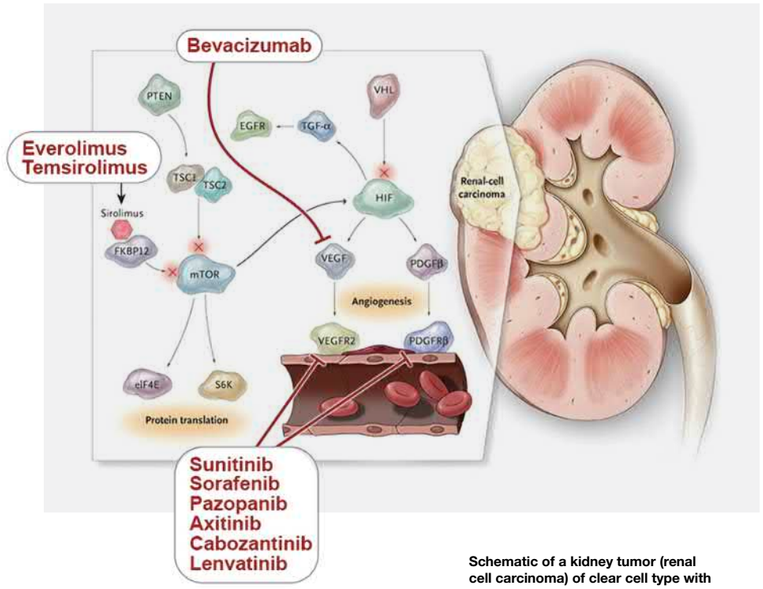
Molecularly Targeted Drugs

Probing kidney cancer’s biological underpinnings has driven a revolution in treatment.

Program Director Dr. Brugarolas was initially drawn to kidney cancer research because of the dearth of treatment options. In 2003, when he finished his oncology training at the Dana-Farber Cancer Institute/Harvard Cancer Center, there was just one treatment for kidney cancer patients: IL-2 (interleukin-2). However, IL-2 is quite toxic and typically administered in an intensive care unit. Few patients could tolerate it. Equipped with a Ph.D. in cancer biology from MIT, he set out to study the biology of the disease, convinced it was the key to new therapies.

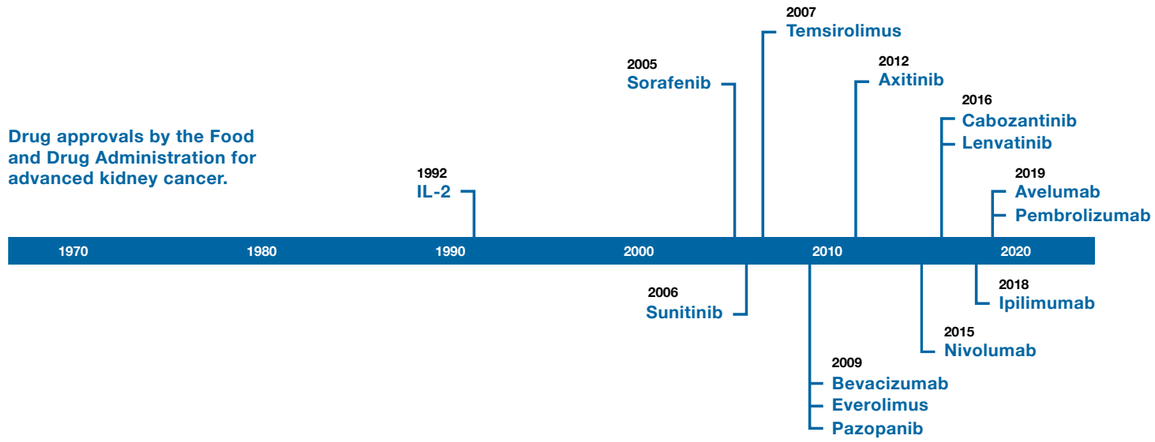
While at Dana-Farber, he joined the laboratory of Dr. William Kaelin, a pioneer in kidney cancer research and recipient of the 2019 Nobel Prize in Physiology or Medicine. Dr. Kaelin had discovered that the gene VHL (von Hippel-Lindau), inactivated in most adult kidney cancers, regulates HIF (hypoxia-inducible factor) (see page 36). HIF activation in cancer cells promotes the development of blood vessels, which carry oxygen and nutrients to the cancer and support its expansion. In response to HIF, cancer cells make VEGF (vascular endothelial growth factor). VEGF is released from the cancer cells and binds to a protein on the surface of blood vessel cells, sending a signal for them to grow.

These discoveries enabled the development and eventual FDA approval of drugs that neutralize VEGF (bevacizumab [Avastin]), or block its effects on the blood vessel cells by inactivating its receptor (sorafenib [Nexavar], sunitinib [Sutent], pazopanib [Votrient], axitinib [Inlyta], cabozantinib [Cabometyx], and lenvatinib [Lenvima]). These drugs interfere with the formation of new blood vessels. They are broadly referred to as blockers of angiogenesis, coming from



Schematic of a kidney tumor (renal cell carcinoma) of clear cell type with deregulated pathways and targeting drugs. Inactivation of VHL leads to activation of HIF. This drives the production of VEGF, which activates the VEGF receptor (VEGFR2) on the surface of blood vessel cells, instructing them to proliferate and make more blood vessels. Drugs that interfere with these processes appear here in red, with blunted ends showing where they block. (Adapted from Brugarolas, J. “Renal Cell Carcinoma – Molecular Pathways and Therapies,” *The New England Journal of Medicine*, 2007)

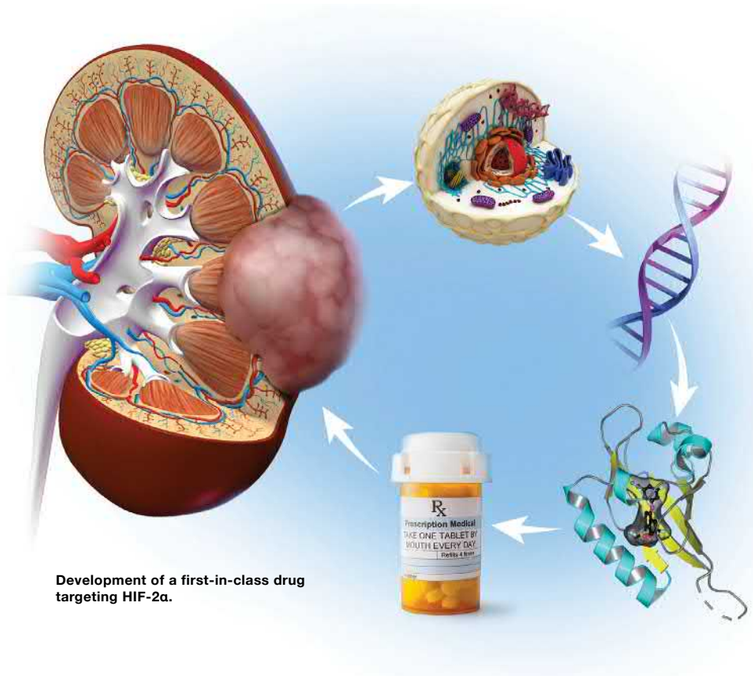
Drug approvals by the Food and Drug Administration for advanced kidney cancer.



the Greek words “angêion,” meaning “vessel,” and from “génesis,” meaning “creation.”

While these drugs are quite effective against kidney cancers, blood vessels are important for cardiovascular health. As such, these drugs cause cardiovascular problems, including hypertension and sometimes weakening of the heart (heart failure).

Research that Dr. Brugarolas conducted in Dr. Kaelin’s laboratory led to the finding that HIF was not only regulated by VHL, but also by mTOR (mechanistic target of rapamycin). This finding provided a rationale for targeting mTOR in renal cancer. Today, there are two mTOR-blocking drugs that have been FDA approved (temsirolimus [Torisel] and everolimus [Afinitor]). (Brugarolas et al., *Cancer Cell*, 2003)



Development of a first-in-class drug targeting HIF-2α.

Discoveries Lead to a First-in-Class Drug

The cellular protein called HIF-2α (or hypoxia-inducible factor-2α) is regarded as the most important driver of kidney cancer. HIF-2α is the key member of a family of HIF proteins activated in kidney cancer.

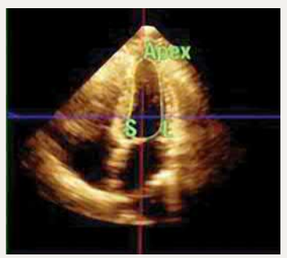
For years, scientists have been interested in blocking HIF-2α to treat kidney cancer and possibly other conditions. However, HIF-2α belongs to a class of proteins, transcription factors, that have a globular, smooth surface – a target too slippery for drugs to bind to. As such, the protein class has been regarded as “undruggable.”

This may be changing. A program of discovery launched at UT Southwestern more than 20 years ago, which is now supported by CPRIT and the SPORE, has challenged these notions.

MINIMIZING KIDNEY CANCER DRUGS’ TOLL ON THE HEART

High blood pressure commonly accompanies renal cancer when the disease is treated with blood vessel (or angiogenesis) blocking drugs.

At UT Southwestern, patients who develop uncontrolled hypertension can see hypertension specialists certified by the American Society of Hypertension, such as Dr. Vongpatanasin, Director of the program. Further support is available from doctors such as Dr. Zaha, one of the few onco-cardiologists in North Texas. Onco-cardiologists are specialized cardiologists focusing on cardiovascular health in cancer patients.



Ultrasound-based imaging of the heart with the four chambers.

Drs. Steven McKnight and David Russell, discoverers of HIF-2α.

The Path to Developing a HIF-2α Inhibitor

1997

UT Southwestern biochemist Steven McKnight, Ph.D., and molecular geneticist David Russell, Ph.D., report the discovery of the EPAS1 gene. This gene contains instructions for the HIF-2α protein. The team shows that HIF-2α binds to another protein, HIF-1β. The HIF-2 partners function like a pair of tweezers to grab DNA. HIF-2 binds DNA at specific places to initiate the production of proteins such as VEGF. (Tian et al., *Genes Dev*, 1997)

2003

The laboratories of Richard Bruick, Ph.D., and Kevin Gardner, Ph.D., uncover aspects of the atomic blueprint of HIF-2α. They show how HIF-2α docks with HIF-1β to assemble into a functional HIF-2 complex. They identify a cavity within the HIF-2α protein, hypothesizing that it may offer a foothold for a drug. (Erbel et al., *Proc Natl Acad Sci USA,* 2003; Yang et al., *J Biol Chem*, 2005; Scheuermann et al., *Proc Natl Acad Sci USA,* 2009)

2007

Working with the Simmons Cancer Center’s High-Throughput Screening laboratory, Drs. Bruick and Gardner develop a test to read out and identify chemicals, among 200,000 drug-like molecules, that bind to the HIF-2α cavity, preventing HIF-2α binding to HIF-1β. By interfering with HIF-2α binding to HIF-1β, these compounds block HIF-2 action. The most promising chemicals undergo a refinement process by medicinal chemists at UT Southwestern. (Scheuermann et al., *Nat Chem Biol*, 2013; Rogers et al., *J Med Chem,* 2013)

2010

Peloton Therapeutics is co-founded by Dr. McKnight to develop the HIF-2α-blocking chemicals into drugs. Based at UT Southwestern’s BioCenter campus, Peloton scientists create libraries of related compounds, ultimately identifying PT2385 and PT2977 to test in humans. A related drug, PT2399, is identified for laboratory work.

2016

Dr. James Brugarolas, in collaboration with Dr. Payal Kapur, validates HIF-2α as a target in ccRCC. In experiments incorporating more than 250 mice transplanted with human kidney cancer (see page 67), it is shown that PT2399 (i) blocks HIF-2α in ccRCC while not affecting related proteins, (ii) is active against 50 percent of human ccRCC tumors transplanted in mice, and (iii) has more activity and is better tolerated than sunitinib (the most commonly used drug for renal cancer treatment at the time). (Chen et al., *Nature*, 2016; Wallace et al., *Cancer Res*, 2016)

2018

Dr. Kevin Courtney reports the results of a phase 1 clinical trial testing PT2385 in humans. The trial represents the first-in-human study of a first-in-class inhibitor of HIF-2α. The trial, which involves 51 patients, shows that PT2385 is safe, well tolerated, and active against ccRCC in humans. More than 50 percent of patients see their cancer regress or stabilize. A patient of Dr. Brugarolas sees benefit for more than a year despite prior progression on seven drugs. (Courtney et al., *J Clin Oncol*, 2018)

2019

U.S. drug manufacturer Merck & Co. acquires Peloton Therapeutics for $1.05 billion with an additional $1.15 billion contingent on sales and regulatory milestones.

2020

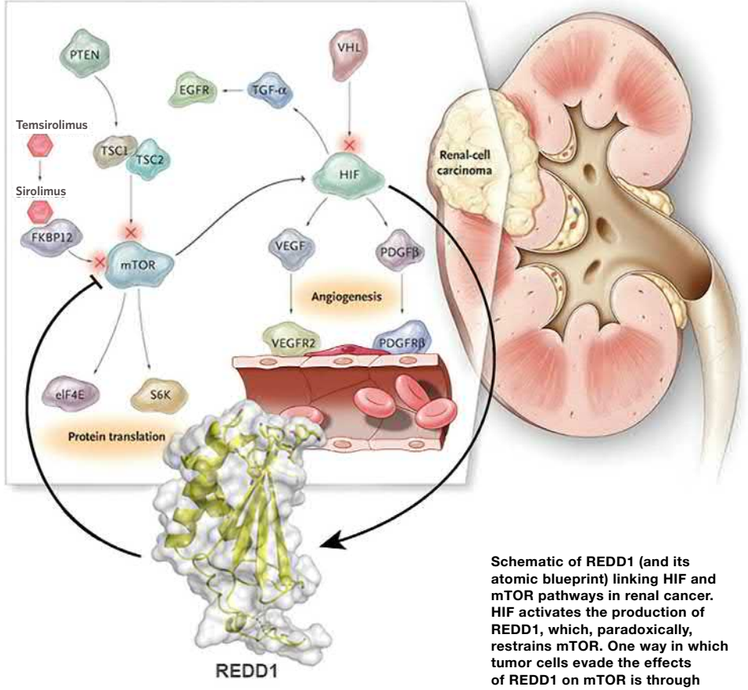
Through studies of biopsy samples from patients who participated in the phase 1 clinical trial, Drs. Courtney, Pedrosa, and Brugarolas report the identification of drug resistance mutations in patients, establishing HIF-2α as the first known core dependency of ccRCC. (Courtney et al., *Clin Cancer Res*, 2020)

ROBOTS SUPPORTING DRUG DISCOVERY

Building on the vision of Steven McKnight, Ph.D., and with support from Dr. James Willson, the director of Simmons Comprehensive Cancer Center at the time, UT Southwestern created a facility able to test hundreds of thousands of chemicals against cancer. Directed by Bruce Posner, Ph.D., the facility is equipped with robots that support high-throughput screening (HTS). Pharmaceutical companies often have such facilities, but they are uncommon in academic centers. UT Southwestern, however, deploys its HTS laboratory to help translate discoveries into new treatments. The facility contains more than 330,000 compounds, including proprietary compounds, and has completed more than 100 screens, filed 18 patents, and has licensed several compounds to third parties.

Promising compounds are evaluated by medicinal chemists such as Joseph Ready, Ph.D. Once optimized, they are tested in animals in the Preclinical Pharmacology Core, led by Noelle Williams, Ph.D. Subsequently, these chemicals may be evaluated in mice transplanted with human kidney tumors (see page 67).

The HTS laboratory is also able to leverage its infrastructure to perform gene inactivation analyses. Using bits of genetic material, the lab can disable each of the approximately 22,000 genes in the human genome. These studies allow investigators to identify cancer-promoting and cancer-protective genes, as well as potential new targets for drug development. (Whitehurst et al., *Nature*, 2007; Phillips et al., *J Med Chem*, 2008; Wolff et al., *Oncotarget*, 2015; Chen et al., *Nature*, 2016; Eskiocak et al., *Nat Commun*, 2016; Kim et al., *Nature*, 2016; Zhang et al., *Sci Transl Med*, 2016)



Schematic of REDD1 (and its atomic blueprint) linking HIF and mTOR pathways in renal cancer. HIF activates the production of REDD1, which, paradoxically, restrains mTOR. One way in which tumor cells evade the effects of REDD1 on mTOR is through inactivation of TSC1/TSC2. (Vega-Rubin-de-Celis et al., *Biochemistry*, 2010; Brugarolas, *N Engl J Med*, 2007)

Bridging Key Pathways in Renal Cancer

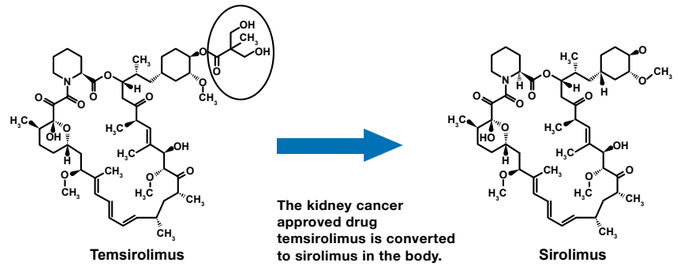
Pinpointing how pathways in cancer cells are coordinated could open new treatment possibilities.

Dr. Brugarolas and his team have found that REDD1 (regulated by development and DNA damage 1) links HIF and mTOR pathways – the most important pathways in kidney cancer cells (see page 35).

Given the important role of REDD1, biophysicist Xuewu Zhang, Ph.D., wanted to know what REDD1 looked like. He crystalized REDD1, which unmasked its atomic blueprint. This showed that REDD1 is a rather unique protein relative to all other known proteins in the cell. (Brugarolas et al., *Genes Dev,* 2004; Vega-Rubin-de-Celis et al., *Biochemistry,* 2010; Kucejova et al., *Mol Cancer Res,* 2011)

The Right Drug for the Right Patient

In 2002, Duojia Pan, Ph.D., discovered that mTOR is regulated by the TSC1 and TSC2 proteins, which bind together. When TSC1/TSC2 is disrupted, mTOR becomes excessively active, leading to the activation of HIF and increasing protein production by cells, including cancer cells. mTOR blockade stops cells from growing and two drugs



targeting mTOR are used for the treatment of kidney cancer (see page 35). These drugs do not work for everyone, however. An important question is, for whom do they work best?

In 2011, the Brugarolas team discovered that the gene encoding TSC1 was mutated (inactivated) in some ccRCC. While the frequency of TSC1 mutations in tumors was low at only 5 percent, the investigators discovered that tumors with TSC1 mutations, which have particularly active mTOR, may be most responsive to the mTOR-targeting drugs. This research provides the first example of how a mutated gene can be linked to a particular treatment in kidney cancer. (Gao and Pan, *Genes Dev,* 2001; Gao et al., *Nat Cell Biol,* 2002; Zhang et al., *Nat Cell Biol,* 2003; Kucejova et al., *Mol Cancer Res,* 2011)

An Option for Kidney Cancer Treatment Where Modern Drugs Don't Reach?

In 2006, a year after the removal of a tennis-ball-sized ccRCC tumor, a 66-year-old patient developed liver and lung metastases. Afflicted with various cardiovascular ailments and having a history of two prior strokes, the man was a poor candidate for sunitinib, sorafenib, and IL-2, the three drugs approved by FDA at that time (see page 35). Temsirolimus, which wasn't approved until 2007, had shown promise but was not available at the time. The patient's cancer was spreading fast, however, and he could not wait.

In 1999, the FDA had approved another drug, sirolimus. Sirolimus was approved for an indication very different from cancer. It was approved as an immunosuppressant in patients with kidney transplants, to prevent the body from rejecting the new kidney.

Nevertheless, sirolimus was very similar to temsirolimus, and both targeted mTOR. Furthermore, a publication had shown that 75 percent of the temsirolimus was converted to sirolimus in the body.

After a discussion with the patient, Dr. Brugarolas offered sirolimus. Sirolimus dosing was adjusted so it matched the levels in the blood of cancer patients treated with temsirolimus. It worked. The cancer's growth was stopped. It was the first example of a kidney cancer treated with sirolimus.

Today, one month of sirolimus costs 10 percent of what temsirolimus costs. Furthermore, unlike temsirolimus, which is given intravenously, sirolimus is taken orally. "For parts of the world where financial resources are limited and modern medications are not available, sirolimus could provide an alternative. Sirolimus could also potentially be used in lieu of everolimus, a related drug also approved for kidney cancer, which is quite expensive," says Dr. Mark Ratain, Director of the Center for Personalized Therapeutics at the University of Chicago, and member of the Scientific Advisory Board of the Kidney Cancer Program. (Brugarolas et al., *J Clin Oncol,* 2008)

Hope Where There Was None

Physicians at the Kidney Cancer Program are often confronted with difficult cases. Often, they involve patients with kidney cancers for which no clear treatment options exist.

For instance, in 2009, a 24-year-old man with familial tuberous sclerosis complex came to UT Southwestern for evaluation of an EAML (epithelioid angiomyolipoma). EAMLs are rare tumors that arise from support cells in the kidney. They have no known treatment.

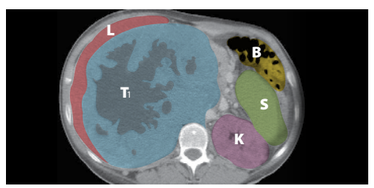
This was a recurrence. The original tumor had been removed just a few months earlier. In the span of five months, the tumor had grown to occupy half of the abdomen. Bleeding was occurring inside the tumor, and the patient was profoundly anemic (blood counts below 25 percent of normal). Left alone, death was likely within days.

Patients with familial tuberous sclerosis complex have a mutation in either TSC1 or TSC2 in all of the cells in their body (see page 59), which makes them more prone to develop cancer. This results in activation of mTOR in tumors, and, as such, Dr. Brugarolas recommended trying an mTOR-blocking drug.

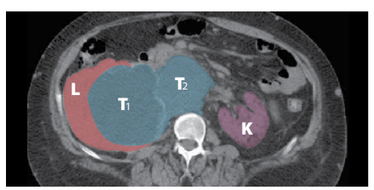
Within days, bleeding stopped. The response was remarkable. The patient went home, and his tumor continued shrinking. The tumor, which was initially the size of a softball, diminished to the size of a golf ball, and the patient survived an additional four years.

Together with a combined study from the Dana-Farber Cancer Institute and Memorial Sloan Kettering Cancer Center of three cases, this study from UT Southwestern, which included a second case from Dr. Thomas Bradley in New York, reported for the first time the potential benefit of mTOR inhibitors for the treatment of EAML. (Wolff et al., *J Clin Oncol*, 2010)

FEBRUARY 2009



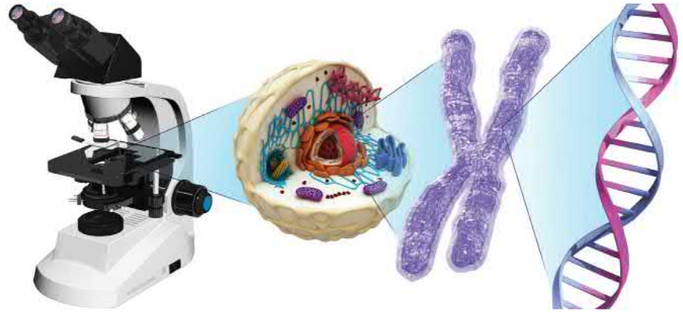
APRIL 2013



CT scans from patient with an EAML tumor (T1) showing an 80 percent tumor reduction after treatment with an mTOR inhibitor. After four years, a second tumor (T2) emerged that was resistant to the treatment, and eventually led to the demise of the patient. (B), bowel; (K), kidney; (L), liver; (S), spleen. (Wolff et al., *J Clin Oncol*, 2010)

Paving the Way with Genomic Discoveries

Genes are key to new treatments. Pioneering discoveries at the Kidney Cancer Program provide insight into the biology and lay the foundation for the next wave of targeted drugs.



Clear cell renal cell carcinoma (ccRCC) is characterized by mutations in the VHL gene (von Hippel-Lindau). VHL is one of some 22,000 genes in the human genome. Each gene represents an instruction. Instructions are stored in the form of DNA. All genes are found in every cell, but in every cell not all instructions are turned on. For an instruction to be turned on, it must be translated into a protein. When a gene instruction becomes a protein in the cell, the instruction is ON.

Genes carrying instructions can be corrupted and become faulty. This process is referred to as mutation. Most often, this means that the particular instruction will no longer function. Less frequently, the instruction can be changed to mean something else or to become super-active.

Mutations can occur in the germ cells (the sperm or the egg). When they occur there, they are found in every cell of the body. They are also transmitted to the offspring (see page 59).

Mutations can also occur during development or after birth. In those instances, they are only passed on to the particular cell's offspring. Cells multiply by copying their contents and dividing. This occurs trillions of times over a human lifetime. When cells copy their contents, errors may be introduced. They are perpetuated from mother to daughter cell, and as such, the number of errors accumulates over time. In addition, some chemicals can damage the genes/instructions, increasing the rate of mutation. Cancer-causing chemicals (carcinogens), such as those from tobacco, are picked up by the blood in the lungs and filtered by the kidneys, where they can cause mutations and increase the risk of kidney cancer.

The VHL gene normally protects kidney cells from cancer development, but when the gene is altered (mutated), the cancer process begins. VHL can be mutated in the germ cells, where it gives rise to VHL syndrome. VHL patients develop multiple cancers over the life span (see page 59) including multiple kidney cancers. Most often, the VHL gene is mutated in kidney cells in adult individuals. In fact, VHL is thought to be the first gene to be mutated in the process of kidney cancer development, and, as such, plays an important role.

DID YOU KNOW?

UT Southwestern investigators implicated several new genes leading to a biological classification of kidney tumors, enabling personalized approaches. (Peña-Llopis et al., *Nat Genet,* 2012; Durinck et al., *Nat Genet,* 2015)

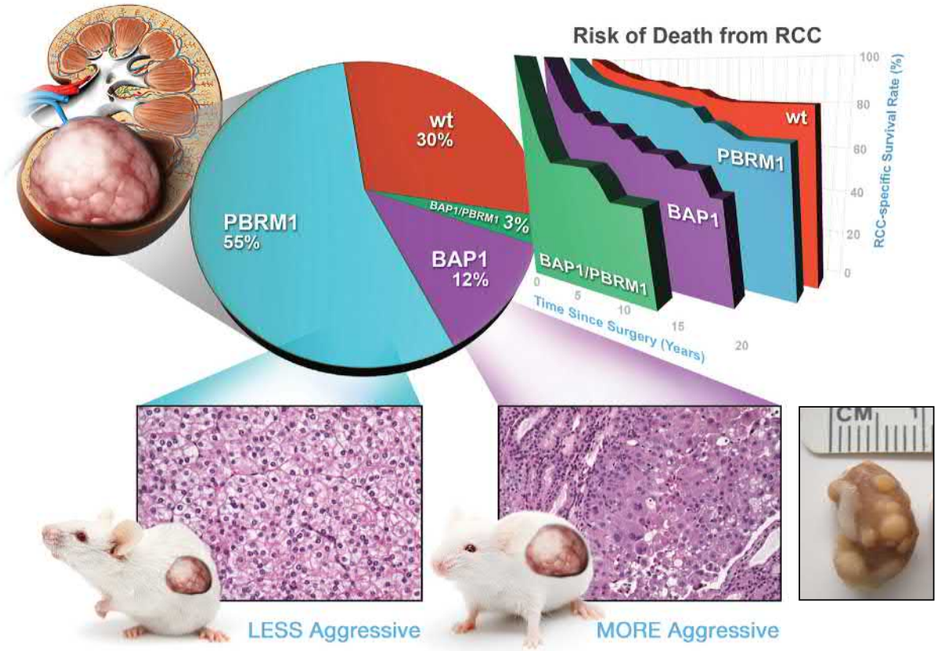
Discovering Kidney Cancer's Source

When the VHL gene was discovered, scientists sought to model von Hippel-Lindau syndrome in mice. Mice were engineered to have a faulty VHL gene. As in humans, the defective copy was passed from parents to offspring. Unlike humans, mice with a VHL mutation did not develop kidney cancer. The same approach had worked with countless other cancer genes, but this was not the case for the VHL gene. This puzzled investigators for more than a decade.

UT Southwestern investigators found the answer. Dr. Brugarolas discovered that in humans there were other genes that, like VHL, also protected kidney cells from cancer development, and that these genes were next to each other in the genome, one might say, on the same page. In contrast, these instructions (BAP1, PBRM1, and SETD2 genes) were located on different "pages" in the mouse genome. What this meant was that a single mutation (like ripping out a page from the instruction book) disrupted all four genes in humans, but three pages needed to be ripped out in the mouse for the same result. Given that ripping out pages of the genome, so-called large deletions, is not frequent, having genes separated protected the mice from kidney cancer development.

In studies funded by the National Institutes of Health and CPRIT (Cancer Prevention and Research Institute of Texas), the Brugarolas team tested this hypothesis: They generated mice in which two genes were inactivated simultaneously. They started with VHL and BAP1. As they had hypothesized, these mice developed kidney cancer.

The findings, which were published in the journal *Proceedings of the National Academy of Sciences*, have profound implications. They not only report the first mouse model to recapitulate ccRCC, but also suggest that cancer predisposition, which varies across species, is a function (at least in part) of the arrangement of genes in the genome. In other words, how instructions are arranged in the pages of one playbook can have a profound impact on whether a species is predisposed to a particular type of cancer. (Wang et al., *Proc Natl Acad Sciences USA,* 2014)



UT Southwestern investigators discovered that ccRCC can be subclassified based on BAP1 and PBRM1 status into four types: wild-type (wt) tumors with normal BAP1 and PBRM1 (associated with best outcomes), tumors with mutant PBRM1 (1.5 times higher odds of mortality), tumors with mutant BAP1 (3 times higher odds), and a subset of infrequent tumors with mutations in both genes (5 times higher odds).

A kidney of a mouse with a mutation in PBRM1 showing multiple tumors.

Why Are Some Renal Tumors So Aggressive?

Kidney tumors behave differently. UT Southwestern investigators have found that the answer is in the genes. Their discoveries are revolutionizing how kidney tumors are classified, launching a modern catalogue. By classifying kidney tumors by their genes rather than their appearance, investigators hope to identify groups of tumors that share the same biology and respond to treatment similarly.

Dr. Brugarolas and colleagues previously discovered a gene, BAP1, that is inactivated in about 15 percent of ccRCCs. Interestingly, ccRCCs with the BAP1 mutation typically lacked a mutation in another gene, PBRM1, which is mutated in almost half of ccRCCs. The finding that either one or the other gene was mutated began to reveal the logic of ccRCC development.

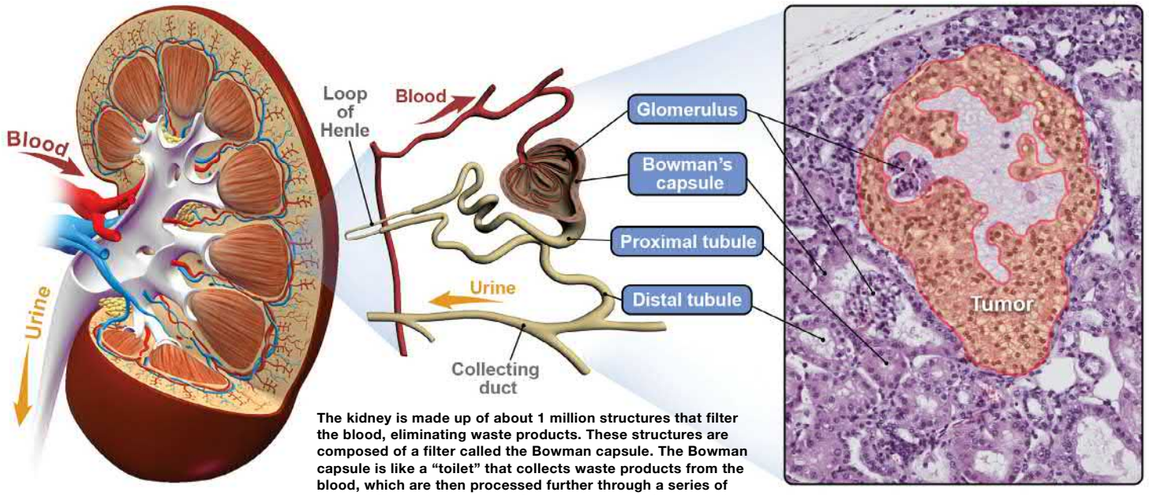
Dr. Kapur noticed that tumors with BAP1 mutations looked more aggressive under the microscope than those with PBRM1 mutations – they had higher grade (see page 67). To explore this notion further, the team compared groups of patients at UT Southwestern whose cancers had one mutation or the other. They found that the life expectancy for patients with BAP1-mutant tumors was about half that of patients with PBRM1-mutated tumors. These results were confirmed using a second nationwide cohort.

According to the status of these two genes, BAP1 and PBRM1, ccRCC could be classified into four subtypes: tumors where both genes were normal, where one or the other was mutated, or where both were mutated.

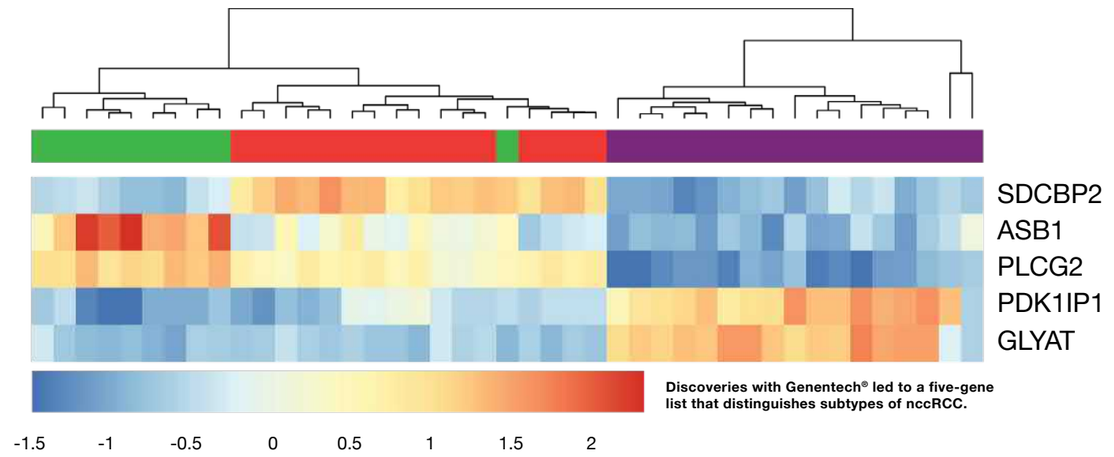
Because the mutations typically result in the loss of the protein inside the cells, protein tests (immunohistochemistry tests) can assess the status of BAP1 and PBRM1 in patient samples. Dr. Kapur has developed a protein test obviating the need for more complex gene testing.

UNDERSTANDING THE LANGUAGE BEHIND KIDNEY CANCER MUTATIONS

The Brugarolas lab previously showed that mutations in BAP1 and PBRM1 tend to be mutually exclusive in ccRCC, and that mutations in PBRM1 and SETD2 tend to occur together. In collaboration with Dr. Kapur and Dr. Thai Ho, from the Mayo Clinic group, they showed that PBRM1-mutant tumors that also acquire mutations in SETD2 tend to be more aggressive. With funding from the Kidney Cancer Program SPORE, molecular biologist Laura Banaszynski, Ph.D., is studying how mutations in SETD2 contribute to kidney cancer development.



The kidney is made up of about 1 million structures that filter the blood, eliminating waste products. These structures are composed of a filter called the Bowman capsule. The Bowman capsule is like a "toilet" that collects waste products from the blood, which are then processed further through a series of pipes or tubules and are eventually discarded in the form of urine. Investigators at UTSW have discovered that cells around the Bowman capsule give rise to kidney cancer. (Gu et al., *Cancer Discov*, 2017)



Discoveries with Genentech® led to a five-gene list that distinguishes subtypes of nccRCC.

Using the protein tests, the team has expanded its studies in collaboration with Mayo Clinic, which has assembled a cohort of more than 1,400 patients with kidney cancer. Samples from these patients were analyzed at UT Southwestern, leading to validation of previous discoveries.

These findings have advanced the field, which now recognizes that ccRCC is made up of these four fundamental subtypes. (Peña-Llopis et al., *Nat Genet,* 2012; Kapur et al., *Lancet Oncol,* 2013; Kapur et al., *J Urol,* 2014; Joseph et al., *Cancer,* 2014; Joseph et al., *J Urol,* 2016)

Genes That Control Tumor Aggressiveness

To address whether BAP1 and PBRM1 are indeed responsible for controlling tumor aggressiveness, the Brugarolas lab genetically engineered mice with either mutant BAP1 or mutant PBRM1 in their kidneys (together with a mutation in VHL). Investigators found that, as for kidney cancer in humans, cancers that arose in the BAP1-mutant kidneys developed early in the life of the mouse and were of high grade (see page 67). In contrast, the cancers that arose in the PBRM1-defective kidneys developed significantly later and were of lower grade. These results strongly suggest that BAP1 and PBRM1 are not just markers of high and low aggressive kidney cancer, but are the very cause of the differential aggressiveness. (Gu et al., *Cancer Discov,* 2017)

Which Kidney Cells Give Rise to Cancer?

Extensive studies have sought to find which cell type in the kidney, among a couple of dozen, gives rise to kidney cancer. Efforts have focused on evaluating tumors for the presence of features (markers) that distinguish the different cell types. Frequently, this involves comparing ON and OFF instructions in tumors to the particular instructions that characterize different kidney cell types. Using this approach, investigators have concluded that ccRCC arises from cells lining the proximal convoluted tubule. However, the analysis assumes that having the particular marker or signature is revealing of the cell of origin.

To address the question more definitively, the Brugarolas team induced mutations in BAP1 and PBRM1 (along with mutations in VHL) in different cell types of the mouse kidney. When mutations were targeted to cells of the proximal convoluted tubule, tumors did not develop. Rather, investigators found that when the mutations were induced in a kidney structure called the Bowman capsule, kidney tumors readily formed.

These results suggest that kidney cancer arises from the Bowman capsule cells. Notably, the Bowman capsule contains "mother" cells that maintain and help repair the kidney when damage occurs. This population of cells may be responsible for cancer development.

Another conclusion of the study is that tumors with BAP1 and PBRM1 mutations may arise from the same cell type.

That the Bowman capsule is the source of kidney cancer is also supported by studies of human kidney specimens by Dr. Kapur. (Gu et al., *Cancer Discov,* 2017)

These results strongly suggest that BAP1 and PBRM1 are not just markers of high and low aggressive kidney cancer, but are the very cause of the differential aggressiveness.

Seeking Drugs Targeting Aggressive BAP1 Mutant Cancers

Kidney tumors with mutations in BAP1 are most aggressive. Biochemist Dr. Yonghao Yu is investigating how BAP1 loss induces aggressive kidney cancer.

The BAP1 protein belongs to a class of proteins that controls the levels of other proteins in the cell. These proteins do this by removing a tag that is placed on proteins to earmark them for shredding. The tag, called ubiquitin, is cleaved off by BAP1 and related proteins. However, precisely which proteins BAP1 controls is poorly understood. Further, ubiquitin tags not only control shredding, but may also influence proteins in other ways.

With funding from the SPORE, Dr. Yu is leveraging mass spectrometry technology to map all the proteins that BAP1 controls. These proteins may then become targets for drug development.

A Better Understanding of Rare Kidney Cancers

NccRCC (non-clear cell RCC) accounts for about 30 percent of all RCC. This group of tumors is made up of different subtypes and it has received less attention. Further, nccRCC lacks specific treatments.

To learn more about nccRCC, Drs. Kapur and Brugarolas teamed up with Dr. Seshagiri and his group at the biotechnology company Genentech® to perform next-generation sequencing analyses. Tumors from 167 patients at UT Southwestern were evaluated. They included 67 papillary cancers, 49 chromophobe, 8 unclassified, 6 translocation RCC, and 2 that were primarily sarcomatoid. The analysis also included 35 oncocytomas.

This study, the first integrated genomic study of nccRCC to be published, made significant discoveries. It implicated several new genes in the development of nccRCC, including NF2, PTEN, TSC1, and MTOR in papillary RCC. In addition, it implicated mutations in LATS1 in papillary RCC.

Additionally, the team identified a set of five genes that distinguished tumors that may be hard to distinguish under the microscope, such as chromophobe RCC and benign renal oncocytoma. Two subtypes of chromophobe tumors were characterized: an aggressive subtype with p53 and PTEN mutations, and a second subtype more akin to benign oncocytomas.

Their findings provide fruitful targets in the development of novel therapies for

Whitney Wheeler was diagnosed with nccRCC at age 28. After radiosurgery for brain metastases and four lines of therapy, she passed away 11 months later. Research is ongoing at the Kidney Cancer Program to find effective treatments.

nccRCC. The research also refined the current classification of nccRCC. (Durinck et al., *Nat Genet*, 2015)

Modeling nccRCC in the Mouse

Developmental biologist Thomas Carroll, Ph.D., is evaluating the role of the LATS1 and the LATS2 genes in kidney cancer development using mice. With funding from the SPORE, Dr. Carroll has

engineered and is characterizing mice with mutations in the LATS1 and the LATS2 genes in their kidneys. The Carroll team has found that inactivation of the LATS genes causes renal cancers that metastasize.

The team also discovered that the genes YAP and TAZ are required for the development of these tumors. Accordingly, YAP and TAZ may represent cancer vulnerabilities that treatment could exploit.

REACHING BEYOND CONVENTION

Most of the research around RCC has focused on genes (e.g., protein coding genes). However, these genes make up only 1 percent of the genome and other genetic elements are likely to also play a role. Dr. Josh Mendell, together with Dr. Tu Dan in Dr. Mendell's laboratory, is investigating the role of long noncoding RNAs (lncRNAs). Unlike conventional genes, lncRNAs are not translated into proteins. To understand the contribution of lncRNAs to kidney cancer, Drs. Dan and Mendell first compared the levels of lncRNAs in tumors and normal kidney samples using UTSW Kidney Cancer Explorer (see page 69) and The Cancer Genome Atlas. Next, they assessed the role of deregulated lncRNAs using the CRISPR/Cas9 genome-editing system. They designed a customized library of guide RNAs to target each lncRNA that was overexpressed in tumors and conducted a pooled screen. Using massively parallel sequencing approaches, they identified lncRNAs that were implicated in cancer cell growth. If successful, their research may not only provide novel insights into ccRCC development and progression, but potentially also novel drug targets.

LOOKING FOR NEW TARGETS

Exploiting a mutant metabolic pathway

In July 2009, a 24-year-old mother (called YM here) was referred to UT Southwestern with a 17-inch tumor in her left kidney that occupied most of her abdomen. The tumor was bleeding and the patient was quite anemic with red blood cell counts down to 20 percent of normal.

At UT Southwestern, interventional radiologists threaded a catheter inserted through the groin to the bleeding artery, where they deployed clogging material to stop the bleeding.

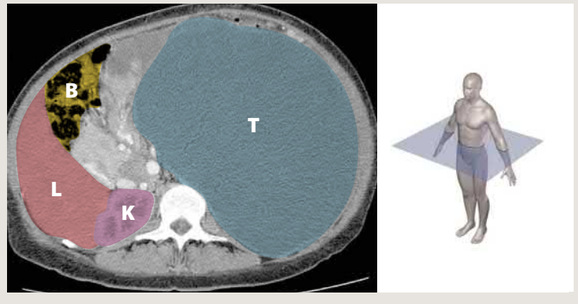
The procedure was successful. Four weeks later, after blood counts had increased, the patient underwent surgery to remove the tumor. It was a massive effort by Dr. Ganesh Raj and his team. The kidney with the tumor was removed, along with some of the pancreas, the spleen, and part of the colon. She recovered, but post-op scans showed that the cancer had spread. She had stage 4 metastatic kidney cancer.

Surprised that a 24-year-old would develop such an advanced cancer, her doctor, Dr. Brugarolas, set out to investigate. The tumor was a relatively infrequent tumor, a pRCC (papillary renal cell carcinoma) of high grade (see page 67). These tumors, referred to as pRCC-2 tumors can run in families and develop at a young age. They arise as a result of a deficient instruction, a mutated gene. This gene, called FH (fumarate hydratase), is one of 22,000 or so genes that constitute the human genome. When it is mutated, it predisposes to pRCC-2. In familial cases, a defective copy of the gene is passed on from parent to offspring. This condition is called HLRCC (hereditary leiomyomatosis and renal cell cancer). The condition is quite rare, with only 300 or so families described worldwide.

However, the patient was the only one in her family to get cancer, and both her parents were alive and well.

Nevertheless, Dr. Brugarolas decided to probe further. He reasoned that perhaps YM was the first one in her family to have developed the condition. This would be the case if the mutation had occurred in the sperm or the egg that gave rise to her. Such a mutation would be found only in her, but it would be in all of her cells, which descend from the fertilized egg. The fertilized egg copies its genetic information and then splits into two. The two cells do the same in turn, and split into four. This process is carried out throughout gestation, infancy, and adulthood.

To test whether this might be the case, a blood test was performed. His concerns proved correct: the FH gene was defective. Normal cells have two copies of each gene (one from the father carried in the sperm and another from the mother in the egg), and one of the two copies was faulty. Further, as typically occurs with cancer genes like FH, the remaining normal copy was lost in the cancer cells. Only the faulty gene was present.



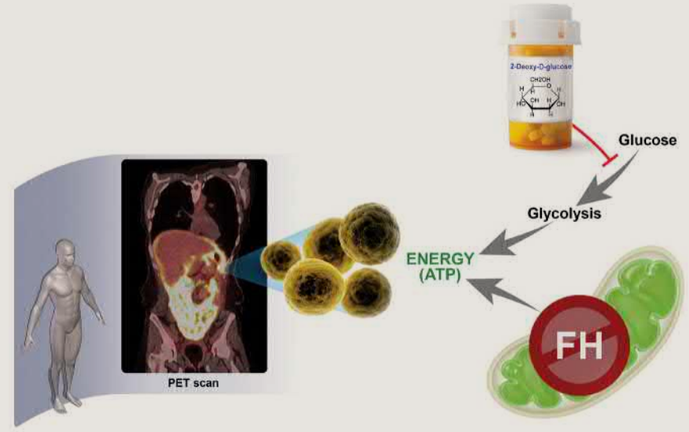
CT scan from 24-year-old mother with massive fluid-filled tumor (T). (B), bowel; (K), kidney; (L), liver.

Thus, the patient was diagnosed with HLRCC, the first member of her family to get the disease. Her daughter, a toddler, has a 50 percent chance of having inherited it.

Unfortunately, the condition is so rare that there are no treatments. However, a drug had been approved by the Food and Drug Administration that had shown activity against kidney cancers regardless of type (see page 35). The drug, temsirolimus, was quite familiar to Dr. Brugarolas. The drug worked, but unfortunately after only a few months the cancer started to grow again.

Dr. Brugarolas then turned to the biology. FH normally functions in an energy production line that breaks down nutrients to extract energy. Because only the faulty copy remained in the tumor, the assembly line would stall. As a result, cancer cells had to rely on another energy manufacturing process – glycolysis. The increased reliance on glycolysis was seen by Dr. Brugarolas and his team as presenting an opportunity to attack the cancer.

While there are no drugs in the clinic that block glycolysis, Dr. Brugarolas found a company, Threshold Pharmaceuticals, that had developed such a drug. Glycolysis breaks down glucose, and the drug was a modified version of glucose that would clog the process. The drug, which is called 2DG (2-deoxy-glucose), enters cells but cannot be broken down, thus blocking the chemical machinery responsible for energy generation.



PET (positron emission tomography) scan from YM. The scan, which uses labeled glucose, shows massive uptake in the patient's tumor throughout the abdomen (yellow signal). The patient's cancer cells had lost FH, interrupting the TCA cycle in tumor cells, causing a reliance on a second energy generation pathway – glycolysis – which could be blocked with an experimental drug, 2DG. (Yamasaki et al., *Nat Rev Urol,* 2011)

To determine whether the approach could work, Dr. Yamasaki, a urologist in the Brugarolas lab, obtained FH-deficient kidney cancer cells from Dr. W. Marston Linehan at the National Cancer Institute and tested the effects of 2DG. Reassuringly, 2DG stopped their growth.

The investigators wrote a report petitioning the FDA to authorize 2DG treatment for the patient. The FDA approved the request, and Threshold Pharmaceuticals made 2DG available to YM. Given that one copy of FH was defective in all her cells, 2DG was started at low doses and progressively increased under direct medical supervision.

Dr. Brugarolas partnered with Dr. DeBerardinis to monitor the effects of 2DG. At higher doses, YM started developing symptoms such as sweating and blurred vision, indicating that energy generation was being blocked. However, even at high levels, her tumor did not respond.

Despite 2DG's efficacy against tumor cells in the lab, it was not effective enough in the patient. (Yamasaki et al., *Nat Rev Urol,* 2011)

Following a fellowship in urologic oncology at Memorial Sloan Kettering, Dr. Aditya Bagrodia returns to UT Southwestern.

> **"The effort to save this patient was monumental. It illustrates the commitment of the members of the Kidney Cancer Program to find a cure, even when that means thinking outside the box." – Dr. Ralph DeBerardinis**

Joe Ungeheier and his family consulting with immunotherapy leader Dr. Hans Hammers. Team Ungeheier, in memory of Joe, has been instrumental in raising awareness and philanthropic funds for the Kidney Cancer Program.

Immunotherapy and Novel Approaches

Immunotherapy has been used to treat kidney cancer since the 1980s. IL-2 (interleukin-2), a substance produced by the body's immune cells, can stall cancer progression in about 30 percent of the patients when administered in high doses. In 7 percent of patients, it can induce a complete response (eliminating all traces of cancer), which can last for many years. IL-2 is administered intravenously, typically in an intensive care unit. It activates the immune system's killer cells. This process of activation and mobilization of killer cells is accompanied by whole-body inflammation. The FDA approved IL-2 in 1992.

Subsequently, several drugs were approved that blocked either blood vessels or mTOR. The drugs controlled the cancer and helped patients live longer. However, they did not cure patients. The drugs also had adverse side effects and lowered quality of life. Further, they had to be taken continuously. If the drug was stopped, the cancer grew back. Thus, it was clear that other treatments were needed.

The Nobel Prize-winning discoveries of Drs. James Allison at MD Anderson Cancer Center and Tasuku Honjo at Kyoto University in Japan ushered in a new era of immunotherapy. In 2015, nivolumab was approved by the FDA. The approval was based on a phase 3, randomized clinical trial (called CheckMate 025) of 821 patients, including participants at UT Southwestern Kidney Cancer Program. The study showed that 25 percent of patients receiving nivolumab had their tumors shrink substantially. This rate was five times higher than that of patients receiving standard-of-care everolimus. Nivolumab also extended patient survival by 25 percent. "These results are quite significant," says Dr. Hammers, an author of the clinical trial report, which was published in the *New England Journal of Medicine*.

Another major immunotherapy clinical trial in which UT Southwestern participated combined nivolumab with a second immunotherapy drug, ipilimumab. The phase 3 clinical trial (CheckMate 214), for which medical oncologist Dr. Hammers was a principal investigator, reported 42 percent response rates in patients with aggressive disease (intermediate and poor risk groups), as well as disappearance of the cancer in 9 percent of the patients. This study was based on a prior clinical trial led by Dr. Hammers and published in the *Journal of Clinical Oncology*, showing promising results in a smaller number of patients.

The combination of ipilimumab and nivolumab can, however, result in significant side effects. Side effects occur in about 30-40 percent of patients. They arise when the immune system fights not just cancer cells, but also normal cells. This causes inflammation in many organs such as the lungs (pneumonitis), the bowel (colitis), or the liver (hepatitis). The reaction can be severe, requiring high doses of steroids or other immunosuppressive drugs. Expert management is imperative. (Motzer et al., *N Engl J Med,* 2015; Hammers et al., *J Clin Oncol,* 2017; Motzer et al., *N Engl J Med,* 2018)

SIX FACTORS ASSOCIATED WITH WORSE METASTATIC KIDNEY CANCER

1. Need for drug therapy within a year from initial diagnosis
2. Debilitation
3. Anemia
4. High neutrophil counts (cell type in the blood)
5. High platelet counts
6. High blood calcium

Number of factors: 0 (good risk), 1-2 (intermediate risk), 3 or more (high risk)

Innovation: Exposing the Enemy with Radiation

Traditionally considered an ineffective treatment with limited use in kidney cancer, the efficacy of radiotherapy has improved markedly. Advancements have been driven in part by UT Southwestern's renowned team of radiation oncologists (see page 52).

High-dose, precisely targeted radiation beams from various angles – called SBRT – can kill kidney tumors while minimizing radiation damage to surrounding healthy tissues.

Animal studies by Drs. Lotan and Timmerman showed that SBRT, unlike conventional radiation, can kill kidney cancer cells. As shown by Dr. Hannan and others, the immune system begins to recognize the radiated tumor cells as enemy invaders.

In exposing cancer cells for what they are, radiation may improve immunotherapy. (Walsh et al., *Eur Urol,* 2006; Takeshima et al., *Proc Natl Acad Sci USA,* 2016)

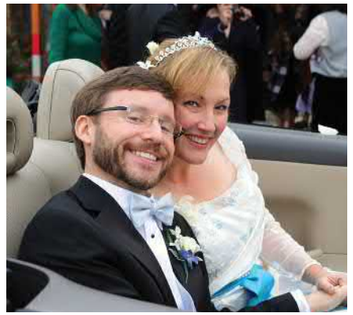
FEATURED KIDNEY CANCER COLLABORATOR

A group of specialists and collaborating physicians works with kidney cancer oncologists to address misdirected attacks from the immune system to tissues other than the cancer. They include experts in gastroenterology, endocrinology, and rheumatology, such as Dr. Bonnie Bermas, who, after fellowship training at the National Institutes of Health, was on faculty at Brigham and Women's Hospital/ Harvard Medical School and is now at UT Southwestern.

Dr. Bonnie Bermas is a specialist in complex systemic rheumatic diseases.

Dr. Raquibul Hannan explaining stereotactic radiation.

Larry Carlson benefited from participating in the RADVAX trial and now volunteers in the clinic.



Kevin Patterson was diagnosed with stage 4 ccRCC just days after his wedding. He had a complete response, with all traces of the cancer disappearing, following the combination of high-dose IL-2 and SBRT in a clinical trial.

SBRT Plus Latest Immunotherapies

A clinical trial is evaluating the combination of SBRT with checkpoint inhibitors, nivolumab and ipilimumab (NCT03065179). Taking its name from the notion that radiation may function as a "vaccine," the study is referred to as RADVAX.

"The addition of SBRT to the combination of nivolumab with ipilimumab may significantly boost response rates from 40 percent to 60 percent," says Dr. Hammers, principal investigator.

Toxicities so far are in the range of what is known when nivolumab and ipilimumab are given together without radiation.

Challenge: Predicting Who Benefits from Checkpoint Inhibitors

One approach that cancer cells employ to avoid being killed by immune cells is to hide from the immune system. They can do so by cloaking themselves with a protein called PD-L1 on their surface. PD-L1 sends a signal to nearby immune system killer cells that turns them off.

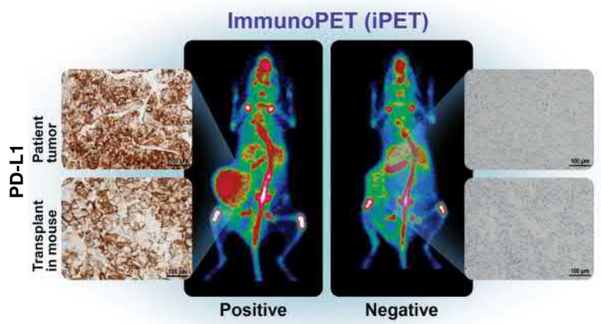
Nivolumab fires up the killer cells against the cancer by disabling the effect of PD-L1. However, not all cancers use this strategy. In fact, only 25 percent of kidney cancers respond to nivolumab.

To identify tumors that have PD-L1, investigators have developed an innovative strategy using UT Southwestern's cyclotron. The team labeled a drug that binds PD-L1 (atezolizumab) with a tracer that can be seen using a PET (positron emission tomography) scanner. By identifying those tumors that have PD-L1, investigators hope to better select patients for PD-L1-targeting drugs such as nivolumab.

To test this notion, investigators evaluated mice transplanted with kidney cancers that had PD-L1 or did not. The mice were then injected with atezolizumab, which had been labeled by Dr. Xiankai Sun's team with a radioactive molecule, zirconium-89 (^{89}Zr). As shown in the figure, mice with tumors that had PD-L1 lit up, and those without did not. (Vento et al., *J Immunother Cancer*, 2019)

The FDA has now granted an IND (Investigational New Drug) to the tracer produced by UT Southwestern, and Dr. Alex Bowman and Dr. Brugarolas are conducting a clinical trial to assess its potential in patients (NCT04006522).

Representing the Simmons Cancer Center, Dr. Brugarolas, along with his colleagues Xiankai Sun, Ph.D., and Dr. Bowman, received a $600,000 grant from the V Foundation in 2018 to identify patients whose renal cancers are most vulnerable to immunotherapies. The grant is designed to support research from "the bench to the bedside."



iPET may identify tumors most likely to respond to immunotherapy. (^{89}Zr) atezolizumab illuminates (red signal) a kidney tumor transplant decorated with PD-L1. Microscopic pictures of tumor cells from the original patient tumor or transplant in the mouse shown on the side. Brown color indicates PD-L1.

Challenge: Dissecting the Battlefront

Understanding how immune cells orchestrate an immune attack against cancer cells and what strategies cancer cells employ to evade them is essential to making progress. However, figuring out the battlefield is challenging. A first approach involves trying to separate cancer cells from noncancer cells in tumors. Separating cancer cells from noncancer cells is difficult, and the process of picking out the different cells may disrupt them, compromising the utility of the approach.

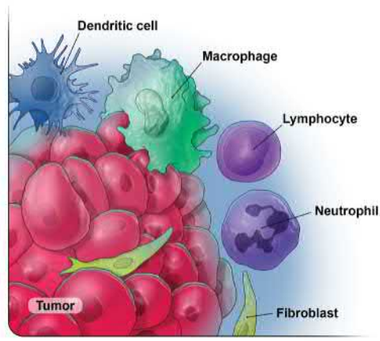
To understand how defenders mount an immune attack, Tao Wang, Ph.D., and Dr. Brugarolas took an innovative approach, which doesn't involve disruptive experimental separation, but leverages a new tool they developed. Patient tumors transplanted in mice grow to form tumors (called tumorgrafts; see page 67), but the only cells that grow and expand are the cancer cells. Other cells in the battlefield don't survive in the mouse.

The investigators reasoned that tumorgrafts may provide a venue to deconvolute the battlefield. If they could subtract the tumorgraft from the corresponding patient's tumor, they would be left with information corresponding to the noncancer cells.

Using RNA sequencing (which scores activated genes) and a new tool Dr. Wang developed called DisHet, investigators were able to accomplish the task. Their approach identified twice as many genes as previously thought to be active. They also found that more than 60 percent of genes previously thought to be activated were in fact not activated.

With this powerful tool, the investigators were able to learn about the immune cell attack. Based on the intensity of the immune attack, they were able to separate tumors into those under heavy attack and those that were not. Interestingly, they discovered that the intensity of the immune attack correlated with particular gene mutations in tumors (specifically BAP1; see page 40) as well as factors used by doctors to predict how aggressive the tumor might be. Their data suggest that factors such as high platelets or low red blood cells (anemia) may be altered in these patients as a consequence of the inflammation in tumors under a heavy immune attack (see page 46). Interestingly, these tumors might be most likely to respond to existing immunotherapies.

Based on this research outcome and with SPORE funding, Dr. Wang is now furthering his research to find features in cancer cells that make them targets for immune cells. (Wang et al., *Cancer Discov*, 2018; Zhang et al., *Genes*, 2019)



Understanding the cancer battlefront.

THE IMPACT OF BODY BACTERIA ON IMMUNOTHERAPY

Trillions of microorganisms live in and on our bodies, including in the gastrointestinal tract. They are referred to as the human "microbiome." They educate and modulate the immune system. Microbiome expert Dr. Andrew Koh believes that there is a unique population of gut bacteria that control responses to immune checkpoint inhibitors. With grant support from the Kidney Cancer Program, Dr. Koh is setting out to identify how the microbiome affects the response of kidney cancer patients to immune checkpoint inhibitors. In the future, precision probiotic therapy with gut bacteria identified in this study could be used to augment cancer immunotherapy efficacy.

Dr. Andrew Koh is partnering with Dr. Lora Hooper, Chair of Immunology, HHMI investigator, and member of the National Academy of Sciences, to determine how bacteria affect immunotherapy treatments.

Next-Generation Immunotherapy

Discoveries made by UT Southwestern scientists have led to new treatments in clinical trials.

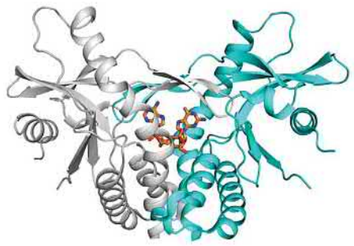
Immunologist Dr. Bruce Beutler received a Nobel Prize for the discovery of TLRs (Toll-like receptors). Made at UT Southwestern, this discovery laid the foundation for the next generation of immunotherapies.

Most therapies enhancing the immune system have focused on one arm of the immune system, the so-called "adaptive" arm. This is fitting, as the adaptive arm is the more sophisticated of the two arms, and is able to develop a focused attack.

However, recent findings suggest that to harness the full potential of the immune system, both arms need to be activated simultaneously, as normally occurs, for instance, during an infection. This requires activation of the "innate" arm. While less focused, the innate arm deploys a rapid-response defense system. By triggering inflammation, it provides an improved foundation for the activation of the adaptive arm.

A major portal of innate immune system activation comes via TLRs. Because of this, pharmaceutical companies have developed drugs that activate TLRs, to be administered in conjunction with immunotherapies that boost the adaptive arm. One such drug is NKTR-262, which activates TLR 7/8. This drug is being studied in a clinical trial at UT Southwestern. The trial (NCT03435640) evaluates NKTR-262 in combination with a modified version of IL-2 and nivolumab. UT Southwestern is one of 10 sites that are testing the TLR-activating drug.

Dr. James Brugarolas (left) conversing with Nobel Prize winner Dr. Bruce Beutler, whose discoveries set the foundation for a new medication being tested in a clinical trial, sponsored by Nektar Therapeutics, that he oversees at UT Southwestern.



Courtesy of Dr. James Chen, the figure shows the atomic blueprint of STING (two molecules shown in gray and cyan) bound to the small molecule compound cGAMP (shown in orange and blue).

Molecular biologist Zhijian "James" Chen, Ph.D., recipient of the 2019 Breakthrough Prize in Life Sciences, is shedding light on a second pathway implicated in the innate immune system response. While TLRs largely sense the environment outside the cell, Dr. Chen discovered a mechanism whereby cells can sense if they have been penetrated by an infectious organism. Dr. Chen discovered a critical sensor of this process, a protein called cGAS (cyclic GMP-AMP synthase). cGAS recognizes penetration by foreign organisms in the form of DNA in the cytosol. In human cells, DNA is found only within the nucleus and inside mitochondria. Outside of these structures, DNA triggers the activation of cGAS. Upon activation, cGAS sends an alert molecule called cGAMP to activate a "manager" of the immune response called STING. Much like TLR activation, STING activation triggers an inflammatory response. Thus, STING is an attractive drug target to activate the immune system. Dr. Chen has licensed his discoveries to a company, Immune Sensor, LLC, which is evaluating IMSA101 in a phase 1 clinical trial at UT Southwestern (NCT04020185).

This research is being further expanded on by chemical biologist Chuo Chen, Ph.D., who, with funding from the Kidney Cancer Program SPORE, is developing drugs that activate the innate and adaptive immune system simultaneously.

A New Strategy When Tumors Are Mostly Controlled

Switching patient treatments might not be the best choice if metastatic cancer is mostly controlled.

In 2013, Drs. Timmerman and Brugarolas published the first report in the literature of a patient with metastatic kidney cancer whose metastases were mostly controlled, but who had progression at one site, which was treated with SBRT. The patient, an 83-year-old man, was on sunitinib, and by radiating the isolated progressive metastasis, sunitinib treatment could be extended from 14 to 22 months.

The situation is referred to as oligoprogression, from the Greek "oligos," meaning "few," and from the English word "progression." Today, more than 30 UT Southwestern patients have been offered this option. Preliminary analyses show that treatment duration can be extended by more than six months in many patients.

To systematically explore the benefit of SBRT in patients with oligoprogression, Drs. Hannan and Brugarolas have opened a clinical trial (NCT03696277). The clinical trial is founded on the notion that while a few tumors in a patient may have developed resistance to a particular therapy, perhaps through the acquisition of a mutation, these events tend to be isolated. By incorporating SBRT treatment of progressive tumors (up to three), investigators hope to maximize the efficacy of each cancer medication. This prolongs quality of life in cases where patients are not adversely affected by the treatment.

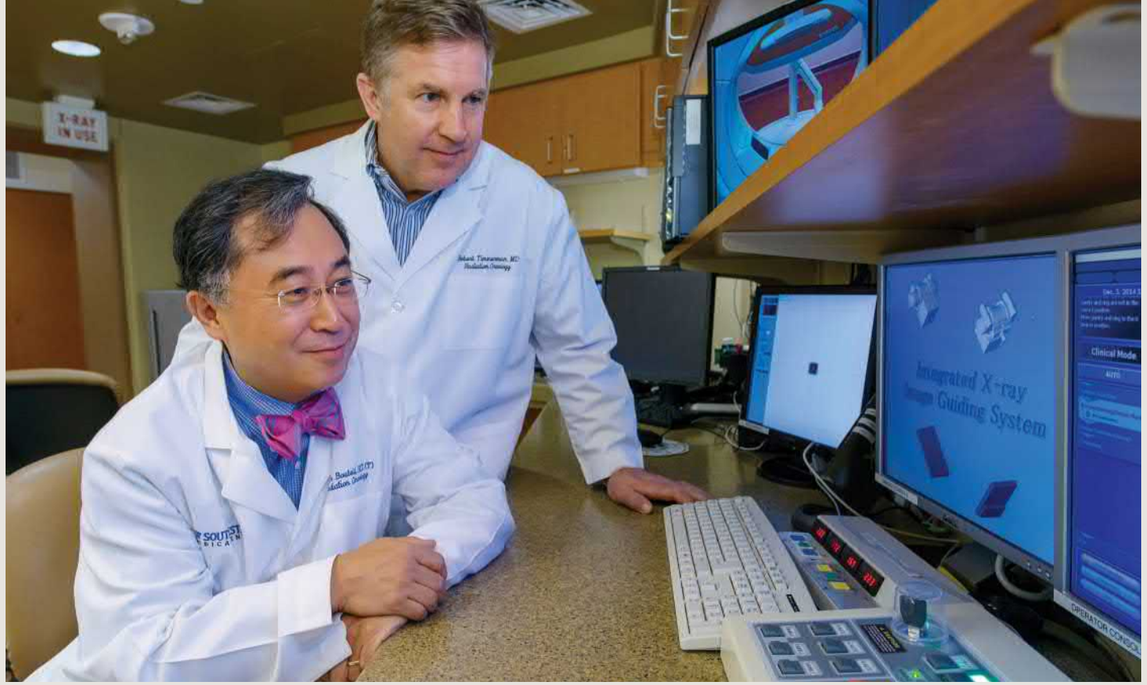
Investigators hope that by prolonging each therapy before the next is started, patient life span will be extended, as ultimately the number of available therapies is limited. (Straka et al., *J Clin Oncol,* 2013; Zhang et al., *Int J Radiat Oncol Biol Phys,* 2019)

The late Dr. Eugene P. Frenkel (left), an internationally recognized cancer researcher, clinician, and educator, pioneered UT Southwestern Medical Center's Hematology and Oncology Division. He is pictured here conferring with his colleagues Drs. Arriaga, Sagalowsky, and Hammers.

MEET RENÉE MCKAY, PH.D., DIRECTOR OF RESEARCH ADMINISTRATION

Renée McKay, Ph.D., has been with the Kidney Cancer Program from the beginning, joining the program in September of 2013, three months before its inauguration by Mayor Rawlings. Her first major task: assisting with the Kidney SPORE grant application. The SPORE was the culmination of many months of work and the combined effort of many investigators. Aside from helping to oversee and coordinate the SPORE grant, Dr. McKay does many other things. As the Director of Research Administration, Dr. McKay assists Dr. Brugarolas with manuscripts; coordinates and helps review applications for funding; organizes conferences and Advisory Board meetings; and manages the lab and Kidney Cancer Program websites, and even the Facebook page! "Renée is the mainstay of our program – she keeps the program running," says Dr. Brugarolas. "I love being part of such a great team of smart and committed people," says Dr. McKay. "It has been very rewarding to see the program grow, and the progress made toward finding better treatments for kidney cancer patients. One highlight has been getting to know our Patient Advocates, some of whom are dealing with the disease themselves. Their selfless dedication to helping other patients as they deal with their own difficult journey is so inspiring."

"I love being part of such a great team of smart and committed people."



Dr. Robert Timmerman (right), a pioneer of stereotactic radiation, with Radiation Oncology Department Chair Dr. Hak Choy.

A Global Leader in Stereotactic Radiotherapy

UT Southwestern's Radiation Oncology Program is a world leader in the use of SBRT for kidney cancer. The Kidney Cancer Program has pioneered the use of SBRT for tumor thrombi as well as for oligoprogression. Beyond conventional uses for bone and brain metastasis, SBRT is being deployed for:

- Small renal masses: tumors that measure about 1.5 inches or less (NCT02141919) (see page 30)
- Tumor thrombi: tumor extensions in the vena cava (NCT02473536) (see page 32)
- Oligometastasis: tumors that have spread to one or a few sites, but not widely (NCT02956798) (see page 34)
- Oligoprogression: metastatic cancers that are mostly stable but progressing at one or a few sites (NCT03696277) (see page 51)
- Metastatic cancer in combination with immunotherapies to prime the immune system for an attack (NCT03065179) (see page 47)

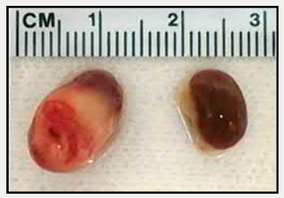
No other program around the world has such a developed repertoire of clinical trials of SBRT for kidney cancer.

The UT Southwestern team recently published its experience with avant-garde stereotactic radiation for kidney cancer – the largest in the world. This involved 175 metastases beyond conventional brain metastases. Analyses as far as two years out found that radiation effectively stopped the growth of the metastases. (Straka et al., *J Clin Oncol,* 2013; Hannan et al., *Cancer Biol Ther,* 2015; Wang et al., *Int J Radiat Oncol Biol Phys,* 2017; Zhang et al., *Int J Radiat Oncol Biol Phys*, 2019; Freifeld et al., *Kidney Cancer*, 2019)

HOW CAN RADIORESISTANCE BE CONQUERED?

With support from the Kidney Cancer Program and SPORE, scientist Benjamin Chen, Ph.D., is studying why some renal tumors are resistant to radiation. Dr. Chen's lab has leveraged the tumorgraft platform (see page 67) to study how human kidney cancer responds to radiation.

Using this platform, his lab is able to evaluate how different kidney tumors respond to doses of radiation comparable to those administered to patients using SBRT. Through the identification of sensitivity and resistance markers, Dr. Chen hopes to better tailor radiation to tumors.



Tumors from patients growing in mouse kidneys, such as the one on the left (see normal kidney on the right), are used by the Chen lab to study radiation response.

Brain neurosurgeon Dr. Bruce Mickey uses a microscope to identify and remove cancer cells that have traveled to the brain and formed metastases.

Treating Cancer at the Destination

Adept UT Southwestern teams navigate intricate procedures.

Treatment of kidney cancer in the brain, bones, or lungs requires special expertise. At Simmons Comprehensive Cancer Center, an array of skilled physicians works closely with patients to ensure optimal patient care and outcomes.

While metastases to the brain have traditionally been regarded as infrequent (generally seen as occurring in about 10 percent of cancer cases), UT Southwestern investigators have found that 20 to 30 percent of patients will develop brain metastases over the course of their disease.

Drs. Bruce Mickey and Toral Patel are part of a team of neurosurgeons who treat more patients with brain tumors than any other institution in North Texas. The surgical team regularly employs computer-assisted neuronavigation and advanced approaches, such as awake craniotomy with brain mapping to identify and protect critical language, visual, and motor regions of the brain. The team carefully strategizes to minimize injury to healthy brain tissue, using minimally invasive procedures, such as laser interstitial thermocoagulation.

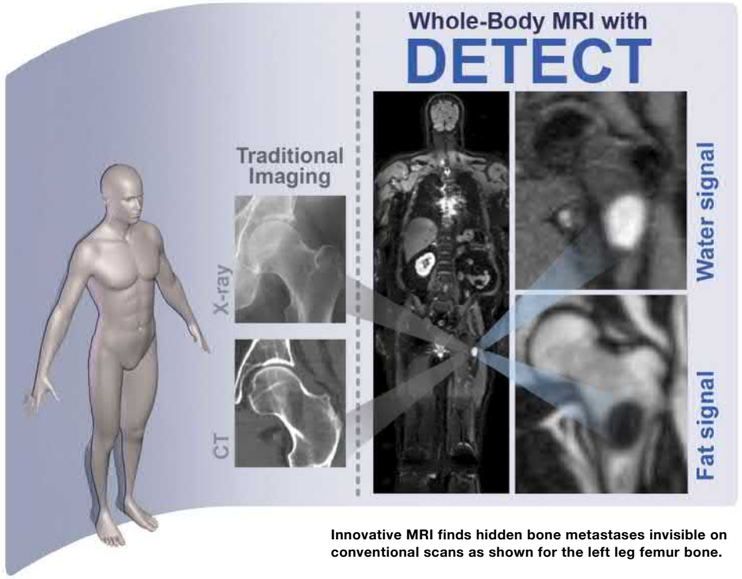
When metastases are multiple, neurosurgeons work closely with radiation oncologists such as Dr. Robert Timmerman to determine the optimal time to perform open surgery or use radiation. The team utilizes highly advanced technologies such as the Gamma Knife® Icon for radiation, the only cancer treatment center in North Texas to do so.

This cutting-edge care is improving survival rates for patients whose kidney cancer has spread to the brain.

Recently, investigators reported their experience in the treatment of 56 patients diagnosed with brain metastases at UTSW early on in the course of their cancer (at presentation or during their first drug treatment). They found that stereotactic radiosurgery effectively treated the brain metastases with control rates over 85 percent at two years. In some patients, as many as 26 brain metastases were radiated in one session. Importantly, life expectancy was increased from a few months (historically) to over 19 months in those patients presenting with brain metastases.

As such, UT Southwestern kidney cancer experts generally recommend aggressive care of patients with brain metastases. Results such as these likely

Dr. Alex Bowman, who completed his fellowship training in oncology and kidney cancer at UT Southwestern, where he was chief fellow, was a first author in a report reviewing how the Kidney Cancer Program cares for patients with brain metastases.



Innovative MRI finds hidden bone metastases invisible on conventional scans as shown for the left leg femur bone.

contribute to the improved survival rates of stage 4 kidney cancer patients at the Kidney Cancer Program, which are triple the national benchmarks (see page 10). (Bowman et al., *Clin Genitourin Cancer,* 2019; Wardak et al., *Clin Genitourin Cancer,* 2019)

When Bones Are the Destination

Renal cancer commonly spreads to bone. Approximately a third of patients will develop bone metastases. When this happens, the cancer can destroy the bone, leading to pain and sometimes spontaneous fractures. Early detection is imperative.

Expert spine surgeon Dr. Carlos Bagley performing a complex procedure.

"When metastases are advanced and threaten the integrity of the bone, stabilization may be required," says Dr. Alexandra Callan, an oncology orthopedic surgeon who trained at MD Anderson Cancer Center.

Metastases are particularly problematic when they occur in the spine, where bone collapse may cause paralysis. At UT Southwestern, Drs. Carlos Bagley and Kevin Morrill and their colleagues in both neurosurgery and orthopedics regularly treat complex spinal column metastases. These surgeries require careful planning and often materials to reconstruct the spinal column.

During these procedures, neurosurgeons and orthopedic surgeons work closely with radiation oncologists.

SBRT, a field in which UT Southwestern is an international leader (see page 52), can also offer an alternative.

Innovative MRI Finds Hidden Bone Metastases

A new MRI (magnetic resonance imaging) protocol developed by UT Southwestern's Dr. Ananth Madhuranthakam promises to improve the detection of bone metastases anywhere in the body. It takes just seven minutes, less time than traditional MRI.

The protocol, dubbed DETECT (dual-echo T2-weighted acquisition for enhanced conspicuity of tumors), was tested on a handful of kidney cancer patients. DETECT identified 30 percent more bone metastases, all missed using conventional techniques. Using this protocol, bone metastases could be detected earlier, reducing risk of bone fractures and other complications. With SPORE funding, a larger clinical trial is ongoing. (Wang et al., *Magn Reson Med,* 2018)

Challenge: Why Does Kidney Cancer Travel to Bone?

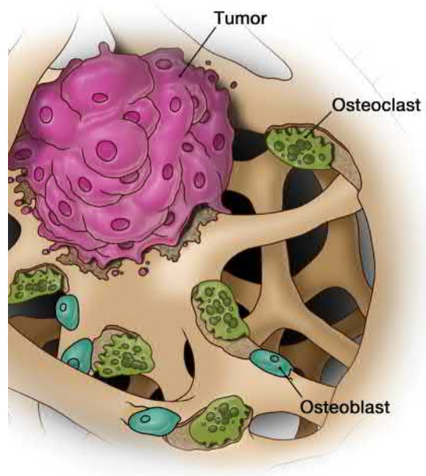
Molecular biologist Yihong Wan, Ph.D., studies the interplay between cancer and the microenvironment. With funds from the Kidney Cancer SPORE, she evaluates why some kidney cancers travel to bone. Her team has developed new approaches to study how kidney cancer cells relate to cells in the bone. These approaches allow her to study the interplay in both the laboratory and in live animals. The Wan team has also developed nanoparticles – tiny particles that can travel through the blood – to deliver a form of gene therapy (a microRNA-34a mimic) to sites of bone metastases.

FIRST TO DEVELOP TOOLS FOR KIDNEY CANCER

Dr. Ananth Madhuranthakam and his team, including Drs. Joseph Maldjian and Ivan Pedrosa, were awarded $3.1 million from the National Cancer Institute in 2017 to become one of 18 institutions in the Quantitative Imaging Network. This Network develops tools to measure response to cancer therapy. The UT Southwestern team is the only team in the Network focusing on kidney cancer.

Kidney Cancer in the Lungs

Lung is the most common site of metastases of kidney cancer, though less problematic than spread to the brain or bone. With state-of-the-art training and equipment, such as endobronchial ultrasound and electromagnetic navigational bronchoscopy, physicians in the Interventional Pulmonology Service, including Dr. Hsienchang Thomas Chiu and Dr. Muhanned Abu-Hijleh, perform advanced procedures to remove metastases that block airway passages. This is to stop bleeding (a life-threatening complication) and open the airways, thereby avoiding pneumonia.



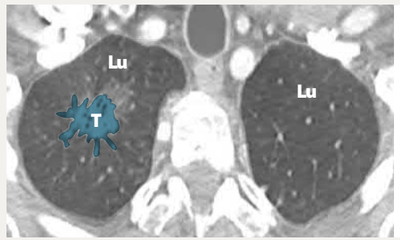
The interventional group works closely with UT Southwestern's thoracic surgeons. The team, which includes Drs. Alberto de Hoyos, Kemp Kernstine, and Scott Reznik, can remove isolated metastases to the lungs. In 85 percent of cases, metastases can be removed using minimally invasive approaches and simplified surgeries with rapid recovery times. The team performs more than 1,000 thoracoscopic or minimally invasive procedures in and around the lungs each year.

Dr. Kemp Kernstine uses minimally invasive approaches to remove isolated kidney cancer metastases from the lungs.

DISCOVERING ANOTHER DEADLY MALIGNANCY

Cancer in the lungs of kidney cancer patients most often represents kidney cancer that has traveled there. According to a recent report by Drs. Bowman and Brugarolas, this is not always the case.

The distinction is crucial. Kidney cancer spreads mainly to the lungs. But it tends to be less aggressive than primary lung cancer, which, if found, should be quickly addressed. Further, failing to establish this distinction can lead to prematurely stopping effective treatments for kidney cancer. Unknowingly, the growth of a tumor in the lung (while other sites may be responding) could be taken to indicate that kidney cancer is resistant to therapy, while in reality it may indicate that the tumor is lung cancer.



A CT scan shows an independent lung cancer tumor (T) in a patient with kidney cancer. (Lu), Lung.

Dr. Bowman reviewed 151 cases of metastatic kidney cancer treated with targeted drugs at Simmons Cancer Center from 2006–2013. More than half the patients had lung metastases, and 3.5 percent were later found to also have an independent lung cancer. Only four other reported cases were found in a review of the literature, which suggests that this is a problem often overlooked.

Imaging findings – such as the presence of irregular, poorly defined edges in the tumor – can help distinguish primary lung cancer from renal cell carcinoma metastases, says Dr. Pedrosa, radiology Co-Leader of the Kidney Cancer Program. The team estimates that as many as 6 percent of all kidney cancer patients with lung involvement may have a primary lung cancer. (Bowman et al., *Clin Genitourin Cancer,* 2017)

Fundraising to find a cure for kidney cancer in children and adolescents.

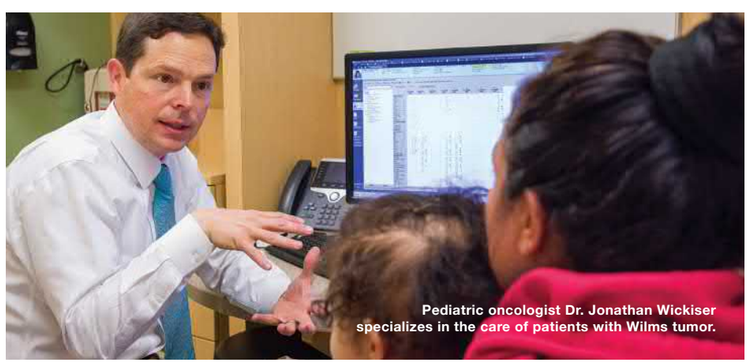
Pediatric Kidney Cancer

UT Southwestern physicians at Children's Health provide cutting-edge care for children with kidney cancers.

Treatment expertise can be vital in treating a rare cancer such as Wilms tumor, diagnosed in fewer than 50 Texas children a year. Many of those children receive treatment and follow-up care from UT Southwestern at the Gill Center for Cancer and Blood Disorders, at Children's Health in Dallas.

The Gill Center treats 1 in 5 children in Texas with cancer. The Center is part of the Children's Oncology Group, funded by the National Cancer Institute, and offers the latest treatments and clinical trials.

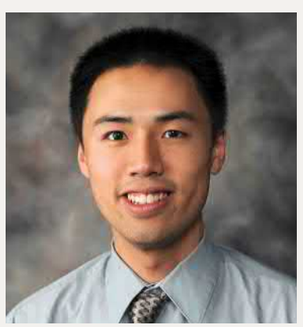
Wilms tumor – also known as nephroblastoma – is typically diagnosed in children ages 3 to 5. It is often not found until the cancer has grown quite large (several inches across) and is felt during a medical exam. Treatment requires a team approach with specialists from surgery, oncology, and radiation oncology. More than 80 percent of children are cured, but current treatments are associated with long-term debilitating effects, including scarring in the lungs, heart failure, and increased chances of leukemia. Additionally, if the cancer recurs it can be difficult to treat.



Pediatric oncologist Dr. Jonathan Wickiser specializes in the care of patients with Wilms tumor.

MEET KENNETH CHEN, M.D., CO-LEADER, PEDIATRICS

Dr. Kenneth Chen, Assistant Professor of Pediatrics, joined the Kidney Cancer Program leadership in 2019. A physician-scientist, he divides his time between his research laboratory and Children's Medical Center Dallas, where he specializes in the treatment and care of children with cancer and blood disorders.



HOW DOES p53 STOP CANCER?

An important gene in Wilms tumors is p53, the most commonly mutated gene across cancers.

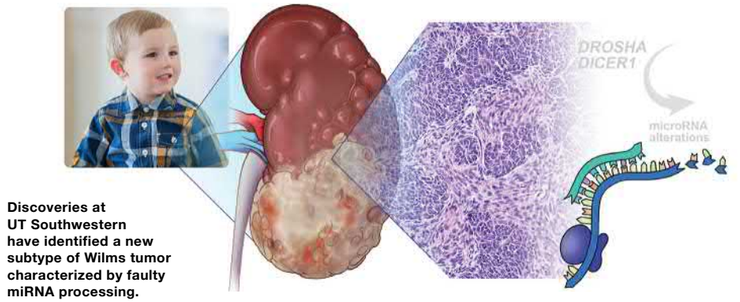
Traditionally, physicians have thought that p53 blocks cancer development by activating a cell suicide program when cells detect mutations or damage in their DNA instructions. However, a recent study led by cell biologist John Abrams, Ph.D., has challenged these assumptions.

Dr. Abrams' team has discovered that p53 prevents the reactivation of remnants from viruses integrated in the human genome. When activated, these segments, known as retrotransposons, can wreak havoc. They have the ability to move from one place in the genome to another, causing mutations. These findings, based on studying fruit flies and mice as well as human samples of Wilms and other tumors, help to explain why cancer genomes are prone to mutations. If validated, the findings will open radically new forms of cancer treatment, employing drugs normally used for viral infections, such as HIV. (Wylie et al., *Genes Dev,* 2016)

A p53 reporter (green) reveals p53 function associated with mobile element activity during meiosis. Nuclei are blue and cell boundaries are red.

Novel Type of Wilms Tumor Identified

Kidney Cancer Program investigators have identified a new subtype of Wilms tumor. The research team includes Drs. Dinesh Rakheja, Kenneth Chen, Joshua Mendell, and James Amatruda. Funded in part by CPRIT (Cancer Prevention and Research Institute of Texas), the team performed next-generation sequencing analyses on 44 Wilms tumors from patients at UT Southwestern. Investigators discovered several genes that were not previously implicated in the disease. Among them were two, DROSHA and DICER1, that control the cellular production of tiny molecules called microRNAs. These microRNAs fine-tune genetic instructions that direct the production of particular proteins.



Discoveries at UT Southwestern have identified a new subtype of Wilms tumor characterized by faulty miRNA processing.

With funding from the SPORE, investigators are seeking clues to determine how mutations in DROSHA and DICER1 affect cancer development. They have discovered that a family of microRNAs called let-7 was missing in tumors with the mutations. As a result, cells produced excessive quantities of proteins that promote cell proliferation.

These efforts are complemented by those of Dr. Keri Drake, a recipient of a career award from the SPORE. Dr. Drake is evaluating the role of another pathway, the beta-catenin pathway, which is activated in up to 50 percent of Wilms tumors.

Ongoing efforts are exploring how the different subtypes respond to therapy, with the goal of developing more tailored treatment approaches. (Rakheja, *Nat Commun,* 2014; Chen et al., *Genes Dev,* 2018)

Physician-scientist Dr. Amatruda (far left) partnered with molecular and RNA biologist Dr. Mendell (right) to show how mutations in DROSHA and DICER1 lead to Wilms tumors.

Kidney Cancer in Adolescents

Young runners fundraise in support of Joey's Wings (an organization dedicated to finding a cure for translocation carcinomas), which supports the Kidney Cancer Program at UT Southwestern.

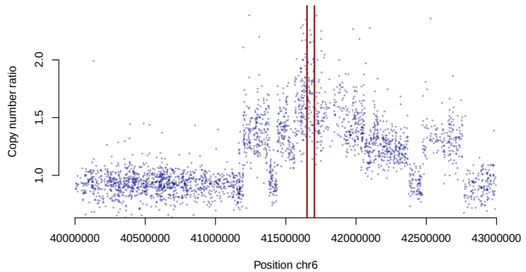
Adolescents are affected by an otherwise rare type of kidney cancer: translocation carcinomas. From the Latin "trans," meaning "across," as well as the English "location," the term refers to a kidney cancer characterized by the swapping of genetic information from one region of the genome to another. Typically, the information is exchanged between two different chromosomes. This results in the abnormal activation of a group of related genes referred to as the MITF family. The most prominent members of the family are TFE3 and TFEB.

Novel Types of 'Translocation' Carcinomas

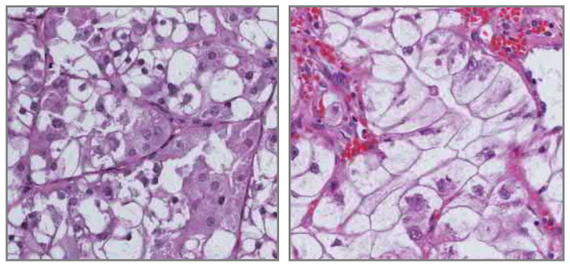
In 2015, UT Southwestern and Genentech® reported the first integrated genomic analysis of non-clear cell kidney tumors. The analysis studied 167 tumors from patients at UT Southwestern, including six translocation carcinomas. The Brugarolas and Seshagiri teams discovered that, like TFE3 and TFEB, the gene MITF (which gives its name to the family) was also translocated in renal cancer. They also found that genes in this family can be activated through a new mechanism: amplification. Amplification refers to an increase in the number of copies of a gene. These results have led UT Southwestern investigators to propose a change in the name of this entity to MITF family tumors. (Durinck et al., *Nat Genet*, 2015)

A Mouse Model Paves the Way for New Therapies

A major challenge in the field of translocation carcinomas has been the lack of an optimal model. Such a model would help unravel how MITF genes cause kidney cancer and would aid in the development of new therapies for this uncommon cancer that lacks treatment options. Propelled by funding from Joey's Wings, a nonprofit organization, the Brugarolas lab recently succeeded in developing such a mouse model. In 2018, the project was awarded a competitive $1.1 million grant from CPRIT (Cancer Prevention and Research Institute of Texas).



Plot showing a novel mechanism of TFEB activation involving gene amplification. Adapted from Durinck et al., *Nat Genet*, 2015.



tRCC (translocation renal cell carcinoma) that develops in a genetically engineered mouse model (left) looks like human tRCC (right).

Families with Kidney Cancer

Up to 5 percent of kidney cancers may be hereditary. Simmons Cancer Center offers a full suite of clinical genetics services.

Most kidney cancers are sporadic, meaning they occur randomly and for poorly understood reasons. But in some patients these cancers are transmitted from parents to offspring. This is typically due to the transmission of a mutated (faulty) gene in the sperm or the egg, a process referred to as germline transmission. Warning signs of hereditary cancer include:

- Young age (under 50)
- Cancer in both kidneys
- Multiple family members
- Kidney cancer types such as papillary or chromophobe

Cancer Genetics Services at Simmons Cancer Center

As North Texas' largest clinical cancer genetics program, Simmons Cancer Center sees more than 3,700 patients a year in more than 20 locations throughout DFW. In addition, the program is accessible through telemedicine to individuals who live in rural counties. Expansion to underserved populations throughout Texas is supported by a grant (over $6 million) from CPRIT.

With 13 board-certified cancer genetic counselors, the program has assisted more than 3,000 patients with hereditary cancer syndromes. Family members are educated on risk of developing cancer and options for prevention, early detection, and treatment. For a referral, call 214-645-2563 or email cancergenetics@utsw.edu.

Hereditary Kidney Cancer Syndromes

Most familial cancer predisposing conditions are passed on to only 50 percent of the individual's offspring.

These syndromes include the following:

- von Hippel-Lindau (VHL) disease (gene: VHL) — while the VHL gene is commonly inactivated in non-familial kidney cancers, it can also be inactivated in the germline. Familial VHL syndrome is associated with clear cell RCC and renal cysts. Other tumors found in these patients include hemangioblastomas (brain, spinal cord, retina), pheochromocytomas (adrenal gland), endolymphatic sac tumors (inner ear), and neuroendocrine tumors of the pancreas.
- Hereditary papillary renal cancer (HPRCC) (gene: MET) is associated with type 1 papillary RCC.
- Birt-Hogg-Dubé (BHD) syndrome (gene: FLCN) is associated with oncocytic renal tumors and often chromophobe RCC. Other features include pulmonary cysts, spontaneous pneumothorax (air buildup between the lung and chest wall), and skin lesions.
- Hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome (gene: FH) involves type 2 papillary RCC. Other tumors include benign smooth muscle tumors in the skin and uterus (fibroids).
- Lynch syndrome (genes: MLH1, MSH2, MSH6, PMS2, EPCAM) is associated with cancer of the renal pelvis. Other tumors may include those in the colon, uterus, and ovaries.
- Cowden syndrome (gene: PTEN) confers an increased risk of RCC. These patients develop tumors in the breast, thyroid, and uterus. Other features include macrocephaly (large head) and mucocutaneous lesions (where skin meets mucous membranes).
- SDH-associated renal cancer (genes: SDHB, SDHC, SDHD, SDHA) is associated with clear cell RCC. Other

tumors may include paragangliomas and pheochromocytomas (adrenal gland).
- Tuberous sclerosis complex (genes: TSC1, TSC2) presents an increased risk for RCC. Other tumors include angiomyolipomas (kidney) and benign brain tumors (subependymal giant cell astrocytomas). Additional features include skin and nail lesions, kidney cysts, and lung abnormalities.

Holistic Care

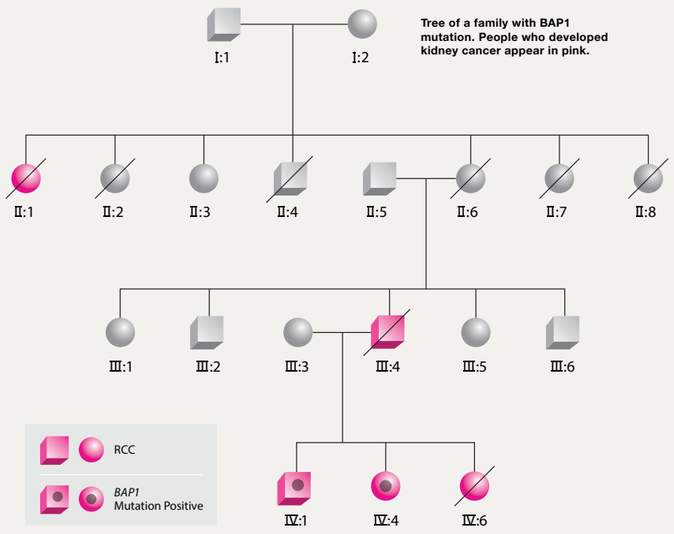
Designated by the VHL Alliance as a Clinical Care Center, UT Southwestern provides holistic care to patients with familial kidney cancer syndromes such as VHL, HPRCC, BHD, and HLRCC.

A NEW HEREDITARY KIDNEY CANCER SYNDROME

While many familial kidney cancers are accounted for by the genes aforementioned, the gene remains unknown in some families. Dr. Brugarolas and colleagues, after discovering that the BAP1 gene is mutated in sporadic (non-hereditary) clear cell RCC (see page 40), asked whether BAP1 mutations could also account for cases of familial kidney cancer.

Previously, BAP1 mutations had been discovered in the germline and found to be associated with skin and eye cancer (melanoma), cancer of the lung outer lining (mesothelioma), and other cancers including kidney cancer. Whether they could account for cases of familial kidney cancer where there were no other features was unknown.

In a collaboration including the National Cancer Institute, Cleveland Clinic, and UT Health Science Center San Antonio, UT Southwestern investigators sequenced BAP1 in individuals from 83 families in a study partly funded by CPRIT (Cancer Prevention and Research Institute of Texas). These individuals had a predisposition to kidney cancer that could not be explained by well-established genes. Investigators identified one family whose members with kidney cancer had defective BAP1. Today, testing for the gene is performed routinely in families with a hereditary risk of kidney cancer. (Farley et al., *Mol Cancer Res,* 2013)



Partners in International Collaboration

The Kidney Cancer Program collaborates with scientists worldwide.

Teaming with dozens of institutions with robust kidney cancer programs around the world, the Kidney Cancer Program is helping reshape medicine's understanding of the disease. The partnership is called the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) and is led by Dr. Daniel Heng (University of Calgary) and Dr. Toni Choueiri (Dana-Farber Cancer Institute).

The consortium's database houses demographic, pathologic, laboratory, and treatment information on more than 6,000 patients. UT Southwestern has contributed data on more than 350 patients with metastatic RCC.

Collectively, the information has resulted in more than 50 scientific publications. Researchers have pinpointed factors associated with prognosis, evaluated how different sequences of treatments affect outcomes, and provided information about how treatments developed for ccRCC impact less frequent tumor types (such as nccRCC).

UT Southwestern scientists have co-authored several publications under the consortium umbrella, including papers characterizing metastatic papillary RCC, and honing prognostic accuracy and drug selection for patients beginning second-line therapy. (Wells et al., *Cancer Med,* 2017; De Velasco et al., *Clin Genitourin Cancer,* 2017; Davis et al., *Eur Urol,* 2017; Wells et al., *Eur Urol,* 2017)

SOME COUNTRIES REPRESENTED IN THE IMDC

AUSTRALIA · BELGIUM · CANADA · DENMARK · GREECE · ITALY
JAPAN · POLAND · SINGAPORE · SOUTH KOREA · SPAIN · UNITED STATES

Clinical Trials

With numerous clinical trials, the Kidney Cancer Program offers patients the latest treatments currently under development. The Kidney Cancer Program is a standard-bearer in testing new approaches, including cutting-edge radiotherapy and immunotherapy, making new progress against the disease. For example, the phase 3 clinical trials leading to the FDA approval of both nivolumab and the combination of nivolumab and ipilimumab were opened at the Kidney Cancer Program. This gave UT Southwestern patients access to these medications before they were commercialized for kidney cancer.

Clinical trials are vetted by an expert panel that includes Dr. Courtney, Disease-Oriented Team oncology leader, Dr. Hammers, Co-Leader for Clinical Research of the Kidney Cancer Program, and Dr. Brugarolas. Together, they ensure that only trials perceived to have a high likelihood of helping patients open at UT Southwestern. In addition, the most challenging kidney cancer cases are reviewed by a group of experts (see page 33) to determine which treatments are most likely to benefit a specific patient. Access to new therapies, along with expert multidisciplinary care, contribute to survival rates for UT Southwestern patients that exceed national averages (see page 10).

UT Southwestern is just one of 30 sites nationwide receiving federal funding as a National Clinical Trials Network Lead Academic Participating Site – a hub for clinical cancer research, especially for large, multi-institution trials sponsored by national cooperative groups.

In addition, UT Southwestern, in partnership with MD Anderson Cancer Center (lead), Cleveland Clinic, and Beth Israel Deaconess/Harvard Cancer Center, received a $1 million award from the Congressionally directed Kidney Cancer Research Program to establish a National Clinical Trials Consortium.

Learn More About Our Clinical Trials

For an updated list of our clinical trials, please visit www.utsouthwestern.edu/departments/kidney-cancer/clinical-trials

Biomarkers/Imaging

Prognostic Significance of Circulating Tumor Cells in Patients with RCC
Principal Investigator:
Vitaly Margulis, M.D.
Contact: Allison Beaver, RN
Phone: 214-645-8787
Email: Allison.Beaver@utsw.edu

89Zr-DFO-Atezolizumab ImmunoPET/CT in Patients with Locally Advanced or Metastatic RCC
ID: NCT04006522
Principal Investigator:
Isaac Bowman, M.D.
Contact: Kelli Key
Phone: 214-648-8152
Email: Kelli.Key@utsw.edu

Advanced MR Imaging in the Characterization of RCC: Correlation with Pathology and Gene Expression Profiles
Principal Investigator:
Ivan Pedrosa, M.D., Ph.D.
Contact: Michael Fulkerson
Phone: 214-648-5984
Email: Michael.Fulkerson@utsw.edu

Multiparametric MRI in T1b-T4 Renal Masses
Principal Investigator:
Ivan Pedrosa, M.D., Ph.D.
Contact: Michael Fulkerson
Phone: 214-648-5984
Email: Michael.Fulkerson@utsw.edu

A Prospective Comparison of Whole-body Magnetic Resonance Imaging, Sodium Fluoride Positron Emission Tomography, and Whole-body Bone Scintigraphy for Diagnosis of RCC Osseous Metastases
Principal Investigator:
Ivan Pedrosa, M.D., Ph.D.
Contact: Sydney Haldeman
Phone: 214-648-5478
Email: Sydney.Haldeman@utsw.edu

Localized RCC

Success of Active Surveillance in Patients with Untreated Small Renal Masses with the Option of Delayed Treatment
Principal Investigator:
Vitaly Margulis, M.D.
Contact: Allison Beaver, RN
Phone: 214-645-8787
Email: Allison.Beaver@utsw.edu

A Phase II Trial of Stereotactic Ablative Body Radiation Therapy (SABR) for Patients with Primary RCC
ID: NCT02141919
Principal Investigator:
Raquibul Hannan, M.D., Ph.D.
Contact: Samantha Mannala
Phone: 214-648-1873
Email: Samantha.Mannala@utsw.edu

Safety Lead-in Phase II Trial of Neo-Adjuvant SABR for IVC Tumor Thrombi in Newly Diagnosed RCC
ID: NCT02473536
Principal Investigator:
Raquibul Hannan, M.D., Ph.D.
Contact: Samantha Mannala
Phone: 214-648-1873
Email: Samantha.Mannala@utsw.edu

Neoadjuvant

A Phase III Randomized Study Comparing Perioperative Nivolumab vs. Observation in Patients with Localized RCC Undergoing Nephrectomy (PROSPER)
ID: NCT03055013
Principal Investigator:
Vitaly Margulis, M.D.
Contact: Allison Beaver, RN
Phone: 214-645-8787
Email: Allison.Beaver@utsw.edu

Adjuvant

A Phase III Multicenter, Randomized, Placebo-Controlled, Double-Blind Study of Atezolizumab (anti-PD-L1 antibody) as Adjuvant Therapy in Patients with RCC at High Risk of Developing Metastasis Following Nephrectomy
ID: NCT03024996
Principal Investigator:
James Brugarolas, M.D., Ph.D.
Contact: Dendra Von Merveldt, RN
Phone: 214-648-8787
Email: Dendra.Vonmerveldt@utsw.edu

A Phase III Randomized, Double-Blind, Placebo-Controlled Trial of Pembrolizumab in Adjuvant RCC
ID: NCT03142334
Principal Investigator:
Hans Hammers, M.D., Ph.D.
Contact: Allison Beaver, RN
Phone: 214-645-8787
Email: Allison.Beaver@utsw.edu

Advanced RCC – No Prior Treatment

A Phase II Trial of Stereotactic Body Radiation Therapy in Combination with Nivolumab plus Ipilimumab in Patients with Metastatic RCC
ID: NCT03065179
Principal Investigator:
Hans Hammers, M.D., Ph.D.
Contact: Allison Beaver, RN
Phone: 214-645-8787
Email: Allison.Beaver@utsw.edu

A Phase II Study of Front-Line Therapy with Nivolumab and Salvage Nivolumab plus Ipilimumab in Patients with Advanced RCC
ID: NCT03117309
Principal Investigator:
Hans Hammers, M.D., Ph.D.
Contact: Allison Beaver, RN
Phone: 214-645-8787
Email: Allison.Beaver@utsw.edu

Immunotherapy with Nivolumab and Ipilimumab Followed by Nivolumab or Nivolumab with Cabozantinib for Patients with Advanced Kidney Cancer, The PDIGREE Study
ID: NCT03793166
Principal Investigator:
Suzanne Cole, M.D.
Contact: Ashley Turk
Phone: 972-669-7044
Email: Ashley.Turk@utsw.edu

Phase II Trial of SABR for Patients with Oligometastatic RCC
ID: NCT02956798
Principal Investigator:
Raquibul Hannan, M.D., Ph.D.
Contact: Samantha Mannala
Phone: 214-648-1873
Email: Samantha.Mannala@utsw.edu

Advanced RCC – Prior Treatment

Phase II Trial of Stereotactic Ablative Radiation Therapy (SAbR) for Oligoprogressive ccRCC
ID: NCT03696277
Principal Investigator:
Raquibul Hannan, M.D., Ph.D.
Contact: Samantha Mannala
Phone: 214-648-1873
Email: Samantha.Mannala@utsw.edu

A Phase I/II Study Exploring the Safety, Tolerability, and Efficacy of Pembrolizumab (MK-3475) in Combination with Epacadostat (INCB024360) in Subjects with Selected Cancers
ID: NCT02178722
Principal Investigator:
Aravind Sanjeevaiah, M.D.
Contact: Pamela Kurian, M.S.
Phone: 214-648-5874
Email: Pamela.Kurian@utsw.edu

A Phase II Study to Evaluate the Safety, Pharmacodynamics, and Efficacy of Entinostat in Combination with Nivolumab/Ipilimumab in Patients with RCC Previously Treated with Nivolumab/Ipilimumab
ID: NCT03552380
Principal Investigator:
Hans Hammers, M.D., Ph.D.
Contact: Mackenzie Tsang-Lee
Phone: 214-648-7001
Email: Mackenzie.Tsang-Lee@utsw.edu

A Phase II Randomized Trial of Radium-223 and Cabozantinib in Patients with Advanced RCC with Bone Metastasis
ID: NCT04071223
Principal Investigator:
Suzanne Cole, M.D.
Contact: Ashley Turk
Phone: 972-669-7044
Email: Ashley.Turk@utsw.edu

A Phase Ib Adaptive Dose-Finding Study of ARO-HIF2 in Patients with Advanced ccRCC
ID: NCT04169711
Principal Investigator:
James Brugarolas, M.D., Ph.D.
Contact: Tomi Fatunde
Phone: 214-648-4972
Email: Oluwatomilade.Fatunde@utsw.edu

Advanced RCC – Prior PD1/PDL1

A Phase I and II, Open-label, Multicenter, Dose Escalation and Dose Expansion Study of NKTR-262 in Combination with NKTR-214 and in Combination with NKTR-214 Plus Nivolumab in Patients with Locally Advanced or Metastatic Solid Tumor Malignancies
ID: NCT03435640
Principal Investigator:
James Brugarolas, M.D., Ph.D.
Contact: Tomi Fatunde
Phone: 214-648-4972
Email: Oluwatomilade.Fatunde@utsw.edu

Phase II BMS FRACTION Study to Test Combination Treatments
Principal Investigator:
Hans Hammers, M.D., Ph.D.
Contact: Allison Beaver, RN
Phone: 214-645-8787
Email: Allison.Beaver@utsw.edu

Phase I/Ib Study to Evaluate the Safety and Tolerability of CPI-444 Alone and in Combination With Atezolizumab in Advanced Cancers
ID: NCT02655822
Principal Investigator:
Kevin Courtney, M.D., Ph.D.
Contact: Nour Sukar
Phone: 214-648-5107
Email: Nour.Sukar@utsw.edu

Safety and Efficacy Study of IMSA101 in Refractory Malignancies
ID: NCT04020185
Principal Investigator:
Shaalan Beg, M.D.
Contact: Melissa Rodriguez
Phone: 214-648-6593
Email: Melissa.Rodriguez@utsw.edu

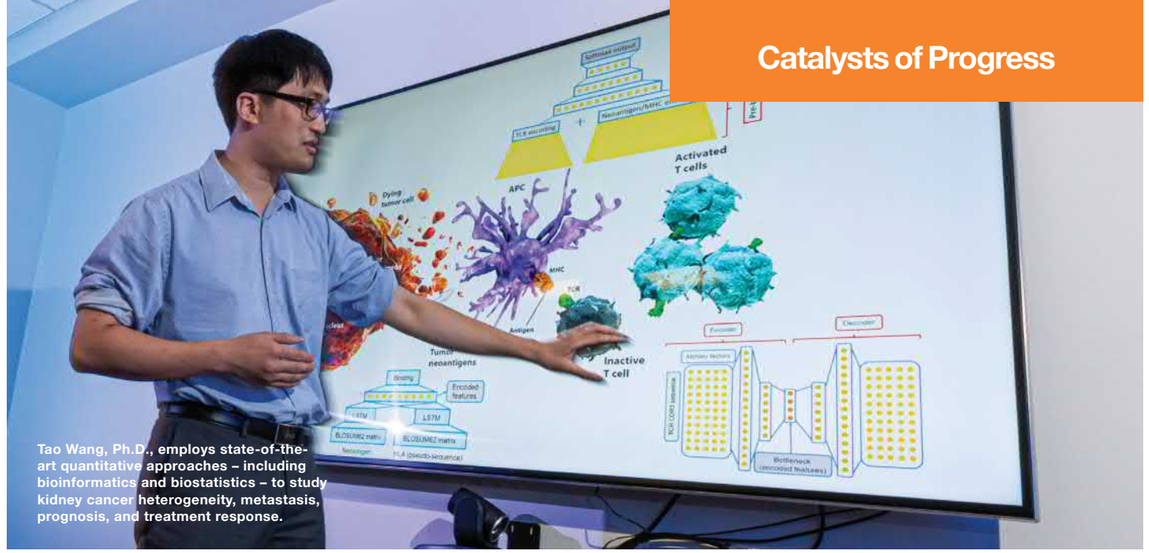
Dr. Payal Kapur, a national expert in kidney cancer, has pioneered a novel classification of kidney cancer.

Technology Driving Progress

Enabled by a partnership with our patients, the UT Southwestern Kidney Cancer Program is developing innovative technologies, infrastructure, and new approaches catalyzing progress.

Catalysts of Progress

Patients play a vital role in driving kidney cancer research forward.



Tao Wang, Ph.D., employs state-of-the-art quantitative approaches – including bioinformatics and biostatistics – to study kidney cancer heterogeneity, metastasis, prognosis, and treatment response.

Innovative Biobanking

Patients at UT Southwestern have supported seminal discoveries by donating tumor samples collected during surgery. For example, discoveries related to genes implicated in kidney cancer have set the foundation of a modern cancer classification (see page 40). These were all based on studies of cancer samples donated by patients.

The biobank is part of the Biospecimen and Pathology Core, a crucial component of the SPORE (see page 13). The biobank collects samples donated by patients undergoing surgery to support genomic analyses and an avatar program.

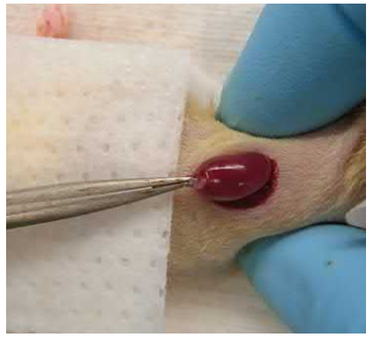
UT Southwestern has pioneered the largest program for the preservation of live tumor samples. Tumor samples are frozen in a way that maintains live cells. With more than 1,500 kidney cancers preserved live, the collection may be the largest in the world. Preserving cancer cells live allows scientists to examine questions that would otherwise not be possible; for example, how cells of the immune system interact with tumor cells.

Live biobank samples are preserved in liquid nitrogen tanks at -320 degrees F (-195 degrees C).

> **"Neither the genomics nor the biobank or the avatar program would have been possible without the strong support from our patients and the gift of their tumor samples for research."**
>
> **Jim Brugarolas, M.D., Ph.D., Director, Kidney Cancer Program**

The Largest 'Avatar' Program Worldwide?

Tumors from patients are transplanted into the kidney of immunocompromised mice. Under the microscope, these tumorgrafts maintain the mutations, gene activation pattern, and appearance of the parent tumor. In most cases, tumors in the mice are more similar to the patient tumor they came from than any two tumors from two different patients. As such, tumorgrafts can also provide personalized models of kidney cancer (avatars). More than 1,400 patient tumors have been transplanted into mice. This resource is likely the largest in the world.



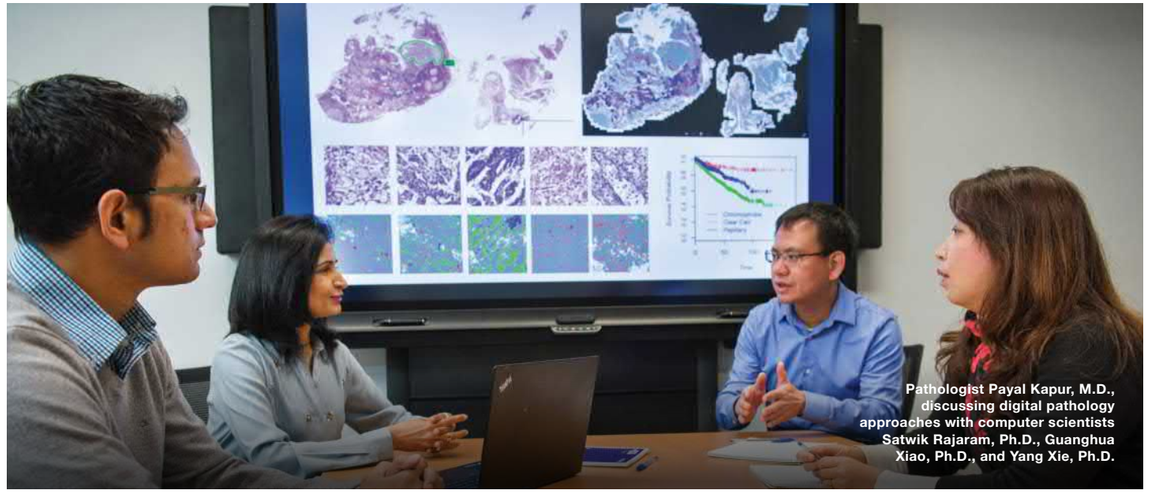
Patient tumors are transplanted into mice to generate avatars.

Importantly, these tumorgrafts also preserve kidney cancer's drug responsiveness. To evaluate this, scientists treated mice bearing tumors with drugs such as sunitinib. With help from the Pharmacokinetic Core Facility, dosing was adjusted to match blood levels in patients. Kidney cancer tumorgrafts responded to sunitinib and other drugs active against kidney cancer, but not against drugs previously shown to be inactive in patients with kidney cancer. These studies established a proof-of-principle for the use of tumorgrafts in programs to evaluate new drugs against kidney cancer in patients, such as PT2399 (see page 37). In addition, they have been used to test candidate drugs emerging from chemical screens;

GRADING SYSTEM

Tumors are classified by grade into more or less aggressive. Higher grades correspond to more aggressive tumors. The International Society of Urological Pathology grades ccRCC from 1 to 4. Grading is based on the appearance of the cell, and, in particular, of a component of the nucleus called the nucleolus. The nucleus is where the DNA and genetic infrastructure are stored. It is typically in the center of the cell. The nucleolus is a "spot" within the nucleus. The more prominent the nucleolus, the higher the grade. The nucleolus is necessary for protein manufacturing in cells. Tumors with sarcomatoid features are considered grade 4.

With support of the SPORE, Maralice Conacci-Sorrell, Ph.D., a cell biologist, is investigating the underpinnings of nuclear grade.

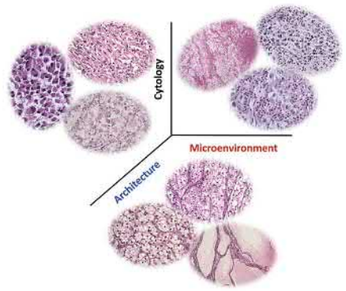


Today, kidney cancer diagnosis is still made by pathologists who look at tissue under a microscope. Researchers at UT Southwestern have developed a novel classification of renal cancer based on gene mutations (see page 40). "Instead of judging a book by its cover, you can actually read what's inside," says Dr. Kapur, lead pathologist of the Kidney Cancer Program.

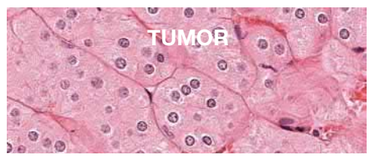
to evaluate the process whereby tumors become resistant to drugs; to develop new radiology tests for kidney cancer (see page 28); to understand the mutations that cause kidney cancer (see page 40); to study how kidney cancer invades and metastasizes (see page 54); and to understand what nutrients kidney cancers use (see page 29). (Sivanand et al., *Sci Transl Med,* 2012; Peña-Llopis et al., *Nat Genet,* 2012; Pavía-Jiménez et al., *Nat Protoc,* 2014; Wolff et al., *Oncotarget,* 2015; Chen et al., *Nature,* 2016; Wang et al., *Cancer Discov,* 2018; Courtney et al., *Cell Metab*, 2018)

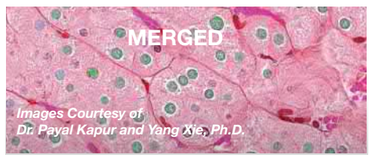
Morphologic Evolutionary Trajectories Underpinning Tumor Growth

Kidney cancer is classified into different types, including most commonly clear cell renal cell carcinoma (ccRCC). However, much like colors, which have infinite shades, no two ccRCCs are identical under the microscope. The complexity of trying to make sense of subtle morphological differences likely accounts for the lack of progress. How does one make sense of a tapestry with millions of cells? This daunting task was tackled by Dr. Payal Kapur. She first defined three different parameters (or axes) to classify tumors: cells, architecture, and borders. She then compiled all of the variants. On the whole, she arrived at 33 descriptors. She and her team then cataloged over 500 tumors according to the 33 variables. By studying how these descriptors relate to each other within a tumor and how they impact tumor aggressiveness and patient prognosis, she unraveled the logic behind the tapestry and provided novel insights into how these patterns evolve over time. Her studies provide an innovative framework to understand kidney cancer. (Cai et al., *EBioMedicine,* 2019)



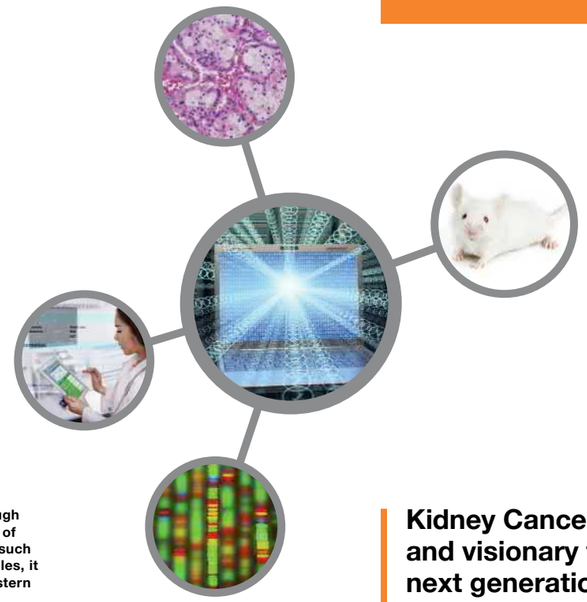
Foundation for novel classification of ccRCC by Dr. Kapur based on 33 descriptors across three axes.





A computer algorithm recognizes different cell types in a tumor.

Red Blood Cell **Support Cell**
Tumor Cell



Kidney Cancer Explorer, accessible through a central web portal, links multiple types of information, both medical and research (such as genomics). By providing links to samples, it enables further research by UT Southwestern investigators.

Kidney Cancer Explorer is a unique and visionary tool to support the next generation of research on kidney cancer.

Artificial Intelligence

A 21st-Century Medical Intelligence Platform

Over the last five years, a team led by Dr. Kapur and including Venkat Malladi and Alana Christie has developed a medical intelligence platform that includes data from over 3,000 patients linked to genomics and sample availability. This platform, referred to simply as KCE (Kidney Cancer Explorer), provides a centralized access point for all kidney cancer research at UT Southwestern. The resource was developed with the Department of Bioinformatics, led by Gaudenz Danuser, Ph.D., and the Quantitative Biomedical Research Center, led by Yang Xie, Ph.D. Funding was provided by the SPORE and CPRIT (Cancer Prevention and Research Institute of Texas).

KCE is a complex informatics system that integrates many types of information: demographic and other general patient characteristics (such as age of diagnosis, gender, height, and weight), comprehensive pathological information (such as tumor stage, histology, and grade), patterns of tumor spread, treatment information (type of surgery, radiation, and drug treatments), longitudinal metrics (such as weight, blood laboratory tests), and research data including next-generation sequencing (which is available for more than 1,500 samples) and our tumor bank.

KCE is accessible through a password-protected web-based interface. By automatically running preset queries on the electronic health record, KCE self-updates and stays permanently current.

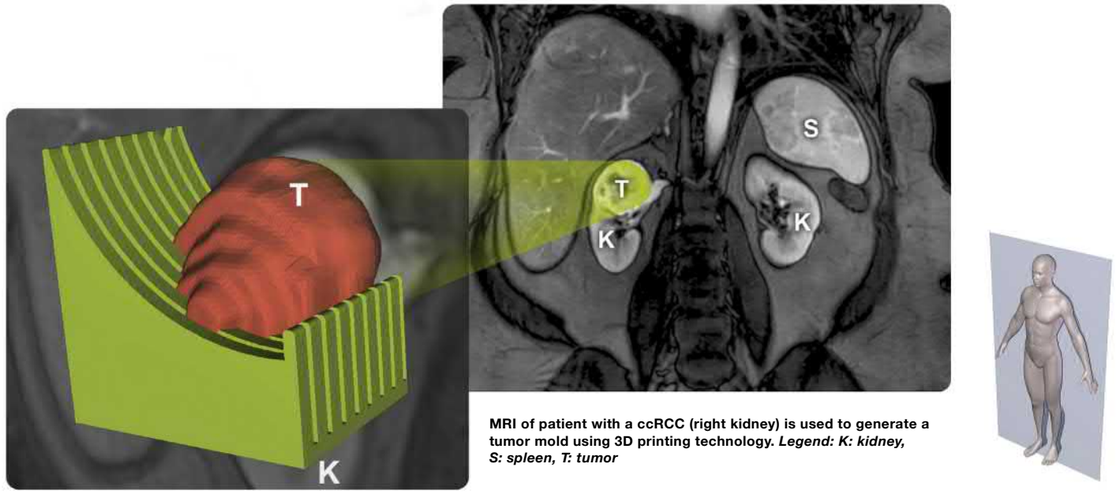
KCE enables a wide variety of analytic functions across the different types of information: clinical, pathological, and genomic. Investigators can ask questions about how genomics or pathological features impact outcomes or treatment responsiveness. The platform is fertile ground for artificial intelligence and machine-learning approaches. Investigator capabilities are further expanded through access to genomic datasets (such as whole exome sequencing and RNA sequencing).

KCE can also be used by healthcare providers, who are able to determine what research data or samples are available for patients they care for.

"KCE is a unique and visionary tool to support the next generation of research on kidney cancer," says Dr. Brugarolas.

Building the Future with Artificial Intelligence and Machine Learning

One application of AI (artificial intelligence) being explored in the Kidney Cancer Program is digital pathology. AI is analyzing tumor samples to understand how cancers develop and how they relate to their environment. Several scientists at UT Southwestern are working on this problem, including Satwik Rajaram, Ph.D., Guanghua Xiao, Ph.D., and Yang Xie, Ph.D., together with pathologist Dr. Payal Kapur. The platform could revolutionize how tumors are defined. With a virtually infinite range of tissue properties that might be captured, AI is set to improve how tumors are classified. Such capability is particularly relevant to tumor behavior driven by interactions with its environment, a feature that only recently is beginning to be explored (see page 49).



MRI of patient with a ccRCC (right kidney) is used to generate a tumor mold using 3D printing technology. ***Legend: K: kidney, S: spleen, T: tumor***

Radiogenomics

An Imaging SPORE Core Facility develops novel imaging technologies to visualize renal tumors. The Core draws from multiple modalities, including MRI (magnetic resonance imaging) and PET (positron emission tomography). It takes advantage of unique capabilities at UT Southwestern, including a team of expert physicists, radiochemists, and imaging specialists.

Novel techniques are expanding the role of current tests to include assessments of tumor aggressiveness, heterogeneity, metabolism (see page 29), and blood flow. These approaches provide new insights in tumor biology and how different interventions (i.e., treatments) affect it.

A distinctive platform using 3D-printed molds of renal tumors was developed by Dr. Pedrosa, Director of the Core, to learn how physical properties of the tumor affect how the tumor is visualized. This process allows "vertical" integration of imaging features and pathology. Overlaid on this architecture are innovative genomic analyses led by Tao Wang, Ph.D., using next-generation sequencing technologies to identify genomic determinants of variation (radiogenomics).

Using a cyclotron, the Core develops tracers to inform on the biology and properties of tumors. Virtually any molecule can be labeled using the cyclotron and turned into a tracer. Recent examples include the labeling of glucose and acetate to evaluate how tumors nurture themselves (see page 29). Another example is the labeling of atezolizumab to measure the expression of PD-L1, a cell surface protein that turns the immune system off (see page 48).

In addition, the Core also supports routine monitoring of tumors in mouse models with MRI and PET systems designed for these tasks. (Zhang et al., *JCI Insight,* 2017; Zhang et al., *Clin Genitourin Cancer,* 2016; Dwivedi et al., *Urology*, 2018)

MEET ALANA CHRISTIE, M.S., BIOSTATISTICS CO-LEADER

With an M.S. in biostatistics from the University of Oklahoma, Alana Christie – a Dallas born and raised professional – has become a cornerstone of the Kidney Cancer Program. Alana oversees all aspects, from data extraction to analyses to experimental design. She plays critical roles in Kidney Cancer Explorer and nearly every research project from the program.

This year, more than 73,000 people will join the nearly half-a-million individuals currently living with a diagnosis of kidney cancer in the U.S. That's 200 new battles every day; 200 lives forever changed.

Since the founding of the Kidney Cancer Program in 2013, the treatment of this disease entered a new era at UT Southwestern Medical Center, where clinicians work together to provide the most technically advanced surgery, radiation, and oncology treatment options with compassionate care. These same specialists partner with scientists focused on unraveling the biology of kidney cancer. Through these partnerships and discoveries, the Kidney Cancer Program is fueling breakthroughs.

And the results are telling. Our survival rates are better than the national averages, most notably for stage 4 cancer, where our five-year survival rates are triple the national benchmark. A shared vision for excellence underlies the success of the Kidney Cancer Program, along with an overarching commitment to our patients, who are the *raison d'être* for everything we do. It is their passion for life, courage, and resilience that inspires our program.

Seven years ago, we were the new kid on the block, compared to similar programs at our peer institutions. But because of our relative youth and flexibility, we developed a culture of collaboration and teamwork, drawing on the strengths of the most creative thinkers within UT Southwestern and beyond. In striving for our own definition of greatness, we've become a place of enterprising agility. The kind of place that is pioneering genetic discoveries, breaking ground in biobanking and artificial intelligence, and developing first-in-class drugs. We are harnessing the strengths of UT Southwestern's Nobel Prize-winning faculty and acclaimed research facilities and combining it with 21st-century problem solving skills.

In the process, our work is being recognized: the Specialized Program of Research Excellence Award in 2016 by the National Cancer Institute, a UT Southwestern Leaders in Clinical Excellence Program Development Award in 2019, and the Innovation in Healthcare Finalist Award by *D Magazine* and *D CEO* in 2020.

The war on kidney cancer is not a single war. It is a series of heroic and exhausting battles fought day after day, one patient at a time, and every fight is different. In the words of one of our wonderful Patient Advocates, Merlinda Chelette, "We strive for our patients to feel known, understood, and cared for."

When patients come to us, we want them to know they have a team with them every step of the way. That they are not alone. For me, helping to build and lead this award-winning program has been a privilege and an honor.

James Brugarolas

James Brugarolas, M.D., Ph.D.
Director, Kidney Cancer Program
Sherry Wigley Crow Endowed Chair in Cancer Research
Professor, Internal Medicine/Hematology-Oncology
Cancer Biology, Genetics, Development and Disease
Simmons Comprehensive Cancer Center
University of Texas Southwestern Medical Center

Timeline

The success and prestige of UT Southwestern's Kidney Cancer Program did not happen overnight. Current breakthroughs have been the result of hard work decades in the making.

1980

Urological Surgeon Dr. Sagalowsky joins the Urology faculty of UT Southwestern.

1997

Drs. McKnight and Russell discover HIF-2α (hypoxia-inducible factor 2α, which they name EPAS1), arguably the most important driver of kidney cancer. (Tian et al., *Genes Dev*, 1997)

1998

Dr. Beutler reports the discovery of the LPS receptor, TLR4, a Toll-like receptor. (Poltorak, *Science*, 1998)

1999

Arriving from Johns Hopkins, Dr. Cadeddu joins the Urology faculty.

2001

Dr. Bruick reports the identification of a family of prolyl-4-hydroxylases that modify HIF. (Bruick and McKnight, *Science*, 2001)

Dr. Cadeddu reports on the first percutaneous kidney tumor (RFA) ablation in Texas. (Corwin and Cadeddu, *J Urol*, 2001; Gettman et al., *Urology*, 2001)

2002

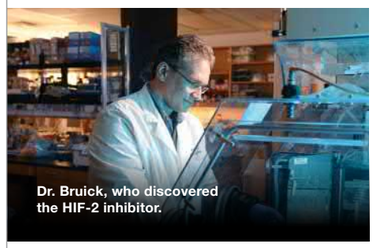
Dr. Bruick reports the discovery of an asparaginyl hydroxylase enzyme that regulates HIF. (Lando et al., *Genes Dev*, 2002)

Dr. Deisenhofer publishes the atomic structure of the asparaginyl hydroxylase enzyme. (Dann et al., *PNAS*, 2002)

Dr. Pan reports that the TSC proteins antagonize mTOR signaling. (Gao et al., *Nat Cell Biol*, 2002)

2003

Drs. Bruick and Gardner report the structural basis for HIF heterodimerization. (Erbel et al., *PNAS*, 2003)



Dr. Bruick, who discovered the HIF-2 inhibitor.

Dr. Garcia reports the generation of HIF-2α deficient mice. (Scortegagna et al., *Nat Genet*, 2003)

Dr. Pan reports that mTOR regulation by the TSC proteins involves RHEB. (Zhang et al., *Nat Cell Biol*, 2003)

2006

Dr. Brugarolas is recruited from the Dana-Farber Cancer Institute/Harvard Cancer Center to UT Southwestern.

Dr. Kapur joins the faculty in the Pathology Department.

Dr. Lotan reports on the efficacy of ablative high-dose-per-fraction radiation in a preclinical model of RCC. (Walsh et al., *Eur Eurol,* 2006)

2007

Dr. Cadeddu reports on the first single incision (transumbilical) laparoscopic nephrectomy in the world. (Raman et al., *Urology*, 2007)

2009

After a fellowship at MD Anderson Cancer Center, Dr. Margulis joins the Urology faculty.

Drs. Bruick and Gardner report the identification of a small molecule that inhibits HIF-2. (Scheuermann et al., *PNAS*, 2009)

Dr. Garcia reports the regulation of HIF by the deacetylase sirtuin 1. (Dioum et al., *Science*, 2009)

Dr. Sagalowsky is elected to the American Association of Genitourinary Surgeons.

2010

Dr. Brugarolas reports on the potential utility of mTORC1 inhibitors for an orphan disease, epithelioid angiomyolipoma. (Wolff et al., *J Clin Oncol*, 2010)

2011

Dr. Pedrosa is recruited to UT Southwestern from the Beth Israel Deaconess/Harvard Cancer Center.

After completing his radiation oncology residency at Albert Einstein College of Medicine, Dr. Hannan joins the faculty at UT Southwestern.

Dr. Pedrosa becomes a member of the Renal Task Force of the Genitourinary Cancer Steering Committee of the National Cancer Institute.

Dr. Brugarolas' group reports the identification of mutations in TSC1 in ccRCC and their potential value in predicting responsiveness to drugs blocking mTOR such as temsirolimus. (Kucejova et al., *Mol Cancer Res*, 2011)

Dr. Brugarolas' group reports the identification of a novel mTORC1 effector, the TFEB transcription factor, which is implicated in translocation carcinomas. (Peña-Llopis et al., *EMBO J*, 2011)

Dr. DeBerardinis et al. team up to treat the first patient with an FH-deficient RCC with a glycolytic inhibitor, 2DG. (Yamasaki et al., *Nat Rev Urol*, 2011)

Dr. Bruce Beutler, along with Jules A. Hoffman, is awarded the Nobel Prize in Physiology or Medicine for their discoveries on activation of the innate immune system.

Dr. Beutler receiving the Nobel Prize.

2012

Arriving from the Dana-Farber Cancer Institute/Harvard Cancer Center, Dr. Courtney joins the faculty of UT Southwestern in Medical Oncology.

Dr. Brugarolas' team reports the identification of BAP1 mutations in ccRCC. (Peña-Llopis et al., *Nat Genet*, 2012)

Dr. Cadeddu reports on the long-term results of renal tumor ablation and shows that results are comparable to partial nephrectomy. (Best et al., *J Urol*, 2012)

Drs. Kapur and Brugarolas report the development of possibly the largest kidney cancer tumorgraft platform, which will become a cornerstone of the SPORE. (Sivanand et al., *Sci Transl Med*, 2012)

2013

Dr. Yan reports that TREX acts as a regulator of lysosomal biogenesis and has a role in interferon-independent activation of antiviral genes. (Hasan et al., *Nat Immunol*, 2013)

Dr. Zhijian "James" Chen reports the identification of cGAS as an innate immune sensor. (Gao et al., *Science*, 2013; Sun et al., *Science*, 2013)

Drs. Bruick and Gardner report the results of a high-throughput screen of the UT Southwestern chemical library leading to the identification of drug-like molecules that block HIF-2. (Scheuermann et al., *Nat Chem Biol, 2013*)

Dr. Cadeddu is elected to the American Association of Genitourinary Surgeons.

Drs. Kapur and Brugarolas report that BAP1 and PBRM1 define distinct subtypes of ccRCC. (Kapur et al., *Lancet Oncol*, 2013)

In collaboration with the National Cancer Institute and several other institutions, a team led by Dr. Brugarolas reports a novel kidney cancer familial syndrome resulting from germline mutation in BAP1. (Farley et al., *Mol Cancer Res*, 2013)

Dr. Brugarolas' group reports that whereas mutations in BAP1 and PBRM1 seem to antagonize each other, SETD2 mutations cooperate with PBRM1 mutations in ccRCC. (Peña-Llopis et al., *Cancer Res*, 2013)

Drs. Timmerman and Brugarolas introduce the concept of SBRT for oligoprogression in kidney cancer. (Straka et al., *J Clin Oncol*, 2013)

Mayor Rawlings inaugurates the Kidney Cancer Program.


Dallas Mayor Mike Rawlings and Dr. Brugarolas at inauguration event.

2014

Drs. Rakheja, Mendell, and Amatruda report the identification of mutations in DROSHA and DICER1 in Wilms tumors. (Rakheja et al., *Nat Commun*, 2014)

Dr. Brugarolas reports the first genetically engineered mouse model reproducing the mutations of human ccRCC. (Wang et al., *PNAS*, 2014)

2015

In collaboration with Genentech®, Drs. Kapur and Brugarolas report the first integrated analysis of non-clear cell renal carcinoma subtypes. (Durinck et al., *Nat Genet*, 2015)

Dr. Cadeddu reports the first experience with irreversible electroporation for percutaneous ablation of kidney tumors. (Trimmer et al., *J Vasc Interv Radiol*, 2015)

Medical Oncologist Dr. Lohrey is recruited to UT Southwestern as Medical Director of the Harold C. Simmons Comprehensive Cancer Center at the Moncrief Cancer Institute in Fort Worth.

Drs. Hannan, Brugarolas, and Timmerman publish the first report of SBRT (stereotactic body radiation therapy) for tumor thrombi. (Hannan et al., *Cancer Biol Ther*, 2015)

UT Southwestern and Texas Health Resources commit to integrating operations to provide affordable, high-quality care for kidney cancer and other patients.

Dr. Zhijian "James" Chen reports on a shared signaling mechanism employed by the innate immune system. (Liu et al., *Science*, 2015)

2016

Dr. Hammers, an immunotherapy thought leader, joins the Kidney Cancer Program from Johns Hopkins as a Co-Leader for Clinical Research. He is the inaugural recipient of the Eugene P. Frenkel Endowed Scholar Award.

Dr. Margulis reports on a 15-year experience with surgery for tumor thrombi. (Gayed et al., *BMC Urol*, 2016)

In a team effort led by Dr. Brugarolas, the program becomes the second program in the U.S. to receive a prestigious $11 million Specialized Program of Research Excellence (SPORE) award from the National Cancer Institute.


NCI SPORE winning team.

Drs. Brugarolas, Kapur, Hammers, and Hannan become members of the Renal Task Force of the Genitourinary Cancer Steering Committee of the National Cancer Institute.

The Kidney Cancer Program and SPORE awards pilot grants ranging from $25,000 to $40,000 to Drs. Carroll, Benjamin Chen, Mason, Wan, and Zhang.

Drs. Kapur and Brugarolas validate HIF-2 as a target in ccRCC. (Chen et al., *Nature*, 2016)

Dr. Cadeddu reports that histologic subtype influences results of percutaneous radiofrequency ablation. (Lay et al., *J Urol*, 2016)

In collaboration with Mayo Clinic, Drs. Kapur and Brugarolas report that ccRCC can be divided into four subtypes according to BAP1 and PBRM1 status with marked differences in patient survival. (Joseph et al., *J Urol*, 2016)

Patients Tony Towler and Merlinda Chelette initiate advocacy program.

2017

Dr. Bowman joins the faculty in Medical Oncology, after finishing his fellowship in Hematology/Oncology and serving as chief fellow at UT Southwestern.

Dr. Zhijian "James" Chen reports that cGAS is required for the antitumor effect of immune checkpoint inhibitors. (Wang et al., *PNAS*, 2017)

Drs. Bowman and Brugarolas report that a primary lung cancer may be identified in more than 5 percent of patients with metastatic kidney cancer. (Bowman et al., *Clin Genitourin Cancer*, 2017)

Patient Advocates supported by the Kidney Cancer Coalition organize first fundraising event at Dallas Country Club, raising over $100,000.

Dr. Hannan reports UT Southwestern experience with SBRT for metastatic renal cancer, the largest worldwide. (Wang et al., *Int J Radiat Oncol Biol Phys*, 2017)

Patient Advocate Tony Towler is nominated Volunteer of the Year by the Dallas-Fort Worth Hospital Council.

Dr. Hammers publishes a landmark clinical trial (NCT01472081) showing a doubling of response rates with combination immunotherapy with ipilimumab plus nivolumab. (Hammers et al., *J Clin Oncol*, 2017)

The program and SPORE awards pilot grants ranging from $25,000 to $40,000 to Drs. Banaszynski, Cadeddu, Chuo Chen, Hammers, Hao, Hsieh, Wan, and Wang.

Drs. Kapur and Brugarolas report the development of mouse models of the two most common types of kidney cancer, and show that BAP1 and PBRM1 control kidney cancer aggressiveness. (Gu et al., *Cancer Discov*, 2017)

Dr. Madhuranthakam is awarded a prestigious National Institutes of Health U01 grant focusing on developing a radiology test to monitor treatment response in renal and other cancers.

Dr. Zhijian "James" Chen reports a novel STING-activating nanovaccine to boost antitumor immunity in cancer immunotherapy. (Luo et al., *Nat Nanotechnol*, 2017)

Dr. Cadeddu serves as a panel member of the American Urological Association Management of Small Renal Mass Guidelines.

With funds raised through Joey's Wings, Kathy Liu provides $100,000 to support research on translocation carcinomas. The award leads to the development of a mouse model and successful competition for a $1.1 million award from Cancer Prevention and Research Institute of Texas (PI, Brugarolas).

Dr. DeBerardinis is awarded an NCI Outstanding Investigator Award.

Patient Advocate Merlinda Chelette, with support from the Kidney Cancer Coalition, organizes a golf tournament fundraiser at the Cowboys Golf Club, raising over $25,000.

The Kidney Cancer Program hosts the first retreat for trainees, and awards prizes to Dr. Ali Pirasteh and medical student Daniel Li for their research.

Dr. Brugarolas is appointed inaugural chair of the programmatic panel of the newly established Congressionally directed Kidney Cancer Research Program.

Drs. Pedrosa and Cadeddu report a new multiparametric MRI approach with high sensitivity and specificity for the detection of ccRCC, which may reduce the need for biopsies. (Canvasser et al., *J Urol*, 2017)

The Urology Department begins providing care at John Peter Smith Hospital, a 573-bed county hospital in Fort Worth, ensuring that Tarrant County residents get state-of-the-art urologic care.

The Health System Office of Quality Improvement performs a study of kidney cancer patient outcomes, showing improved survival rates across stages, including rates that are double national benchmarks for stage 4 patients.

2018

Dr. Courtney reports the results of a phase 1 clinical trial of a first-in-class HIF-2 inhibitor (PT2385) developed by Peloton Therapeutics, Inc. in the UT Southwestern BioCenter, showing excellent tolerability and activity in extensively pretreated patients. (Courtney et al., *J Clin Oncol*, 2018)

With support from the Kidney Cancer Coalition, Patient Advocates Merlinda Chelette and Brenda Stinson organize the second Dallas Country Club fundraising event, raising $100,000.

Dr. Hannan reports the UT Southwestern experience combining immune checkpoint inhibitors and SBRT. (Mohamad et al., *Oncoimmunology*, 2018)


Dallas Morning News journalist and reporter Robert Wilonsky discusses his battle with kidney cancer at the KCP Annual Event.

The program and SPORE awards $25,000 in pilot grants to Drs. Ariizumi, Diaz de Leon, Drake, Grishin, Huen, Jiang, Koh, Malladi, Mani, Rethorst, and Wang.

Dr. Hammers, one of three co-principal investigators, reports the results of CheckMate-214, a phase 3 clinical trial of ipilimumab/nivolumab, heralding the most important FDA approval for kidney cancer. (Motzer et al., *N Engl J Med*, 2018)

The American Urological Association selects for presentation at the Plenary Session of its Annual Meeting an abstract from UT Southwestern's groundbreaking clinical trial (NCT02473536) incorporating stereotactic radiation for kidney cancer tumor thrombi prior to surgery, led by Drs. Hannan and Margulis.

Dr. DeBerardinis is appointed investigator of the Howard Hughes Medical Institute.

Dr. Banaszynski is a funding recipient of the first national Kidney Cancer Research Program.

UT Southwestern is ranked world's No. 1 academic medical center for published research in the healthcare area by *Nature Index*.

UT Southwestern is recognized by the VHL Alliance as a VHL Clinical Care Center.

Dr. Zhijian "James" Chen reports on the mechanism by which droplet-size microreactors form when cGAS, a critical sensor that activates innate immunity, encounters pathogenic DNA. (Du and Chen, *Science*, 2018)

UT Southwestern is selected as one of four institutions to receive a national Consortium Development Award from the Congressionally directed Kidney Cancer Research Program.

Drs. Chen, Amatruda, and Mendell report molecular insights into the development of Wilms tumors by DROSHA and DICER1 mutations. (Chen et al., *Genes Dev*, 2018; Hunter et al., *Genes Dev*, 2018)

Dr. Suzanne Cole is recruited to UT Southwestern as Director of the University Hospital Simmons Cancer Clinic at the UT Southwestern Medical Center in Richardson/Plano, Texas.

Drs. Wang and Brugarolas report the first empirical approach using tumorgrafts to dissect the tumor microenvironment. (Wang et al., *Cancer Discov*, 2018)

Dr. Madhuranthakam develops a whole-body MRI protocol that improves the detection of bone metastases by 30 percent. (Wang et al., *Magn Reson Med*, 2018)

Dr. Timmerman receives ASTRO Fellow designation.

Drs. Courtney and DeBerardinis report the results of the first radioactively labeled nutrient studies in humans to understand how kidney cancer grows. (Courtney et al., *Cell Metab*, 2018)

Dr. Zhijian "James" Chen reports on the role of NLRP3 in activating the inflammasome during the innate immune response. (Chen and Chen, *Nature*, 2018)

Dr. Cadeddu receives the 2018 Patricia and William L. Watson Award for Excellence in Clinical Medicine.

Drs. Chintalapati and Cai and medical student Jonathan Schoenhals receive prizes at the Second Annual Kidney Cancer Program retreat.

2019

Drs. Bowman, Wardak, Brugarolas and Timmerman report on the treatment of patients with brain metastases, with outcomes approaching those of patients without brain metastases. (Bowman et al., *Clin Genitourin Cancer*, 2019; Wardak et al., *Clin Genitourin Cancer*, 2019)

Dr. Koh is the inaugural recipient of the KCP/SPORE yearlong grant funding opportunity for his proposal to study the role of the microbiome in the response to immunotherapy.

The Health System Office of Quality Improvement releases an updated report of outcomes of kidney cancer patients compared to national benchmarks, showing improved survival across stages with rates that are triple national benchmarks for stage 4 patients.

The KCP and SPORE awards pilot grants ranging from $20,000 to $40,000 to Drs. Artunduaga, Conacci-Sorrell, D'Orso, Garant, and Patel.

Dr. Cadeddu first reports 10-year outcomes of radiofrequency ablation, establishing its role in primary tumor management. (Johnson et al., *J Urol*, 2019)

Drs. Timmerman, Hannan, and Brugarolas report innovative use of stereotactic ablative radiotherapy to effectively treat oligometastatic disease and delay need for systemic drug therapy. (Zhang et al., *Int. J Radiat Oncol Biol Phys*, 2019)

UT Southwestern is ranked world's No. 2 academic medical center for published research in healthcare area by *Nature Index*.

Drs. Bowman, Sun and Brugarolas receive V Foundation Award to develop immunoPET test to predict immunotherapy responsiveness and report their experience in preclinical models. (Vento et al., *J Immunother Cancer*, 2019)

Dr. Zhijian "James" Chen reports the near-atomic structure of STING. (Shang et al., *Nature*, 2019)

Dr. Zhijian "James" Chen, Professor and Member of the National Academy of Sciences, receives the Breakthrough Prize in Life Sciences for his discoveries about the innate immune system.

Dr. Zhijian "James" Chen receiving Breakthrough Prize.
(© Steve Jennings/Getty Images)

Dr. Kenneth Chen, Assistant Professor of Pediatrics, joins the Kidney Cancer Program leadership team.

The Kidney Cancer Program is the recipient of the Leaders in Clinical Excellence Program Development Award recognizing UT Southwestern faculty and staff for innovations that advance patient care.

Dr. DeBerardinis receives the 2019 Edith and Peter O'Donnell Award from The Academy of Medicine, Engineering and Science of Texas (TAMEST).

2020

Drs. Courtney, Pedrosa, and Brugarolas report the identification of resistance mutations in patients participating in the HIF-2α clinical trials, establishing HIF-2α as the first known core dependency of RCC. (Courtney et al., *Clin Cancer Res*, 2020)

Dr. Kapur reports on a detailed classification of ccRCC based on 33 parameters she identified. (Cai et al., *EBioMedicine*, 2020)

The Kidney Cancer Program is named a finalist for the Innovation in Healthcare award as part of *D Magazine* and *D CEO*'s inaugural Innovation Awards, recognizing companies, entrepreneurs, and business leaders who are redefining their industries.

Directory

Director

James Brugarolas, M.D., Ph.D.

Co-Leaders

Biostatistics
Alana Christie, M.S.

Clinical Research
Hans Hammers, M.D., Ph.D.

Education
Roy Elias, M.D.

Epidemiology
Bijal Balasubramanian, M.B.B.S., Ph.D.

Metabolism
Ralph DeBerardinis, M.D., Ph.D.

Pathology
Payal Kapur, M.D.

Pediatrics
Kenneth Chen, M.D.

Radiation Oncology
Raquibul Hannan, M.D., Ph.D.

Radiology
Ivan Pedrosa, M.D., Ph.D.

Urology
Jeffrey Cadeddu, M.D.

Administration

Director, Research Administration
Renée McKay, Ph.D.

Director of Communications
Michelle Parish

Senior Administrative Assistant
Deborah Harvey

Kidney Cancer Experts

ADULT UROLOGY
Aditya Bagrodia, M.D.
Jeffrey Cadeddu, M.D.
Jeffrey Gahan, M.D.
Ryan Hutchinson, M.D.
Yair Lotan, M.D.
Vitaly Margulis, M.D.
Ganesh Raj, M.D., Ph.D.
Arthur Sagalowsky, M.D.

MEDICAL ONCOLOGY
Waddah Arafat, M.D.
Isaac Bowman, M.D.
James Brugarolas, M.D., Ph.D.
Kevin Courtney, M.D., Ph.D.
Hans Hammers, M.D., Ph.D.
Aravind Sanjeevaiah, M.D.

MEDICAL ONCOLOGY (SATELLITE FACILITIES)
Suzanne Cole, M.D.
John Lohrey, M.D.

RADIATION ONCOLOGY
Tu Dan, M.D.
Neil Desai, M.D.
Michael Folkert, M.D., Ph.D.
Aurelie Garant, M.D.
Raquibul Hannan, M.D., Ph.D.
Lucien Nedzi, M.D.
Robert Timmerman, M.D.
Zabihullah Wardak, M.D.

PEDIATRIC ONCOLOGY
Kenneth Chen, M.D.
Jonathan Wickiser, M.D.

PEDIATRIC UROLOGY
Linda Baker, M.D.
Micah Jacobs, M.D.
Bruce Schlomer, M.D.

RADIOLOGY
Alberto Diaz de Leon, M.D.
John Leyendecker, M.D.
Ivan Pedrosa, M.D., Ph.D.
Lori Watumull, M.D.

PATHOLOGY
Liwei Jia, M.D., Ph.D.
Payal Kapur, M.D.
Dinesh Rakheja, M.D.
Rajal Shah, M.D.

CLINICAL GENETICS
Remington Fenter, M.S., C.G.C.
Amber Gemmell, M.S., C.G.C.
Brian Reys, M.S., C.G.C.

CLINICAL RESEARCH COORDINATORS
Allison Beaver, R.N.
Christina Carrigan, R.N.
Renee Davis, R.N.
Dendra von Merveldt, R.N.
Jess Ramos, M.H.A.
Mackenzie Tsang-Lee, R.N.

Patient Council

Carole Baas, Ph.D.
Larry Carlson
William Marx
Sophia Moschos
Brenda Stinson
Anthony Towler
Jürgen von Hövell

Business Advisory Committee

Andy Geisse
Bill Huber
Frank Stinson

Scientific Advisory Board

Dror Michaelson, M.D., Ph.D. (Chair)
Massachusetts General Hospital

E. Jason Abel, M.D., F.A.C.S.
University of Wisconsin School of Medicine and Public Health

Daniel George, M.D.
Duke University Medical Center

William Oh, M.D.
Mount Sinai School of Medicine

Mark Ratain, M.D.
University of Chicago Medical School

Brian Rini, M.D.
Vanderbilt-Ingram Cancer Center

Yu Shyr, Ph.D.
Vanderbilt-Ingram Cancer Center

M. Celeste Simon, Ph.D.
University of Pennsylvania Medical School

Research Tracks and Investigators

BIOINFORMATICS AND MACHINE LEARNING
Gaudenz Danuser, Ph.D.
Nick Grishin, Ph.D.
Lisa Kinch, Ph.D.
Bo Li, Ph.D.
Venkat Malladi, M.S.
Jimin Pei, Ph.D.
Satwik Rajaram, Ph.D.
Tao Wang, Ph.D.
Guanghua (Andy) Xiao, Ph.D.
Yang Xie, Ph.D.
He Zhang, Ph.D.

BIOMARKERS
Payal Kapur, M.D.
Dinesh Rakheja, M.D.

CLINICAL SCIENCES
Bijal Balasubramanian, M.B.B.S., Ph.D.
Simon Lee, Ph.D.
Sandi Pruitt, Ph.D.
Celette Skinner, Ph.D.
Jasmin Tiro, Ph.D.

DEVELOPMENT
Thomas Carroll, Ph.D.
Kenneth Chen, M.D.
Ondine Cleaver, Ph.D.
Ivan D'Orso, Ph.D.
Keri Drake, M.D.
Jin Jiang, Ph.D.
Christopher Lu, M.D.
Denise Marciano, M.D., Ph.D.

DRUG DISCOVERY
Chuo Chen, Ph.D.
David Corey, Ph.D.
J. Falck, Ph.D.
Steven McKnight, Ph.D.
Bruce Posner, Ph.D.
Joseph Ready, Ph.D.
Michael Roth, Ph.D.
Uttam Tambar, Ph.D.
Noelle Williams, Ph.D.
Yonghao Yu, Ph.D.

EPIGENETICS
Laura Banaszynski, Ph.D.
Cheng-Ming Chiang, Ph.D.
William Kraus, Ph.D.
Xin Liu, Ph.D.
Ram Mani, Ph.D.
Joshua Mendell, M.D., Ph.D.
Jose Rizo-Rey, Ph.D.
Hao Zhu, Ph.D.

GENOMICS
James Brugarolas, M.D., Ph.D.
Chao Xing, Ph.D.

HIF/VHL
Weibo Luo, Ph.D.
Wanpen Vongpatanasin, M.D.

IMAGING
Alberto Diaz de León, M.D.
David Fetzer, M.D.
Guiyang Hao, Ph.D.
Kenneth Hoyt, Ph.D.
Ananth Madhuranthakam, Ph.D.
Ralph Mason, Ph.D.
Ivan Pedrosa, M.D., Ph.D.
Fangyu Peng, M.D., Ph.D.
Rathan Subramaniam, M.D.
Xiankai Sun, Ph.D.
Jing Wang, Ph.D.
Takeshi Yokoo, M.D., Ph.D.
Qing Yuan, Ph.D.

IMMUNOLOGY
Esra Akbay, Ph.D.
Kiyoshi Ariizumi, Ph.D.
Bruce Beutler, M.D.
Zhijian "James" Chen, Ph.D.
Mingyi Chen, M.D., Ph.D.
David Farrar, Ph.D.
Beatriz Fontoura, Ph.D.
Yang-Xin Fu, M.D., Ph.D.
Hans Hammers, M.D., Ph.D.
Wen Jiang, M.D., Ph.D.
Nan Yan, Ph.D.

METABOLISM
Shawn Burgess, Ph.D.
Kevin Courtney, M.D., Ph.D.
Ralph DeBerardinis, M.D., Ph.D.
Sarah Huen, M.D., Ph.D.

Craig Malloy, M.D.
Dean Sherry, Ph.D.
Benjamin Tu, Ph.D.
Jin Ye, Ph.D.

MICROBIOME
Lora Hooper, Ph.D.
Andrew Koh, M.D.
Sebastian Winter, Ph.D.
Hasan Zaki, Ph.D.

mTOR
Jenna Jewel, Ph.D.
Peter Michaely, Ph.D.

QUANTITATIVE RESEARCH
Song Zhang, Ph.D.
Hong Zhu, Ph.D.

RADIATION BIOLOGY
Benjamin Chen, Ph.D.
Raquibul Hannan, M.D., Ph.D.

SIGNALING/METASTASIS
John Abrams, Ph.D.
Joseph Albanesi, Ph.D.
Rolf Brekken, Ph.D.
Maralice Conacci-Sorrell, Ph.D.
Jer-Tsong Hsieh, Ph.D.
Khuloud Jaqaman, Ph.D.
Srinivas Malladi, Ph.D.
Saikat Mukhopadhyay, M.D., Ph.D.
Duojia (D.J.) Pan, Ph.D.
Qing Zhang, Ph.D.

TECHNOLOGICAL INNOVATION
Jeffrey Cadeddu, M.D.
Vitaly Margulis, M.D.
Arthur Sagalowsky, M.D.

Collaborating Physicians*

CARDIOLOGY
Jarett Berry, M.D.
Katy Lonergan, M.D.
Shawna Nesbitt, M.D.
Angela Price, M.D.
Sharon Reimold, M.D.
Wanpen Vongpatanasin, M.D.
Vlad Zaha, M.D.

CARDIOTHORACIC SURGERY
Kemp Kernstine, M.D., Ph.D.
Michael A. Wait, M.D.

DENTISTRY
Dennis Abbott, D.D.S.

DERMATOLOGY
Arturo Dominguez, M.D.
Lu Le, M.D., Ph.D.
Travis Vandergriff, M.D.
Richard Wang, M.D., Ph.D.

DIAGNOSTIC RADIOLOGY
Lakshmi Ananthakrishnan, M.D.
Richard Batz, M.D.
Daniel Costa, M.D.
Theresa Huang, M.D.
Gaurav Khatri, M.D.
Dianne Mendelsohn, M.D.
Fangyu Peng, M.D., Ph.D.
Neil Rofsky, M.D.
Takeshi Yokoo, M.D., Ph.D.

ENDOCRINOLOGY
Jessica Abramowitz, M.D.
Marconi Abreu, M.D.
Zahid Ahmad, M.D.
Sadia Ali, M.D.
Oksana Hamidi, D.O.
Iram Hussain, M.D.
Asra Kermani, M.D.
Ildiko Lingvay, M.D.
Sasan Mirfakhraee, M.D.
Alex Tessnow, M.D.

GASTROENTEROLOGY
Nisa Kubiliun, M.D.
William Lee, M.D.
Roopa Vemulapalli, M.D.

GENERAL SURGERY
Farshid Araghizadeh, M.D.
John Mansour, M.D.
Ohwofiemu Nwariaku, M.D.
Craig Olson, M.D.

HEMATOLOGY
Cynthia Rutherford, M.D.
Yu-Min Shen, M.D.

INFECTIOUS DISEASES
James Luby, M.D.

INTERNAL MEDICINE
Carol Croft, M.D.
Emilia Thomas, M.D.

INTERVENTIONAL RADIOLOGY
Harold Park, M.D.
Abhinav Vij, M.D., M.P.H.
Dianbo Zhang, M.D.

MINERAL METABOLISM
Naim Maalouf, M.D.

NEPHROLOGY
Christopher Lu, M.D.
Orson Moe, M.D.
Ramesh Saxena, M.D., Ph.D.
Shani Shastri, M.D.
Robert Toto, M.D.
Peter Van Buren, M.D.
Miguel Vazquez, M.D.

NEUROSURGERY
Mazin Al Tamimi, M.D.
Carlos Bagley, M.D.
Bradley Lega, M.D.
Bruce Mickey, M.D.
Kevin Morrill, M.D.
Toral Patel, M.D.
Bryan Wohlfeld, M.D.

ORTHOPEDIC SURGERY
Alexandra Callan, M.D.
Adam Starr, M.D.

OTOLARYNGOLOGY
Andrew Day, M.D.
Barbara Schultz, M.D.

PATHOLOGY
Jyoti Balani, M.D.
Qi Cai, M.D., Ph.D.
Mingyi Chen, M.D., Ph.D.
Liwei Jia, M.D., Ph.D.
Elizabeth Kurian, M.D.
Elena Lucas, M.D.
Dinesh Rakheja, M.D.

PRIMARY CARE
Magda Hennes, M.D.
Manjula Julka, M.D.
Hugh McClung, M.D.

PSYCHOLOGY
Martin Deschner, Ph.D.
Brittany Hall, Ph.D.
Alice Holland, Ph.D.
Laura Howe-Martin, Ph.D.

PULMONOLOGY
Muhanned Abu-Hijleh, M.D.
Hsienchang Thomas Chiu, M.D.
Carlos Girod, M.D.
Corey Kershaw, M.D.

RHEUMATOLOGY
Bonnie Bermas, M.D.
Luigino Bernabela, M.D.
David Minna, M.D.

SUPPORTIVE AND PALLIATIVE CARE
Caitlin Siropaides, D.O.
Stephanie Terauchi, M.D.

*Open to all physicians at UTSW committed to providing superb care to patients in a team approach. For the most updated list, click here.

ACKNOWLEDGMENTS

The Kidney Cancer Program would like to thank everyone who helped put this report together and who has contributed to the program. This includes the doctors, researchers, staff, patients, and volunteers. There are too many to name individually, but please know that we appreciate everyone's efforts. At the Kidney Cancer Program, we strive for excellence and will continue to do so as we grow and remain cure committed. Thank you.

UT Southwestern
Simmons Cancer Center

utsouthwestern.edu/departments/kidney-cancer