CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Published Research Findings

A summary of research findings published by CPRIT grantees
September 1, 2021 – August 31, 2022.

For Fiscal Year 2022

1. Researchers from Baylor College of Medicine developed a drug-based platform that allows scientists to study biological processes more efficiently. In their work published on September 14, 2021, in *Cell Reports*, CPRIT Scholar Koen Venken, Ph.D., assistant professor, Department of Biochemistry and Molecular Biology, and fellow researchers explained how they used the platform to track genetic manipulations in fruit flies, which are widely used in animal models to study the function of genes and mutations. To distinguish the flies carrying the gene of interest from those that do not, a sort of 'tag' is added to the gene. The idea behind this novel technology is that, instead of tagging the genes of interest with a physical trait, they are tagged with another gene that confers the flies either resistance or sensitivity to specific drugs. "Researchers can make many combinations of genes and select them, and then counter-select them in a subsequent step quickly and at very little cost," Dr. Venken said. Baylor College of Medicine recruited Dr. Venken in January 2014 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (R1313).

2. In a study published in *Science* on September 17, 2021, researchers from The University of Texas MD Anderson Cancer Center shed light on the connection between inflammation and pancreatic cancer development. Pancreatic cells display an adaptive response to repeated inflammatory episodes that initially protects against tissue damage but can promote tumor formation in the presence of mutant KRAS. The researchers stimulated transient inflammation in a model system of inducible KRAS-driven pancreatic cancer. Inflammation caused immediate pathological changes in pancreatic cells, but they resolved within one week. However, activation of KRAS even months following the resolution of inflammation resulted in accelerated tumor formation compared with controls, suggesting that inflammation drives long-term changes in epithelial cells that cooperate with mutant KRAS to promote cancer development. Corresponding author Andrea Viale, M.D., assistant professor of genomic medicine said, "In the setting of repeated pancreatitis, KRAS mutations can be acquired early on to limit tissue damage, suggesting the existence of a strong evolutionary pressure to select mutated cells and providing a possible explanation for the nearly universal presence of mutant KRAS in pancreatic cancers." These findings also clarify that acinar-to-ductal metaplasia is not a cancer precursor state, but rather an adaptive response to inflammation. The University of Texas MD Anderson Cancer Center received a $200,000 CPRIT High Impact/High Risk grant (RP190599) in 2019.

3. Pulmotect, Inc., a clinical-stage biotechnology company based in Houston, announced positive topline results from the first of two Phase 2 clinical trials undertaken with the support of the U.S. Department of Defense to evaluate PUL-042 against COVID-19 in September 2021. The double blind, randomized, placebo-controlled Phase 2 clinical trial randomized 101 patients with early COVID-19 in the U.S. Inhaled PUL-042 stimulates the lung's innate immune system with the potential to protect against a wide variety of respiratory pathogens. There was low incidence of adverse effects with no drug related serious adverse events reported in the trial and no deaths in this patient population. Patients treated with inhaled PUL-042 had a statistically significant reduction in the time to improvement of the combined respiratory symptoms of cough and shortness of breath. "As an easily administered inhaled therapy, PUL-042 could have value in reducing the impact of COVID-19 irrespective of the development of further variants and has potential utility for other patient populations which we plan to explore including immunosuppressed cancer patients," said Colin Broom, M.D., Pulmotect's CEO. Pulmotect received a $7.1 million CPRIT Product Development Research, Company Formation grant (CP120014) in 2014.

4. A team led by researchers at Baylor College of Medicine discovered a new mechanism by which transcription factor KLF4 influences gene expression - the process by which the instructions in our DNA convert into a functional product, such as a protein. A cell's genetic information is packed in chromatin, a complex, compact, dense structure made of DNA and proteins. Expressing a particular gene requires that the gene expression molecular machinery has access to that stretch of DNA.

Transcription factors such as KLF4 regulate diverse cellular processes such as cell growth, proliferation, and differentiation. By conducting experiments with cells grown in the lab, co-corresponding author Josephine C. Ferreon, Ph.D., assistant professor of pharmacology, and team found that KLF4 forms droplets in the cell nucleus that recruit other transcription factors. The results, published in the journal *Nature Communications* on September 22, 2021, revealed that KLF4 droplet formation depends on regions called zinc fingers, which are known to bind DNA. Single molecule fluorescence experiments showed that the three KLF4 zinc fingers, which usually bind in a row to one DNA, can 'bridge' between two DNA molecules. Baylor College of Medicine received a $6 million CPRIT Core Facility Support Award grant (RP160805) in May 2016.

5. Researchers from The University of Texas MD Anderson Cancer Center reported that breast cancer survivors who participated in "Active Living After Cancer," an evidence-based 12-week group program, markedly increased their physical activity and ability to accomplish the basic pursuits of daily life. "After a cancer diagnosis, survivors' physical functioning declines much faster than their peers of the same age and gender who don't have cancer, which can ultimately affect their ability to remain independent and mobile," said Karen Basen-Engquist, Ph.D., professor of behavioral science and senior author of the paper. The findings, published in the journal *Cancer* on September 23, 2021, were based on 127 breast cancer survivors who completed the program between 2014 and 2017. During this time, 34 Active Living After Cancer groups (12-week sessions with the same cohort) were completed at health care organizations, community organizations and churches across the greater Houston area. The program is unsupervised and free and was offered to breast cancer survivors who had completed primary cancer treatment. Facilitators from community organizations follow a 12-week curriculum that introduces a different low-impact exercise, cognitive/behavioral skill and survivorship resource each week to help participants increase their physical activity at home, learn how to build healthier habits and cope with the challenges of survivorship. Self-reported physical activity nearly doubled at the 12-week follow-up and participants reported an 8% increase in physical quality of life and a 6% improvement in mental health. The results show the program could serve as a model to deliver a community-based physical activity program to minority and medically underserved cancer survivors. The University of Texas MD Anderson Cancer Center received a $630,000 CPRIT Evidence-Based Prevention Programs and Services grant (PP130079) in November 2013.

6. Scientists from The University of Texas Southwestern Medical Center and The University of Texas MD Anderson Cancer Center developed an artificial intelligence model to predict anti-cancer immunity. Mutations in the genome of cancer cells cause them to display different neoantigens on their surfaces. Immune T cells that hunt for signs of cancer and foreign invaders recognized some of these neoantigens, allowing the immune system to destroy the cancer cells. Other neoantigens seem invisible to T cells, allowing cancers to grow unchecked. To predict which neoantigens T cells will recognize and to help researchers develop personalized cancer vaccines, engineer better T cell-based therapies, or predict how well patients might respond to other types of immunotherapies, senior author Tao Wang, Ph.D., assistant professor of population and data sciences, The University of Texas Southwestern Medical Center, and team built a transfer learning-based model named the pMHC–TCR binding prediction network (pMTnet). The team used this tool, as described in the September 23, 2021, issue of the journal *Nature Machine Intelligence*, to gather insights on neoantigens cataloged in The Cancer Genome Atlas, a public database that holds information from more than 11,000 primary tumors. The pMTnet showed that neoantigens generally trigger a stronger immune response compared with tumor-associated antigens. It also predicted which patients had better responses to immune checkpoint blockade therapies and had better overall survival rates. The University of Texas Southwestern Medical Center received a $900,000 CPRIT Individual Investigator Research Awards for Computational Biology grant (RP190208) in 2019.

7. Salarius Pharmaceuticals, Inc., a Houston-based clinical-stage biopharmaceutical company, announced research findings at the 2021 AACR-NCI-EORTC Virtual International Conference on Molecular Targets and Cancer Therapeutics in October 2021. The presentation disclosed preclinical research that demonstrated seclidemstat (SP-2577), Salarius' lead drug candidate, has a differentiated mechanism of action that gives it potent activity in sarcomas compared to another LSD1 inhibitor. The presented preclinical data, in combination with results from the ongoing dose-expansion Phase 1/2 trial of seclidemstat in select sarcoma patients, demonstrate that seclidemstat's differentiated mechanism of action gives it unique anti-cancer activity in FET-rearranged sarcomas compared to other LSD1 inhibitors. Ongoing research will focus on identifying potential biomarkers for selecting patients with increased sensitivity to seclidemstat. Salarius Pharmaceuticals received a $16 million CPRIT Product Development Research grant (DP160014) in May 2016.

8. CPRIT Scholar Julian West, Ph.D., assistant professor of chemistry, and graduate student, Yen-Chu Lu, both of Rice University, set out to improve a technique to make a common building block for drugs. The complex method required catalysts of expensive silver until the West lab figured out how to replace it with a cerium-based compound. As reported in the journal *ACS Catalysis* in October 2021, the researchers found that an Earth-abundant salt of manganese, which is far superior to silver and cerium for drug design and manufacture, further simplifies the process of synthesizing fluoroketones, precursor molecules for drug design and manufacture. Attaching negatively charged fluorine atoms to ketones helps direct the functional groups toward desired reactions when used in anticancer and other compounds. "With manganese, we required less than a 10th as much catalyst -- and more importantly, it just works better. We would rather use a trace amount of catalyst to save on material costs and to simplify purification," explained Dr. West. Head-to-head comparisons with silver catalysts proved manganese delivered more product molecules with half the amount of catalyst. "I think we're getting to state-of-the-art catalysis with this reaction." Rice University recruited Dr. West from the California Institute of Technology in February 2019 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR190025).

9. Senior chemist at OncoNano Medicine, Inc., Qingtai Su, Ph.D., presented positive results from their preclinical study of ONM-501, a novel, dual-activating polyvalent STING agonist for immuno-oncology applications. The data, presented at The American Association for Cancer Research (AACR) Virtual Conference in October 2021 on Tumor Immunology and Immunotherapy, demonstrate strong efficacy in multiple tumor models. "STING plays a crucial role in mediating our innate immune systems but has consistently been a challenging pathway to target," reported Martin Driscoll, Chief Executive Officer of OncoNano Medicine. The preclinical data demonstrates ONM-501 could have a clinical profile differentiated from earlier generation cyclic dinucleotide STING agonist compounds. The researchers at OncoNano Medicine, Inc. continue their IND-enabling activities as they advance ONM-501 in human trials with the support of a $9.96 million CPRIT Product Development Research grant (DP200081) awarded in 2020.

10. Researchers at The University of Texas Southwestern Medical Center found a way to help better understand how one of the most commonly mutated genetic drivers of cancer passes signals that cause the disease. The study, published on October 8, 2021, in *Nature Structural & Molecular Biology*, focuses on a family of proteins called RAS, which is mutated in 20 to 25% of all cancers, especially in lethal cancers such as pancreatic, colorectal and lung cancers. "A framework to develop RAS inhibitor strategies is badly needed because recently approved RAS inhibitors such as sotorasib only work against one specific mutation, and many other RAS mutations also cause cancer," said CPRIT Scholar Kenneth Westover, M.D., Ph.D., associate professor of radiation oncology and biochemistry. Dr. Westover and collaborators used computer simulations to arrive at an atomistic structural model of an RAS assembly and validated the model using biological systems. This work sets the stage for development of new targeted RAS inhibitors to address major drivers of

lethal cancers, such as pancreatic and colon cancer. This structural model is now available to the wider RAS research community. The University of Texas Southwestern Medical Center recruited Dr. Westover in January 2012 from Harvard University with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (R1207) and received an $823,500 CPRIT Individual Investigator Academic Research grant (RP170373) in August 2017.

11. OncoNano Medicine, Inc. announced results from a Phase 2 study of its lead clinical development candidate, pegsitacianine, at the October 2021 World Molecular Imaging Congress. Pegsitacianine is an intraoperative fluorescence imaging agent under development by OncoNano Medicine for the detection of cancerous tissue in patients undergoing removal of their solid tumor. The Phase 2 study was a non-randomized, open-label, multi-center study conducted at three U.S. sites. The Phase 2 study results for pegsitacianine confirmed the selected dose schedule, expanded upon the drug's safety profile and is well-tolerated in patients. The findings suggest that doctors now have a tool that offers real-time surgical imaging on margin status and provides a greater degree of confidence in achieving complete tumor resection. Onco Nano Medicine received a $6 million CPRIT Product Development Research grant (DP140072) in 2014.

12. The University of Texas Southwestern Medical Center researchers have identified a new mechanism by which stress causes cells to stop dividing. The researchers used a microscopy technique and identified a protein in yeast that plays a previously unrecognized role in halting the cell cycle, the process by which one cell reproduces itself by splitting into two. The researchers were able to study individual cells in that state by using a technique called microfluidics six-color imaging pioneered at UT Southwestern in 2018. The researchers also used machine learning to track and detect up to six biochemical reactions in single cells in real time. After accumulating in response to stressful events, the Xbp1 protein appeared to suppress the cell cycle. The findings, published on October 25, 2021, in the *Journal of Cell Biology*, suggest that if scientists can identify a protein in mammals with a similar function, the research might lead to new ways to accelerate wound healing by encouraging cell division or improve cancer treatment by doing the opposite. "Scientists have been studying this fundamental process for nearly seven decades," said Orlando Argüello-Miranda, Ph.D., who co-led the study with Jungsik Noh, Ph.D., both of UT Southwestern's department of bioinformatics. "We've essentially identified a protein that can stop the cell cycle in response to stressful conditions." The University of Texas Southwestern Medical Center received a $5.6 million CPRIT Academic Research grant (RP150596) in 2015.

13. In a new single-arm study, researchers at The University of Texas MD Anderson Cancer Center reported that radiation therapy as monotherapy is a safe and effective noninvasive treatment for oligometastatic renal cell carcinoma (RCC). The findings were published on December 1, 2021, in *The Lancet Oncology*. The RCC Oligometastasis Phase II trial is the first study to investigate and report the use of stereotactic body radiation therapy (SBRT) as an alternative treatment to standard-of-care systemic therapy for oligometastatic RCC, the most common type of kidney cancer. SBRT uses highly concentrated doses of radiation to precisely treat tumor sites without damaging surrounding healthy tissue. "By developing this novel radiation treatment strategy, we sought to shift the treatment paradigm in an effort to provide select RCC patients with a lower-cost, less toxic alternative treatment to systemic therapy," said Chad Tang, M.D., assistant professor of radiation oncology. Serial SBRT as monotherapy demonstrated antitumor activity and achieved a median progression-free survival of 22.7 months in patients with RCC. The University of Texas MD Anderson Cancer Center received a $2.4 million CPRIT Individual Investigator Research Awards for Clinical Translation grant (RP180140) in 2018.

14. A team of scientists, including Mark T. Bedford, Ph.D., professor, Department of Epigenetics and Molecular Carcinogenesis, The University of Texas MD Anderson Cancer Center, announced the de-

velopment a new drug-like molecule that can counteract the effects of mutated epigenetic regulators, which are known to drive certain types of cancer, including lymphoma. In this study, published in October 2021 in *Cell Chemical Biology*, the scientists designed a drug-like molecule to reverse the cancer-causing gene repression by EZH2, an epigenetic regulator. Researchers specifically targeted CBX8, a second epigenetic regulator and engineered mouse stem cells in which they could easily screen many drug-like molecules. When they had succeeded in synthesizing a potent molecule that worked well in the engineered mouse cells, they tested human cancer cells by exposing lymphoma and colorectal cancer cells to their newly synthesized drug-like molecule in the laboratory. These malignant cells ceased to proliferate and began to behave more like healthy cells. The University of Texas MD Anderson Cancer Center received a $2.6 million CPRIT Core Facility Support Award grant (RP180804) in 2018.

15. Scientists introduced an online "user-friendly" web server offering scientists the chance to screen their drug candidates virtually in relation to known protein binding pockets on the SARS-CoV-2 virus. The project, detailed in an open-access paper in December 2021 in *Computers in Biology and Medicine,* incorporates models of three drug targets for ensemble docking through DINC-COVID. Docking INCrementally (DINC), is a protocol developed in 2013 in the lab of Lydia Kavraki, Ph.D., professor of computer science and bioengineering, electrical and computer engineering, and mechanical engineering at Rice University. Researchers upgraded DINC in 2017 to speed protein-peptide docking simulations that help researchers design drugs, vaccines and other processes involving large ligands. The team used several programs to narrow the ensembles from the 100,000 possible conformations generated by a molecular dynamics simulation, for instance, to a set of representative conformations. Understanding these structures allows researchers to find binding partners that could, ideally, deactivate the virus. Dr. Kavraki reported that 500 researchers in 16 different countries have used DINC-COVID, while their earlier web server DINC has been accessed by 11,000 users. The University of Texas Medical Branch in Galveston received a $4 million CPRIT Academic Research grant (RP170593) in November 2016.

16. In a study published in December 2021 in *Molecular Cancer Therapeutics,* researchers reported heme sequestration as an effective strategy for the suppression of tumor growth and progression. Heme is an essential nutritional, metabolic, and signaling molecule in living organisms. Li Zhang, Ph.D., professor of biological sciences at The University of Texas at Dallas, and team examined human non-small cell lung cancer (NSCLC) cells grafted onto mice. The results showed that heme-sequestering proteins (HeSPs) act by affecting oxygen levels and blood-vessel growth in tumor environments. The HeSPs designed by Dr. Zhang's research group slowed the growth of NSCLC cells in mice. Although they are not a stand-alone treatment; when employed, their deceleration of tumor proliferation, diminished tumor hypoxia and normalized tumor vasculature would improve the chances of radiation, chemotherapy or immunotherapy destroying the tumors. The researchers also tested the HeSPs on a second type of lung cancer cell, as well as in a breast cancer model. The effect was the same — lowered heme uptake, and tumor proliferation dropped significantly. In February 2020, The University of Texas at Dallas received a $900,000 CPRIT Individual Investigator Academic Research grant (RP200021).

17. The rotavirus causes approximately 179 million cases of acute gastroenteritis and about 128,000 deaths annually, particularly in children. Baylor College of Medicine researchers Sarah Blutt, Ph.D., associate professor of molecular virology and microbiology, and Mary Estes, Ph.D., professor of molecular virology and microbiology, uncovered a more detailed picture of how the intestinal epithelium – the lining of the intestines – heals itself after infection with rotavirus. Researchers already knew that rotavirus typically infects enterocytes. An unexpected discovery in this study showed that rotavirus infects anther cell type in the intestinal epithelium, tuft cells. Tuft cells may contribute to the repair response of the epithelium following damage. The findings, published on November 3,

2021, in *Proceedings of the National Academy of Sciences,* not only provide a better understanding of the healing process following rotavirus infection, but also may reveal new clues about how the virus causes disease. Baylor College of Medicine received a $5.2 million CPRIT Core Facility Support Award grant (RP180672) in 2018.

18. In November 2021, Immatics, Inc. announced an interim clinical data update from its TCR-engineered cell therapy (TCR-T) approach ACTengine® IMA203 targeting PRAME. Immatics is treating advanced solid cancer patients utilizing TCR-T cells directed against an HLA-A*02-presented peptide derived from preferentially expressed antigen in melanoma (PRAME). Immatics' proprietary mass spectrometry-based target discovery platform XPRESIDENT® identified the chosen PRAME target peptide, demonstrating natural and specific occurrence of the target on tumors at high copy numbers. Researchers observed multiple clinical responses early-on during dose escalation and saw anti-tumor activity at much lower doses than expected in the field of TCR-T. Cedrik Britten, M.D., Chief Medical Officer at Immatics, commented, "The unexpected high clinical response rate in PRAME-positive patients before reaching our target cell dose has shifted our expectations of what cell therapy could potentially achieve in solid cancers. This is a very promising first step, which encourages us to double down efforts for a focused development strategy of our programs targeting PRAME." Immatics, Inc. received a $19.7 million CPRIT Product Development Research grant (DP150029) in 2015.

19. Iterion Therapeutics, Inc. announced the Phase 1/2 clinical trial to investigate tegavivint as a potential treatment for pediatric cancers, including sarcomas, lymphomas and other solid tumors that are prevalent in pediatric populations. This clinical trial, led by Sarah Whittle, M.D. assistant professor, Department of Pediatrics, Baylor College of Medicine started recruiting patients in November 2021. The team's goal is to develop safer and potentially curative treatments that spare children from short-term and long-term treatment side effects. "This trial gives us the ability to enrich our understanding of tegavivint's utility in multiple cancer types that specifically impact children and for which few treatments exist other than chemotherapy," said Dr. Whittle. The Phase 1/2 study of tegavivint in pediatric cancer patients follows compelling clinical data establishing the drug's safety and clinical activity in adults with progressive and nonresectable desmoid tumors. The Phase 1/2a desmoid study enrolled 24 patients who received tegavivint. The treatment was well-tolerated with no observed dose-limiting toxicities with several patients having received treatment for more than a year. Iterion Therapeutics, Inc. received a $15.9 million CPRIT Product Development grant (CP130058) in 2014.

20. In November 2021, Yue Liao, Ph.D., assistant professor of kinesiology at The University of Texas at Arlington, announced a pilot project titled "Project REMOTE: Research to Examine Motivation to Exercise." It incorporates the use of wearable sensors to monitor participants' daily activities and uses a smartphone app to survey feelings, symptoms, perceptions and motivations, along with contextual factors related to their physical activity behaviors. This strategy provides high-resolution data about determinants of motivation and barriers to exercise in daily life. The results, published in September 2021 in *Cancer*, reported that cancer survivors improved their quality of life, physical activity level and physical functioning after completing a 12-week group-based exercise program. The team focused its research on minority and medically underserved cancer survivors who often lack access to physical activity resources. Dr. Liao is continuing the research by investigating how survivors can maintain the positive benefits achieved through these evidence-based programs. The University of Texas MD Anderson Cancer Center received a $2 million CPRIT Prevention grant (PP200028) in November of 2020.

21. A team led by scientists at Baylor College of Medicine announced that they uncovered new evidence supporting a cancer-promoting role for enzyme MAPK6. The study, published in November

2021 in the journal *Science Advances*, shows that MAPK6 furthers cancer growth by activating the AKT pathway, a known cancer-promoting cellular mechanism. Corresponding author, Feng Yang, Ph.D., assistant professor, Department of Molecular and Cellular Biology at Baylor College of Medicine, and colleagues began by investigating the effect of overexpressing the MAPK6 gene in normal human prostate or breast epithelial cells grown in the lab. They found that overexpressing MAPK6 can transform normal cells into tumor-like cells, which suggests that genetically knocking down MAPK6 significantly reduced the growth of several types of cancer cells in the lab. They discovered that MAPK6 also activates AKT to promote cancer growth. These findings show that while inhibiting MAPK6 and mTOR activities separately reduces AKT phosphorylation and cancer cell growth, inhibiting both simultaneously achieves a more robust tumor-suppressing activity. Baylor College of Medicine received a $580,000 CPRIT Academic Research Individual Investigator grant (RP130651) in 2012.

22. In November 2021, a team of researchers led by The University of Texas at Dallas announced that they had developed a new technique to open the blood-brain barrier temporarily to deliver medication to the brain. Zhenpeng Qin, Ph.D., associate professor, Department of Mechanical Engineering at The University of Texas at Dallas, reported that getting medication past the blood-brain barrier is one of the biggest challenges in treating brain and central nervous system diseases. This new technique uses light and nanoparticles to temporarily pry open these barriers to allow medication to reach its target. Dr. Qin and his colleagues demonstrated the approach in mice in a study published in September 2021 in the journal *Nano Letters*. These findings could lead to treatments for brain tumors and Lou Gehrig's disease (amyotrophic lateral sclerosis), aid in stroke recovery, and deliver gene therapy. The study demonstrated that the technique did not damage the blood-brain barrier or vasomotion. The University of Texas at Dallas received three CPRIT Academic Research grants in support of this research (RP190278, RP180846, RP160770) in 2018 and 2019, for a total of $1.3 million.

23. Researchers at The University of Texas Southwestern Medical Center led an international team that used artificial intelligence (AI) and evolutionary analysis to produce 3D models of eukaryotic protein interactions. In this study published in November 2021 in *Science*, a team of structural biologists examined all known gene sequences in yeast to map the interactions that give rise to protein complexes. Using advanced statistical analyses, they identified pairs of genes that naturally acquire mutations in a linked fashion. By combining the 3D models with information from collaborators, the teams were able to gain new insights into protein complexes involved in maintenance and processing of genetic information, cellular construction and transport systems, metabolism, DNA repair, and other areas. The scientists identified more than 100 probable protein complexes for the first time and provided structural models for more than 700 previously uncharacterized ones. Senior author Qian Cong, Ph.D., assistant professor of biophysics, noted that these results could lead to a wealth of new drug targets and represent a significant advance in the new era in structural biology in which computation plays a fundamental role. The University of Texas Southwestern Medical Center received a $3.75 million CPRIT Academic Research grant (RP210041) in 2021.

24. Data from an article published in *Medicine & Science in Sports & Exercise* in November 2021, showed strong evidence that moderate-intensity aerobic training alleviated anxiety, depressive symptoms and fatigue and improved health-related quality of life and overall physical function. Karen Basen-Engquist, Ph.D., MPH, professor of behavioral science and director of the Center for Energy Balance in Cancer Prevention and Survivorship at The University of Texas MD Anderson Cancer Center, led the team that developed the 12-week "Active Living After Cancer" program. The development of the program followed data from Cooper Institute's Project ACTIVE, which showed that a focus on activities that individuals can incorporate into daily life without having to go to a gym or requiring specific time goals, improved physical activity and cardiorespiratory health in the

general population. Dr. Basen-Engquist and colleagues simplified the text, translated the program into Spanish, and developed a training program for community health educators. The researchers had originally focused their sights on underserved and minority populations, but the Active Living After Cancer program is now virtual, so it is available to anyone throughout the state. The University of Texas MD Anderson Cancer Center received a CPRIT Competitive Continuation/Expansion - Evidence-Based Cancer Prevention Services grant in 2017 (PP170023) and a CPRIT Expansion of Cancer Prevention Services to Rural and Medically Underserved Populations Prevention award in 2020 (PP200028) for a total of $3.5 million.

25. Researchers at the Kidney Cancer Program (KCP) at The University of Texas Southwestern Medical Center reported the largest and most diverse catalog of kidney cancer tumor models to date. Kidney cancer remains largely incurable when metastatic, despite the development of new drugs. Described in a paper published on November 23, 2021, in *Cell Reports*, the KCP platform includes a wide array of models for the scientific community. KCP researchers transplanted tumors into mice from 926 ethnically diverse patients from UT Southwestern Medical Center and its affiliated Parkland Memorial Hospital for more than a decade, generating a library of 172 tumorgraft lines. In 2016, they used the platform to test a new type of kidney cancer drug, HIF-2α inhibitors, which the FDA recently approved. Using the same platform, investigators confirmed HIF-2 resistance mutations in patients, advanced precision diagnostics and supported two investigational new drug (IND) approvals from the FDA. Researchers are deploying the platform to develop second-generation HIF-2α drugs, as well as to determine whether cancer drugs FDA-approved for other tumor types may work against kidney cancers with particular mutations that may make them vulnerable. UT Southwestern received a $4.2 million CPRIT Academic Research grant (RP110771) in 2011 and a $5.65 million CPRIT Core Facility Support Awards grant (RP170638) in 2017.

26. Pulmotect, Inc. announced results in December 2021 from the second of two Phase 2 clinical trials with the support of the U.S. Department of Defense to evaluate PUL-042 against COVID-19. Inhaled PUL-042 stimulates the lung's powerful immune system to protect against a wide range of respiratory pathogens in multiple animal models. In the two Phase 2 trials, PUL-042 was evaluated in one trial as preemptive treatment in patients with early, symptomatic infection and in a second trial in the prophylactic settings in subjects with known exposure to SARS-CoV-2. Based on the remarkable activity of PUL-042 in animal models and the more than 200 subjects, PUL-042 has potential for treatment of COVID-19 irrespective of future SARS-CoV-2 variants and supports the clinical proof-of-concept for protection against respiratory pathogens in other patient populations. Time to complete resolution of respiratory symptoms trended in favor of PUL-042 and was well tolerated with a low incidence of adverse effects and no drug related serious adverse events or deaths were reported in either trial. Pulmotect received a $7.12 million CPRIT Product Development Research, Company Formation grant (CP120014) in 2012.

27. Recommendations about whether to use chemotherapy or hormone therapy have historically been based on how large populations of patients responded when treated with certain drugs. In this study, a standard measure of gene expression known as the sensitivity-to-endocrine-therapy (SET2,3) index suggested that the 21-gene Oncotype DX Breast Recurrence Score (RS) test could predict which patients would benefit from chemotherapy and which could safely be treated with endocrine therapy alone. Thus, recommendations can be personalized for the individual patient and the results underscore the continued utility of gene expression-based molecular tests in identifying women at higher or lower risk of their cancer coming back with treatment. This data, analyzed from a large randomized clinical trial of postmenopausal women with hormone receptor-positive breast cancer, was presented on December 9, 2021, at the San Antonio Breast Cancer Symposium. The work, co-led by W. Fraser Symmans, M.D., professor, Department of Pathology at The University of Texas MD Anderson Cancer Center, demonstrates the value and utility of using both clini-

cal and molecular information from a patient's tumor to guide decision making during treatment. MD Anderson received a $6 million CPRIT Multi-Investigator Research Awards (Version 2) grant (RP180712) in August 2018.

28. The results of a single-arm, phase 2 feasibility trial completed at The University of Texas MD Anderson Cancer Center in Houston were published in October 2021 in *The Lancet Oncology*. The research team prospectively tested the feasibility and efficacy of radiotherapy to defer systemic therapy for patients with oligometastatic renal cell carcinoma (RCC) in adult patients. Co-author Chad Tang, M.D., assistant professor, Department of Radiation, reported that they enrolled 30 adults with oligometastatic RCC treated with no more than one prior systemic therapy. Each lesion was treated with stereotactic body radiotherapy monotherapy (SBRT). The trial had co-primary endpoints: feasibility (all planned RT completed with fewer than 7 days of unplanned breaks) and progression-free survival (PFS). Median PFS was 22.7 months, and two-thirds of patients were alive without disease progression at 12 months. The team found that this strategy is feasible and leads to encouraging progression-free and systemic therapy-free survival with modest toxicity. MD Anderson received a $2.4 million CPRIT Individual Investigator Research Awards for Clinical Translation grant (RP180140) in 2018.

29. In response to adverse environmental conditions, living cells activate certain genes and repress others to survive and thrive. A variety of environmental insults, such as temperature variations, osmotic changes, antibiotics, solvents, and host immune response, can all elicit a stress response in bacteria. Among these, sudden temperature increase is the most widely used model for studying the impact of stress. In a study published in *Frontiers in Microbiology* on January 3, 2022, researchers demonstrated that *Chlamydia trachomatis* can mount a very robust heat shock response. In this study, researchers performed transcriptomic analyses to investigate heat shock response in the obligate intracellular bacterium *C. trachomatis*. The findings reveal that *C. trachomatis* utilizes multiple novel survival strategies to cope with environmental stress and even to replicate. Co-author Zhao Lai, Ph.D., assistant professor/research, molecular medicine at The University of Texas Health Science Center at San Antonio, and contributing scientists, reported that these findings have important implications for chlamydial physiology and pathogenesis. Future strategies that specifically target and disrupt the heat shock response of *C. trachomatis* will likely be of therapeutic value. The University of Texas Health Science Center at San Antonio received a $3.68 million CPRIT Core Facility Support Award (RP160732) in 2016.

30. Alzheimer's disease (AD) is a progressive neurodegenerative disorder which severely disrupts activities of daily living. People with mild cognitive impairment (MCI) exhibit many of the early clinical symptoms of patients with AD and have a high chance of converting to AD in their lifetime. In an article published in *Frontiers in Neuroscience* on January 3, 2022, Luca Giancardo, Ph.D., associate professor, School of Biomedical Informatics, The University of Texas Health Science Center, reported that early detection and identification of AD will facilitate the development of biomarkers and support the discovery of novel molecules by providing the right population for clinical trials. The researchers introduced a novel method that utilizes T1-weighted MRI and clinical data at two-time points to diagnose AD in patients with MCI that leverages longitudinal data that can be easily acquired in a clinical setting. Primary care providers can use automated computer-assisted diagnosis (CAD) systems to monitor patients with MCI because it has a fast image processing and prediction pipeline. The University of Texas Health Science Center at Houston received a $5.85 million CPRIT Core Facility Support Award grant (RP170668) in August 2017.

31. Nearly five million Americans will develop progressive congestive heart failure, but heart transplantation or mechanical circulatory assisted transplantation have limitations. In a study published in

Scientific Reports in November 2021, Todd Rosengart, M.D., professor and chair of the Department of Surgery at Baylor College of Medicine, and his colleagues sought new strategies to increase the efficiency of reprogramming human fibroblasts to promote the desired changes to the myocardium. "The idea behind cell reprogramming is to guide the heart to heal itself by transforming scar tissue, primarily made up of fibroblasts, into functional heart muscle," explained Dr. Rosengart. Although human fibroblasts resist reprogramming, the endothelial cells that line blood vessels are known to be more flexible. The team leveraged the endothelial cell plasticity which has significantly improved reprogramming efficiency in both human and rat fibroblasts. Previously, direct derivation of cardiomyocytes from fibroblasts was only 3% efficient. The new approach increased efficiency by a factor of five. The team expects this new approach to become part of the next generation of biological therapies. Texas A&M University System Health Science Center received two CPRIT Core Facility Support Awards (RP150578, RP170719) in 2015 and 2017 for a total of $11.74 million.

32. A team of researchers at Baylor College of Medicine and collaborating institutions studied two rare inherited vitamin B_{12} conditions that affect the same gene but are clinically distinct from the most common genetic vitamin B_{12} disorder. In this study, published in *SciTech Daily* in January 2022, the team searched for those genes and their function. Working with mouse models, the team confirmed that the genes involved in the more complex forms of the condition not only cause the expected typical vitamin B_{12} disease but also affect the generation of ribosomes, the protein-building machinery of the cell. "Mutations in the genes encoding the proteins responsible for the metabolic processes involving vitamin B_{12} result in rare human inborn errors of cobalamin (vitamin B_{12}) metabolism," said Ross A. Poché, Ph.D., associate professor, Department of Integrative Physiology at Baylor College of Medicine. The team plans to functionally characterize the altered ribosomes at the molecular level to identify how their function is disrupted. Baylor College of Medicine received a $5 million CPRIT Core Facility Award grant (RP170005) in September 2016.

33. In a study published in *Frontiers in Immunology* on January 13, 2022, Mauricio Menegatti Rigo, Ph.D., postdoctoral research associate, Department of Computer Science at Rice University, and fellow researchers highlighted the importance of developing additional therapeutic strategies against SARS-CoV-2 and other coronaviruses. They reported that at the beginning of the pandemic, countries with Bacillus Calmette-Guérin (BCG) vaccination programs could be associated with a reduced number and/or severity of COVID-19 cases. In order to identify potential targets of T cell cross-reactivity, the researchers implemented an in-silico strategy to screen over 13.5 million possible cross-reactive peptide pairs from BCG and SARS-CoV-2. This analysis produced a short list of immunogenic BCG-derived peptides that are the most likely primers for T cell cross-reactivity against SARS-CoV-2. It also produced a longer list of cross-reactivity clusters involving one SARS-CoV-2 peptide and multiple BCG-targets, in some cases binding multiple HLA-I alleles, which could represent interesting targets for vaccine development. The University of Texas Medical Branch at Galveston received a $4 million CPRIT Academic Research grant (RP170593) in November 2016.

34. Results from a study published in January 2022 in *Cell Metabolism*, highlight metabolic vulnerabilities in malignant cells that could eventually lead to new cancer therapies. The University of Texas Southwestern Medical Center scientists reported that metabolic differences could explain why some metastatic breast cancer cells rapidly generate tumors after migrating from primary tumors to the brain, while others linger for months or years before forming these secondary tumors. "Brain metastasis is a major problem for breast cancer patients, and most of the treatments that we have are not that effective. We have identified unique features of metastatic breast cancer cells that could serve as new targets," explained CPRIT Scholar Srinivas Malladi, Ph.D., assistant professor of pathology. The team employed brain metastatic models, which showed that metabolic diversity and plasticity within brain-tropic cells determine metastatic fitness. This study suggests several potential approaches to limit residual disease and outgrowth of brain metastasis and may have

broader therapeutic applicability to other cancers with a propensity to disseminate to the brain. UT Southwestern recruited Dr. Malladi in November 2016 from Memorial Sloan-Kettering Cancer Center with the support of a $2 million CPRIT First-Time, Tenure-Track Award grant (RR170003) and received a $3.75 million CPRIT Academic Research grant (RP210041) in May 2021.

35. T cell-mediated cancer immunosurveillance can recognize and attack tumor cells presenting neoantigens. However, tumors can develop different strategies to avoid recognition and elimination by the immune system. CPRIT Scholar Chao Cheng, Ph.D., associate professor at the Institute for Clinical and Translational Research at Baylor College of Medicine, and fellow researchers proposed a model to explain how T cell-mediated immunosurveillance shapes the mutational landscape in tumors. The researchers found that neoantigens of recurrent mutations have significantly lower MHC-I binding affinity than those from non-recurrent mutations. These results, published on January 17, 2022, in *Frontiers in Immunology,* were observed for somatic mutations presenting in both melanoma-specific driver and passenger genes and suggest that the somatic mutation landscape in melanoma is shaped by T cell-mediated immunosurveillance. Baylor College of Medicine recruited Dr. Cheng from the Geisel School of Medicine at Dartmouth in August 2018 with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR180061).

36. Melanoma is the fifth most common cancer in both men and women in the United States. According to data, patients with metastatic melanoma tumors have a 27% 5-year relative survival rate. Just under half of metastatic melanoma tumors contain a B-Raf (BRAF) mutation which are known to promote cancer evasiveness and enhance oncogenic activity, providing a possible mechanism of resistance to PD-1/PD-L1 immunotherapy. CPRIT Scholar Chao Cheng, Ph.D., associate professor, Institute for Clinical and Translational Research at Baylor College of Medicine, and colleagues developed a gene signature for the BRAF V600E mutation that captures pathway activity, predicts prognosis, and correlates with sensitivity to BRAF inhibitors and other targeted therapies. This methodology, as described in *Cancer Medicine* on January 19, 2022, may guide clinical decisions and save clinicians' time in sequencing the gene mutation profile of the patient. BRAF inhibitors score may warn physicians to prescribe more aggressive forms of treatment, especially if the patient has a high score, and can be generalizable and applied to other cancers and targeted therapies. Baylor College of Medicine recruited Dr. Cheng from the Geisel School of Medicine at Dartmouth in August 2018 with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR180061).

37. Carrie Daniel, Ph.D., MPH, associate professor, Department of Epidemiology, and Jennifer Wargo, M.D., professor, Departments of Genomic Medicine and Surgical Oncology, both from The University of Texas MD Anderson Cancer Center, examined the links between diet, gut microbes, and response to immunotherapy in 128 people with melanoma. While tumors shrink or even disappear in some people given immunotherapy, others have no response at all. The microbes found in the gut, called the gut microbiome, have emerged as one factor. The research, published in *Science* in December 2021, reported that gut bacteria modulate the response to immune checkpoint blockade (ICB) treatment in cancer. Early studies found that modifying the gut microbiome may improve the odds of tumor response to immunotherapy. People who ate a high-fiber diet and didn't use over-the-counter probiotic supplements lived the longest after immunotherapy for melanoma and had better responses to treatment overall. The findings, which were confirmed in mouse studies, suggest that microbes in the gut can be modified to improve immunotherapy results. The University of Texas MD Anderson Cancer Center received a $250,000 CPRIT High Impact/High Risk Academic Research grant (RP200574) in August 2020.

38. Clinicians have used monoclonal antibodies like daratumumab and isatuximab, which link the immune system to a target like CD38 on the surface of myeloma cells, to treat a type of blood cancer

called multiple myeloma. Molecular Templates, Inc. is developing a new treatment targeting CD38 using Engineered Toxin Bodies (ETBs). Shaji Kumar, M.D., primary investigator on this study, reported that unlike other CD38 targeted therapies, ETBs do not rely on the body's own immune system (the patient's T cells or natural killer cells) for effective myeloma-killing responses. ETBs deliver a modified bacterial toxin into the inner liquid material of cancerous plasma cells (the cytosol). When the cell internalizes this toxin, it destroys the ribosomes, the location responsible for cell life or death. CD38 is present in a variety of cells, particularly in the myeloma cells, expressing at very high density. The antibodies can very effectively bind to the CD38 on the end, which is an excellent way to target the myeloma cells. In 2016, Molecular Templates, Inc. received a $15.2 million CPRIT Product Development Research grant (DP160071).

39. The Breast Screening and Patient Navigation (BSPAN) Program provides access to no-cost breast cancer screening services to uninsured women in North Texas. Using data from the longitudinal BSPAN program (2012–2019), researchers assessed prevalence and correlates of baseline adherence and longitudinal adherence to screening mammograms. The results, published in the *American Association of Cancer Research* on January 11, 2022, found that out of 19,292 women, only 5,382 (27.9%) were baseline adherent. Keith Argenbright, M.D., professor at the Harold C. Simmons Comprehensive Cancer Center, noted that the results revealed that adherence was more likely among women who were partnered, preferred speaking Spanish, had poor reading ability, had prior Papanicolaou (PAP) testing, and prior screening mammograms. More than 80% of these baseline adherent women achieved longitudinal adherence. These results may be generalizable to other areas introducing no-cost screening to low-income women, independent of any regular patient-centered medical home. The University of Texas Southwestern Medical Center received three CPRIT Evidence-Based Prevention Programs and Services grants (PP120097, PP150053, PP180018) in 2012, 2015, and 2018, respectively, for a total of $5.55 million.

40. One of the central questions in developmental biology is how spatial distributions of extracellular morphogens are controlled and interpreted to produce patterns of cell fates. CPRIT Scholar Aryeh Warmflash, Ph.D., Departments of Bioengineering and Biosciences, and Lizhong Liu, Ph.D., Department of Biosciences, both of Rice University, have visualized for the first time the mechanism by which Nodal and Lefty proteins interact to specify the future body plan in a mammalian embryo. Nodal and its antagonist, Lefty, are important mediators specifying the laterality of the organs during embryogenesis. The results appear the January 25, 2022, issue of the open-access journal, *Nature Communications*. "Basically, we show that the molecules involved do not diffuse at all," said Dr. Warmflash. "Instead, cells relay the signal so that each cell produces the signal and passes it to its neighbor, which causes the neighbor to produce it and so on. It's kind of like a game of telephone." The protein known as Lefty pumps the brakes as human embryos begin to differentiate into the bones, soft tissues and organs that make us. The unique experimental model developed by Dr. Warmflash and his team allows them to see early stages of gastrulation, the stage in the early embryonic development of most animals. Dr. Liu found a way to add fluorescent tags to the Nodal protein that did not compromise gastrulation in any way which allows scientists to track individual proteins in a mammalian system. This could lead to discoveries about the mechanisms by which the morphogen and its inhibitor claim their territories. Rice University recruited Dr. Warmflash in August 2014 from the Rockefeller University with the support of a $2 million Recruitment of First-time, Tenure-Track Faculty Members grant (RR140073).

41. Medicenna Therapeutics,Corp. announced preclinical data on MDNA11, the company's selective, long-acting and novel IL-2 super-agonist. The findings, published in the *Journal for ImmunoTherapy of Cancer* on January 26, 2022, showed potent and long-lasting anti-cancer activity in mice and a pharmacokinetic profile that was vastly superior to recombinant human IL-2. While recombinant human IL-2 has been approved for the treatment of metastatic melanoma and kidney cancer, its

use is limited and leads to preferential activation of pro-tumor Treg cells and toxicity. MDNA11 was engineered to overcome these shortcomings by virtue of its vastly superior selectivity and activation of cancer fighting immune cells, via IL-2R beta (IL-2Rβ). In non-human primates, the long-acting Superkine selectively induced durable proliferation and expansion of anti-cancer immune cells without safety issues typically associated with IL-2. Fahar Merchant, Ph.D., President and CEO of Medicenna, reports that MDNA11 is currently being evaluated in patients with advanced, relapsed or refractory solid tumors in the Phase 1/2 ABILITY (A Beta-only IL-2 ImmunoTherapY) study. Medicenna Therapeutics Corp. was awarded a $14.1 million CPRIT Product Development Research grant (DP150031) in 2015.

42. Neural crest cells (NCCs) are a temporary group of stem cells in early embryonic development that are unique to vertebrates. These later develop into many different types of cells in the body, including neurons, cartilage, and skin cells. CPRIT Scholar Rosa Uribe, Ph.D., assistant professor of biosciences at Rice University, reported that if these NCCs are compromised during development, they can lead to cancer or other diseases in babies and very young children. In this study published in *Frontiers in Cell Development and Biology* in January 2022, the team of researchers found that elevated Hoxb5b expands vagal neural crest pool and blocks enteric neuronal development in zebrafish. The elevated Hoxb5b levels promoted an expansion of zebrafish NCCs, which persisted throughout multiple stages of development. When the data are considered together with mammalian suppression of activity studies, the gain of function results suggest that the vertebrate embryo is exquisitely sensitive to perturbations in Hoxb5 activity, where either elevations or reductions in Hoxb5 lead to severe enteric nervous system defects. This data position Hoxb5b as a potent regulator of NCC patterning and number during early embryonic development. Rice University recruited Dr. Uribe in August 2017 from California Institute of Technology with the support of a $2 million CPRIT Recruitment of First-Time Tenure-Track Faculty Members grant (RR170062).

43. CPRIT Scholar Omid Veiseh, Ph.D., assistant professor of bioengineering, Rice University, announced on January 12, 2022, that he expects human clinical trials to begin later this year on ovarian cancer patients using the immunotherapy technology developed in his lab. Dr. Veiseh is co-founder and chair of the scientific advisory board at Avenge Bio, the newly founded company that has licensed the technology developed to treat several forms of cancer. One site for the clinical trials will be The University of Texas MD Cancer Center in Houston. "We're aiming at patients with refractory/recurrent ovarian cancer," said Dr. Veiseh. "Most are diagnosed at a late stage and given a poor prognosis. We're focused on significantly improving the current standard of care with the goal of long-term, durable remissions." Rice recruited Dr. Veiseh to Texas in May 2016 from Massachusetts Institute of Technology with the help of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160047).

44. Single-cell RNA sequencing (scRNAseq) technology plays a vital role in medical fields such as oncology, digestive and urinary systems, microbiology, neurology, reproduction, and immunology. The major interest domains of single-cell RNA sequential analysis are identification of existing and novel types of cells, depiction of cells, cell fate prediction, classification of several types of tumors, and investigation of heterogeneity in different cells. Zhongming Zhao, Ph.D., professor at the School of Biomedical Informatics, The University of Texas Health Science Center, noted that single-cell clustering plays an important role in solving these questions of interest. In this article published in *Frontiers in Genetics* in February 2022, researchers provided a dimensionality reduction integrated clustering model for detecting cluster-specific biomarkers in single-cell sequencing data. They applied this in a single-cell RNA sequential dataset for a rare intestinal cell type in mice. Their proposed framework integrates dimensionality reduction and agglomerative hierarchical clustering, providing a robust approach to efficiently discover cluster-specific frequent biomarkers, i.e., overlapping biomarkers from single-cell RNA sequencing data. The University of Texas Health Science

Center at Houston received a CPRIT Core Facility grant (RP180734) in 2018 and a CPRIT Research Training grant (RP210045) in 2021 for a total of $8.4 million.

45. Current therapeutic strategies for the treatment of pulmonary fibrosis, a chronic lung disease, are not curative and are limited to delaying disease progression. There is a need to understand the molecular and cellular mechanisms involved in lung fibrosis in order to identify targets for intervention to stop the disease from progressing. In a novel study published in *Frontiers in Immunology* on February 8, 2022, Sandeep K. Agarwal, M.D., Ph.D., associate professor, Department of Immunology, Allergy & Rheumatology at Baylor College of Medicine, noted that macrophages are the key players in lung fibrosis. The results provided insight into how Cadherin-11 (CDH11), a cell-cell adhesion protein, regulates the development of macrophages and alters its M2 program and phagocytic function during pulmonary fibrosis. Using flow cytometric analysis, the scientists showed that in the IP bleomycin model of pulmonary fibrosis, interstitial macrophages (IMs) and monocyte-derived alveolar macrophages (MoAMs) increased in both frequency and total number after bleomycin administration in wild-type mice and the number of both populations were markedly reduced in *Cdh11*$^{-/-}$ mice. These data suggest that the fewer numbers of IMs and MoAMs in *Cdh11*$^{-/-}$ mice may contribute to the attenuation of pulmonary fibrosis in these mice. Collectively, these findings provide insight into the role of CDH11 in macrophages and pulmonary fibrosis. Baylor College of Medicine received a $5.17 million CPRIT Core Facility Support grant (RP180672) in 2018.

46. Scientists at The University of Texas Southwestern Medical Center found that melanoma cells become more dependent upon the oxidative pentose phosphate pathway to manage oxidative stress (an imbalance of free radicals and antioxidants in the body), during metastasis. The pentose phosphate pathway is a major source of NADPH for oxidative stress resistance in cancer cells but there is limited insight into its role in metastasis, when some cancer cells experience high levels of oxidative stress. To address this, CPRIT Scholar Sean Morrison, Ph.D., professor and director of Children's Medical Center Research Institute, The University of Texas Southwestern Medical Center, and fellow researchers found when pentose phosphate pathway function was impaired by reduced glucose 6-phosphate dehydrogenase (G6PD) function, melanoma cells increased malic enzyme activity and glutamine consumption. The results, published in February 2022 in the journal *Proceedings of the National Academy of Sciences* (PNAS), report that melanoma cells thus have redundant layers of protection against oxidative stress during metastasis, including the abilities to alter fuel consumption and antioxidant pathway utilization, and provide insight into the role of CDH11 in macrophages and pulmonary fibrosis. The University of Texas Southwestern Medical Center recruited Dr. Morrison in 2011 from the University of Michigan with the support of a $10 million Recruitment of Established Investigators grant (R1109), and received a CPRIT Individual Investigator grant (RP170114) in 2016 and a Multi-Investigator Research Awards grant (RP180778) in 2018 for a total of $6.9 million.

47. Despite significant progress in cancer immunotherapy in recent years, resistance to existing immune checkpoint therapies is common. V-domain Ig suppressor of T cell activation (VISTA), a predominantly myeloid immune checkpoint regulator, represents a promising therapeutic target due to its role in suppressing proinflammatory antitumor responses in myeloid-enriched tumor microenvironments. In a new study published in the *Journal for ImmunoTherapy of Cancer* on February 8, 2022, Hummingbird Bioscience researchers highlighted how HMBD-002, an IgG4 isotype anti-VISTA neutralizing antibody rationally developed with Hummingbird Bioscience's Rational Antibody Discovery (RAD) platform, binds specifically and with high affinity to a binding site distinct from other published VISTA antibodies, and significantly inhibits tumor growth in syngeneic and humanized murine models of cancer. Corresponding author, Jerome Boyd-Kirkup, Ph.D., Chief Scientific Officer at Hummingbird Bioscience, noted that this antibody represents a highly promising novel therapy in the VISTA-suppressed ICT non-responder population. HMBD-002 is currently being developed

for patients with VISTA-expressing cancers, including triple-negative breast cancer and non-small cell lung cancer. The Phase 1 clinical trial (NCT05082610) is open and enrolling. Hummingbird Bioscience, Inc. received a $13.1 million CPRIT Product Development Research grant (DP190027) in 2019.

48. Tvardi Therapeutics, Inc., a privately held, clinical-stage biopharmaceutical company focused on the development of STAT3 inhibitors, announced on April 21, 2022, that the FDA granted its lead product, TTI-101, Orphan Drug Designation (ODD) for the treatment of hepatocellular carcinoma (HCC). Khandan Keyomarsi, Ph.D., professor of experimental radiation oncology at The University of Texas MD Anderson Cancer Center, was an integral part of the research that demonstrated that TTI-101 overcomes palbociclib resistance in metastatic breast cancer murine models. TTI-101 is an orally delivered, small molecule, direct inhibitor of STAT3. STAT3 is a key regulatory protein which plays a critical role in the pathogenesis of HCC by initiating tumorigenesis as well as promoting an immunosuppressive tumor microenvironment. The University of Texas MD Anderson Cancer Center received a $900,000 CPRIT Individual Investigator grant (RP170079) in 2016 and a $4 million Research Training grant (RP210028) in 2021.

49. Stem cells are present throughout all tissues and have the capacity to self-renew and the potential to differentiate into multiple types of cells. Cristian Coarfa, Ph.D., associate professor of molecular and cell biology, Baylor College of Medicine, and colleagues showed how the protein ΔNp63 contributes to disease development through the regulation of stem cells and crucial elements known as enhancers, which regulate genes that control cell identity. As reported in an article published in *Nature Communications* on February 1, 2022, researchers performed a series of laboratory experiments using preclinical mouse models of lung adenocarcinoma and squamous cell carcinoma, and human cancer cell lines to define the role of ΔNp63 in lung cancer development. Their observations suggest that ΔNp63 may function as a tumor promoter and regulate the self-renewal and differentiation process of stem cells in the lung, as it does in the skin. Researchers also discovered that the protein regulates the enhancer region of genes involved in cell differentiation and cell identity, and found that BCL9L, one of these key genes, mediates the tumor promoting effects of ΔNp63 in the lung cancer subtypes adenocarcinoma and squamous cell carcinoma. The researchers will use these findings to develop novel therapeutic approaches to inhibit development of these highly deadly tumor types. The University of Texas MD Anderson Cancer Center received a $900,000 CPRIT Individual Investigator Academic Research grant (RP140271) in August 2014. The Baylor College of Medicine received a $4 million CPRIT Core Facility Support Award grant (RP200504) in August 2020.

50. CPRIT Scholar Piya Ghose, Ph.D., assistant professor at The University of Texas at Arlington, aimed to highlight novel non-canonical roles of classical cell death genes in neurons and to speculate on where the new horizon lies for these genes in the nervous system. The *Caenorhabditis elegans* (*C. elegans*) system, a model organism of choice for a growing number of researchers, has emerged seemingly tailored to study nervous system function and development. Since cell death genes are very much active embryonically, it is conceivable that many events in embryonic neurodevelopment may be linked to cell death gene function. The results, published in *Frontiers in Cell Development Biology* in February 2022, demonstrate the increasingly divergent functions of the *C. elegans* cell elimination genes in the nervous system. The study concludes that, as in other systems, apoptotic genes have several non-apoptotic roles in the *C. elegans* nervous system. Researchers predict that the new horizon likely lies in neurodevelopment and the nematode system can be efficiently leveraged to better understand nervous system development by examining the role of cell death genes in embryonic neurodevelopment. The University of Texas at Arlington recruited Dr. Ghose in August 2019 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR190091).

51. A recent discovery could advance food and chemical production by enhancing lactic acid bacteria's (LAB) metabolic processes with a little electronic encouragement. The hybrid metabolism of LAB is the focus of a study published in *eLife* and led by CPRIT Scholar Caroline Ajo-Franklin, Ph.D., professor of biosciences at Rice University, and Maria Marco, Ph.D., professor of food science and technology at University of California Davis. According to the study, bacteria used widely in fermentation combine two systems not previously known to coexist to acquire the fuel they burn for energy. "What we discovered is a LAB that blends the two, like an organism that's not warm- or cold-blooded but has features of both," said Dr. Ajo-Franklin. They also found that this blended metabolism has benefits in other habitats, such as the digestive tract, which could improve gut health. Dr. Ajo-Franklin anticipates that if they provide another electron donor or acceptor, they could promote the growth of positive bacteria over negative bacteria. Rice University recruited of Dr. Ajo-Franklin in November 2019 from the Ernest Orlando Lawrence Berkeley National Laboratory with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR190063).

52. In a study published in the journal *mBIO* in February 2022, researchers at Baylor College of Medicine aimed to understand the interactions between virus and human cells. In this study, the researchers report the development of a versatile human nose organoid – a laboratory representation of the cells layering the inside of the nose where the first events of a natural viral infection take place. Using these novel nose organoids, the team showed key differences between the infection by SARS-CoV-2, the virus that causes COVID-19, and that of respiratory syncytial virus (RSV), a major pediatric respiratory virus. The model was also used to test the efficacy of therapeutics such as palivizumab, an FDA-approved monoclonal antibody to prevent severe RSV disease in high-risk infants. The organoids developed from both adults and infants provide access to the inside of the human nose, "enabling us to study the early events of the infection in the lab, something we had not had before," said corresponding author Pedro Piedra, Ph.D., professor of molecular virology and microbiology, pediatrics, and pharmacology and chemical biology at Baylor College of Medicine. The researchers developed these human nose organoids with a noninvasive, reproducible and reliable approach that can be used to study other respiratory viruses and potentially other disease-causing microbes. Texas A&M University System Health Science Center received two CPRIT Core Facility Support Awards grants (RP150578, RP170719) in 2015 and 2017 for a total of $11.7 million.

53. CPRIT Scholar José N. Onuchic, Ph.D., chair, Department of Physics at Rice University, and colleagues reported that Mitochondrial inner NEET (MiNT) overexpression in human breast cancer cells enhanced reactive oxygen species (ROS) resistance and tumor growth. In the study published in *Proceedings of the National Academy of Sciences* (PNAS) on February 15, 2022, the team chose triple-negative human breast cancer cells, because they represent a major form of human epithelial cancers with a high demand for cellular iron for the analyses of MiNT function. Using the MiNT(−) and MiNT(+) MDA-MB-231 cell lines, xenograft breast cancer tumors were generated to characterize the relationship between MiNT and tumor growth. MiNT(+) showed increased tumor growth compared to control, while MiNT(−) displayed decreased tumor growth compared to control or the MiNT(+) line. This work further supports the involvement of NEET proteins in [2Fe-2S] cross-talk between the mitochondria and cytosol. The existence of this pathway and the central role it plays in cellular metabolism, regulating iron, ROS, and overall Fe-S metabolism can affect the understanding of many different biochemical, molecular, and cellular processes key to diseases such as diabetes, cancer, and neurodegeneration. Rice University recruited Dr. Onuchic from the University of California, San Diego in July 2011 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (R1110).

54. New therapeutic strategies to reduce sepsis-related mortality are urgently needed, as sepsis accounts for one in five deaths worldwide. Since hematopoietic stem and progenitor cells (HSPCs)

are responsible for producing blood and immune cells, Katherine Y. King, M.D., Ph.D., associate professor, pediatrics-infectious disease at Baylor College of Medicine, and colleagues explored their potential for treating sepsis in a pre-clinical study. To understand the role of HSPCs during acute infection, the researchers studied infection with *Streptococcus pyogenes*, common bacteria that cause several diseases, including sepsis. As reported in the journal *eLife* in February 2022, the inflammatory environment of Group A *Streptococcus* (GAS) infection drives rapid HSPC differentiation and depletion that can be rescued by infusion of donor HSPCs. In a mouse model of GAS-induced sepsis, severe immunological stress was associated with significant depletion of bone marrow HSPCs and mortality within approximately 5–7 days. Infusion of 10,000 naïve HSPCs into GAS-infected mice resulted in rapid myelopoiesis, the formation of bone marrow and blood cells, and a 50–60% increase in overall survival. These findings suggest that HSPCs play an essential immunomodulatory role that may translate into new therapeutic strategies for sepsis, warranting further investigation of this novel concept. Baylor College of Medicine was awarded a $5.17 million CPRIT Core Facility Support Awards grant (RP180672) in 2018.

55. The human population is exposed to an increasing number of chemicals and complex mixtures that pose significant health risks. A subset of these is referred to as endocrine-disrupting chemicals (EDCs), because they interfere with actions of natural hormones altering central physiological mechanisms, ultimately causing disease. One of the many potential EDC targets is the estrogen receptor-*a*receptor-α (ER), a transcription factor that regulates, among other physiological processes, female reproductive biology and is involved in several diseases, including obesity and breast cancer. In this study published in February 2022 in *Environmental Health Perspectives*, Michael A. Mancini, Ph.D., professor and Core Director, Baylor College of Medicine, and fellow researchers developed single-cell imaging and informatic workflows to query whether the single cell distribution of the ER, used as a model system, can be used to measure effects of EDCs in a sensitive and reproducible manner. The team identified a number of new toxicants that directly and indirectly affected ER levels and activity and envision that similar approaches will greatly aid researchers venturing in single cell analysis of environmental toxicant actions. "What our team did was to create this imaging assay able to find the most accurate results by employing single-cell analytics across a population of cells," said Dr. Mancini. Texas A&M University System Health Science Center received a $5.8 million CPRIT Core Facility Support Awards grant (RP170719) in 2017.

56. Unified airway disease, including concurrent asthma and chronic rhinosinusitis (CRS), is a common, but poorly understood disorder with no curative treatment options. In an article published in *Frontiers in Immunology* in February 2022, David Corry, M.D., professor and Fulbright Endowed Chair in Pathology at Baylor College of Medicine, and colleagues pioneered the emerging paradigm that fungi, such as *Alternaria alternata* and *Aspergillus niger*, are fundamental causes of both asthma and CRS through the elaboration of key virulence factors. Utilizing a specific inhibitor and gene-deficient mice, they demonstrated that STAT6 is required for mycosis-induced sinus inflammation. When mice were exposed to *A. niger*, they developed airway hyperresponsiveness, the physiologic *sine qua non* of asthma, increased production of the type 2 cytokines IL-4, IL-5, and IL-13 in the lungs, along with an influx of eosinophils and elevated serum IgE levels. However, STAT6-deficient mice failed to develop airway hyperresponsiveness and pulmonary eosinophilia as well as near-complete suppression of all other inflammatory cells including macrophages, neutrophils, and T cells after 12 weeks. These findings confirm the relevance of this new model and portend future studies that further evaluate the central role of STAT6. Baylor College of Medicine received a $5.17 million CPRIT Core Facility Support Awards grant (RP180672) in 2018.

57. Single-cell RNA sequencing (scRNA-seq) is a powerful technology used to study the ecosystems of normal and disease tissues. Gene expression signatures can be used to interrogate single cells for cell identities and other cellular properties using signature-scoring methods. CPRIT Scholar Si-

yuan Zheng, Ph.D., assistant professor department of population health sciences, The University of Texas Health Science Center at San Antonio, and colleagues proposed that signature-scoring methods developed for bulk samples are not adequate for cancer scRNA-seq data. In order to account for the variability of expression within the signature, researchers benchmarked five such methods, including a new method developed by the team, Jointly Assessing Signature Mean and Inferring Enrichment (JASMINE). This study, published in *eLife* in February 2022, shows cancer cells consistently express more genes than normal cells. These results suggest caution should be exercised when using bulk-sample-based methods in scRNA-seq analyses, and cellular contexts should be taken into consideration when designing benchmarking strategies. The University of Texas Health Science Center at San Antonio received a CPRIT Academic Research grant (RP170345) in 2016 and a Recruitment of First-Time, Tenure-Track Faculty Members grant (RR170055) in 2017 for a total of $5.99 million.

58. CRISPR is a powerful tool that allows researchers to easily alter DNA sequences and modify gene function. One of the challenges with using CRISPR-based gene editing on humans is that the molecular machinery sometimes makes changes to the wrong section of a host's genome. Co-senior author, CPRIT Scholar David W. Taylor, Ph.D., assistant professor, Department of Molecular Biosciences, and colleagues at The University of Texas at Austin have redesigned a key component of a widely used CRISPR-based gene-editing tool, called Cas9. Described in a March 2022 edition of the journal *Nature*, this redesigned tool, dubbed SuperFi-Cas9, is 4,000 times less likely to cut off-target sites but just as fast as naturally occurring Cas9. It remains just as efficient as the original version, making it potentially much safer. The researchers have demonstrated the use of SuperFi-Cas9 on DNA in test tubes and are now collaborating with other researchers who plan to test SuperFi-Cas9 for gene editing in living cells. The team is also working to develop still safer and more active versions of Cas9. The University of Texas at Austin recruited Dr. Taylor in September 2016 from the University of California Berkely with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160088).

59. *Helicobacter pylori (H. pylori)* have colonized the stomachs of billions of people worldwide. Once an *H. pylori* infection occurs, it is challenging to eradicate. This is a significant biomedical problem as *H. pylori* can promote stomach ulcers and gastric cancers. Pushkar Lele, Ph.D., associate professor, Department of Chemical Engineering at Texas A&M University received an R01 research grant in January 2022 from the National Institute of General Medical Sciences totaling over $1.3 million to investigate the mechanisms that enable H. pylori to navigate with the aid of motility appendages called the flagella. To do this work, his group will combine experimental techniques such as optical trapping and Förster resonance energy transfer (FRET) with computational modeling. The proposed work will build on the group's previous efforts funded by CPRIT where the researchers developed a novel method to quantify the effect of the environment by exploiting fluid drag on each bacterium. "Chemotaxis strategies are well understood in only a few bacterial species, and successful execution of our projects will provide insights into the diverse strategies employed by pathogens to evade our immune systems," said Dr. Lele. "As *H. pylori* continue to become resistant to antibiotics, such mechanistic studies on the different facets of host invasion and colonization will address critical medical needs.» Texas A&M Engineering Experiment Station received a $200,000 CPRIT High-Impact High-Risk grant (RP170805) in 2017. Awards and Prestigious Appointments?

60. Bioengineers from Rice University and colleagues have shown they can eradicate advanced-stage ovarian and colorectal cancer in mice in as little as six days with a treatment that could be ready for human clinical trials later this year. In this study, published in the peer-reviewed journal *Science Advances* in March 2022, the researchers used implantable drug factories the size of a pinhead to deliver continuous, high doses of interleukin 2 (IL-2), a natural activator of white blood cells and

U.S. Food and Drug Administration (FDA)-approved cancer treatment. The drug-producing beads, licensed exclusively to Avenge Bio, Inc., can be implanted with minimally invasive surgery. Research team leader, CPRIT Scholar Omid Veiseh, Ph.D., assistant professor of bioengineering at Rice University, and a founder of Avenge Bio, reported that the study showed no systemic toxicity and allowed both spatial and temporal control. Once they determined the correct dose, they were able to eradicate tumors in 100% of animals with ovarian cancer and in seven of eight animals with colorectal cancer. "We just administer once, but the drug factories keep making the dose every day, where it's needed until the cancer is eliminated," Dr. Veiseh said. The same general approach used in the study could be applied to treat cancers of the pancreas, liver, lungs and other organs. If these implants are effective in humans, as the researchers expect, it holds the promise of replacing the toxic, high-dosage infusions associated with cytokine therapy today. Rice University recruited Dr. Veiseh in May 2016 from the Massachusetts Institute of Technology with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160047).

61. Researchers from The University of Texas MD Anderson Cancer Center discovered that treatment resistance in patients with myelodysplastic syndromes (MDS) is caused by two distinct classes of stem cells and identified possible therapeutic approaches that target these cells. Their findings, which span preclinical and clinical studies, were published in *Nature Medicine* in March 2022. The investigators analyzed more than 400 samples from patients with MDS taken at different stages of disease. Using integrative molecular profiling of HSCs, they found that hypomethylating agents (HMA) eliminated mature cancer cells but left the stem cells alive, leading to disease relapse. Based on these results, the researchers performed a retrospective analysis of 21 MDS patients with blast progression after treatment with HMA therapy and venetoclax. Researchers observed a significant decrease in stem cells following treatment in patients with CMP pattern disease. "The majority of MDS cases do not respond to current therapies or relapse," said Simona Colla, Ph.D., associate professor, Department of Leukemia and senior author of the study. "This study provides new insight into what causes therapy failure and disease progression in MDS and possibly provides targeted treatment options for these patients." The University of Texas MD Anderson Cancer Center received two CPRIT Individual Investigator grants (RP140500, RP190295) in 2014 and 2019 for a total of $1.8 million.
62. South Texas Latinas experience higher cervical cancer incidence and mortality compared to Latinas nationwide. Principal Investigator Daisy Morales-Campos, Ph.D., assistant professor at The University of Texas at Austin, stated that despite the availability of effective human papillomavirus vaccines, South Texas Latino/a adolescents sub-optimally complete the series. The specific aims of this study were to explore healthcare providers' perceptions of the process of administering the HPV vaccine to patients in their practices within the geographical and cultural context of South Texas; and to identify facilitators and barriers to administering the HPV vaccine to Latino/a adolescents that may shape Latino parent's perceptions and decisions to vaccinate their child. Published in March 2022 in *BMC Public Health,* the study used qualitative description to describe the experience of 15 South Texas healthcare providers (doctors and nurses) with the process of HPV vaccine administration in their practices. Barriers ranged from parental fears of adolescent sexual activity and potential vaccine side effects to lack of transportation and the cost of the vaccine. This research clearly supports the need for broader policy changes aimed at addressing the various organizational and structural challenges to implementing and sustaining effective HPV vaccine coverage. The University of Texas Health Science Center at San Antonio received a $1.3 million CPRIT Evidence-Based Prevention Programs and Services grant (PP160042) in 2015, and The University of Texas at Austin received a $1.3 million CPRIT Evidence-Based Prevention Programs and Services grant (PP160080) in 2016.

63. Researchers at The University of Texas Southwestern Medical Center have found that a single protein can reverse the developmental clock on adult brain cells called astrocytes. Chun-Li Zhang,

Ph.D., professor of molecular biology, explained that the mature brain largely loses stem cell capacity, leaving only two small regenerative zones with extremely limited capacity to heal itself following injury or disease. The team's experiments showed that a single transcription factor – a protein known as DLX2 – appeared to reprogram astrocytes into neural stem-like cells capable of producing neurons and multiple subtypes of glial cells. CPRIT Scholar Gary Hon, Ph.D., assistant professor, Departments of Obstetrics & Gynecology and Bioinformatics, reported that global gene expression analysis showed that prompting astrocytes to produce DLX2 appeared to reprogram them into stem-like cells with features of both immature brain cells found earlier in development and cells found in the regenerative niches of the adult brain. The results, published in March 2022 in *PNAS,* suggest that DLX2 might someday be used as a tool to treat traumatic brain injuries, strokes, and degenerative conditions such as Huntington's disease. The University of Texas Southwestern Medical Center recruited Dr. Hon from the Ludwig Institute for Cancer Research, San Diego with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR140023) in 2014 and received a $900,000 CPRIT Individual Investigator grant (RP190451) in 2019.

64. Neurologic cancer surgery requires specialized tools that can enhance precise cutting and removal of tumor cells and tissues without damage to nerves. Thomas E. Milner, Ph.D., former professor of engineering in the Department of Biomedical Engineering at The University of Texas at Austin, and colleagues demonstrated a novel fiber-laser platform for performing precise brain surgery in a murine brain model. Although *in vivo* brain surgery with thulium lasers has been reported before, none of the previous studies reported a bloodless resection which is unique to the current study. The researchers utilized a dual-wavelength strategy with a pulsed nanosecond thulium laser for resection and vascular specific fiber-laser for coagulation. The demonstrated fiber-laser platform, if successfully configured for use in the operating room, can provide surgeons a tool for rapid removal of tissue while making surgical resections of brain regions more precise, and can be a basis for a flexible cutting tool capable of reaching hard-to-operate regions. The University of Texas at Austin received a $1.7 million CPRIT Bridging the Gap: Early Translational Research Awards grant (DP150102) in 2014.

65. Although estrogen-receptor-positive (ER+) breast cancer is generally associated with favorable prognosis, clinical outcome varies substantially among patients. A team, led by Chao Cheng, Ph.D., associate professor, Department of Medicine at Baylor College of Medicine, hypothesized that the recurrence risk of ER+ breast cancer patients is determined by both genomic mutations intrinsic to tumor cells and extrinsic immunological features in the tumor microenvironment. They applied this framework to ER+ breast cancer and defined gene signatures for a total of 72 most commonly observed genomic events. The team combined these tumor-intrinsic signatures with infiltration signatures for major immune cell types to construct integrative models for prognosis prediction. The results, published in March 2022, in *PLOS Computational Biology*, indicated that many of their individual signatures and immune cell infiltration scores are predictive of patient prognosis in ER+ breast cancer and predict the recurrence risk of patients with significantly better performance than the Oncotype DX (genomic biomarker test) assay. Baylor College of Medicine recruited Dr. Cheng from the Geisel School of Medicine at Dartmouth in 2018 with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR180061).

66. Liquid biopsies are minimally invasive and have the potential to provide diagnostic and prognostic information that can aid in the treatment of patients with various solid tumors. Circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA), two prime biomarker candidates detected through liquid biopsy, can provide insight into tumor evolution, tumor biology, cancer progression and therapy resistance. Sendurai A. Mani, Ph.D., professor, Department of Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, and team reported that isolation

and analysis of CTCs from liquid biopsies can offer non-invasive diagnostic and therapeutic information in breast cancer and other cancers. Single-cell multi-omics approaches have the potential to map the evolution of CTCs and thereby build an atlas of tumor evolution that includes a plethora of therapeutically viable targets. As reported in *British Journal of Cancer* in March 2022, profiling of CTC-derived biomarkers holds greater clinical significance than the current diagnostic and prognostic tools alone. Liquid biopsies have the potential to become a routine for screening and monitoring cancer patients, paving the way toward more personalized therapies. The University of Texas MD Anderson Cancer Center received a $5.99 million CPRIT Multi-Investigator Research Awards grant (RP160710) in 2016. Baylor College of Medicine received an $823,500 CPRIT Individual Investigator grant (RP170172) in 2017.

67. Mitochondrial health is important for organismal survival. Multiple cellular pathways are dedicated to actively monitoring mitochondrial status, termed as the mitochondrial surveillance system, to provide better defense towards variety of stresses. These systems are highly conserved and present in both *C. elegans* and humans. CPRIT Scholar Natalia Kirienko, Ph.D., assistant professor, Department of Biosciences, Rice University, reported that the Box C/D snoRNA core proteins (snoRNPs), normally associated with modification of ribosomal RNA, play a role in mitochondrial surveillance and innate immune pathways. As illustrated in an open access article in *PLOS Genetics* in March 2022, the loss of this protein complex reduced mitochondrial surveillance pathway activation after stress but increased immune responses. As mitochondrial surveillance, innate immunity, and box C/D snoRNP pathways are conserved in humans, understanding this mechanism is likely to be important for understanding multifactorial processes, including responses to infection and aging. Rice University recruited Dr. Kirienko in May 2015 from Massachusetts General Hospital and Harvard Medical School with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR150044).

68. Cancer research has seen explosive development exploring deep learning (DL) techniques for analyzing magnetic resonance imaging (MRI) images for predicting brain tumors. A global team of researchers, including Zhongming Zhao, Ph.D., M.S., chair, professor for precision health, The University of Texas Health Science Center, observed a substantial gap in explanation, interpretability, and high accuracy for DL models. They proposed an explanation-driven DL model by utilizing a convolutional neural network (CNN), local interpretable model-agnostic explanation (LIME), and Shapley additive explanation (SHAP) for the prediction of discrete subtypes of brain tumors (meningioma, glioma, and pituitary) using an MRI image dataset. As explained in March 2022 in *Frontiers in Genetics*, this model used a dual-input CNN approach which revealed 94.64% accuracy as compared to other state-of-the-art methods. This study will help the users (medical professionals, clinicians, etc.) in comprehending and efficiently managing the ever-increasing number of trustable and reliable AI partners. The University of Texas Health Science Center at Houston was awarded a $4.2 million CPRIT Core Facility Support Awards grant (RP180734) in 2018.

69. Osteosarcoma (OS) is the most common primary bone malignancy and accounts for approximately 9% of pediatric cancer deaths. In spite of the benefits, long-term chemotherapy results in side effects that can be catastrophic to patients' health and quality of life. Many patients also experience pain and immobility as a result of osteolytic bone lesions (OLs), which increase the risk of fracture and contribute to the vicious cycle between cancer cells, osteoblasts and osteoclasts providing the ideal environment for tumor propagation. Carl A. Gregory, Ph.D., associate professor of molecular and cellular medicine at Texas A&M Health Science Center, and colleagues reported that reducing the dependence on chemotherapy and the OL burden would significantly improve the impact of OS treatment strategies. The results published in the *British Journal of Cancer* in March 2022, indicated that administration of DkkMo in the presence or absence of chemotherapeutics has the capacity to substantially improve outcomes with respect to OS tumor expansion and osteolytic corruption of

bone. Texas A&M University System Health Science Center received a CPRIT High-Risk High Return grant (RP160765) and a CPRIT Investigator-Initiated grant (RP170496) for approximately $1.1 million in 2016.

70. Some of the same researchers at The University of Texas at Austin who created a key to all coronavirus vaccines used in the U.S. have made a similar advance against the human metapneumovirus (hMPV), one of a handful of remaining respiratory viruses for which there is currently no vaccine. Ching-Lin Hsieh, Ph.D., and CPRIT Scholar Jason McLellan, Ph.D., both from the Department of Molecular Biosciences, are among the UT Austin scientists who have engineered a protein of hMPV for use in vaccines. In an article published in *Nature Communications* in March 2022, these scientists described how to engineer the hMPV fusion protein to increase its stability and usefulness in vaccines. The researchers, including graduate student, Scott Rush, reported that they stripped the viral protein of its shape-shifting ability by introducing some genetic modifications that act like molecular staples and lock the structure in the optimal form for use in a vaccine. Hsieh, Rush and McLellan have filed a patent application on the protein technology described in the paper. The company Icosavax describes plans to begin clinical trials later this year for a vaccine that uses the protein mutations Dr. McLellan and the Texas team worked on for hMPV. The University of Texas at Austin received a $6 million CPRIT Recruitment of Established Investigators grant (RR160023) in support of the advancement against hMPV.

71. Chronically immunocompromised individuals and recipients of solid organ transplants are susceptible to severe diseases including fatal hepatitis and encephalitis associated with human cytomegalovirus (HCMV) infection. In addition, congenital HCMV infection can cause debilitating and permanent birth defects. Despite the prevalence of this pathogen, there are currently no U.S. Food and Drug Administration–approved vaccines and therapeutic options remain limited. In a study published in March 2022 in the journal *Science Advances*, researchers identified for the first time the structure of a key infectious part of HCMV. Jason McLellan, Ph.D., chair in Chemistry and Department of Molecular Biosciences, The University of Texas at Austin, reported that they uncovered part of the process by which HCMV infects host cells and how naturally produced antibodies neutralize the virus— insights that could help scientists develop new vaccines or therapeutics. Using a state-of-the-art imaging technique called cryo-EM, the researchers for the first time created a 3D atomic-scale map, or structure, of a protein complex called the HCMV Pentamer that helps the HCMV infect host cells by binding to a receptor called NRP2. In addition to detailing the molecular determinants that mediate HCMV infection, these findings expand understanding of how antibody-mediated neutralization of HCMV can be achieved. The University of Texas at Austin recruited Dr. Leahy in February 2016 from Johns Hopkins University School of Medicine with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR160023).

72. For patients diagnosed with extensive small cell lung cancer (SCLC), the treatment plans are mostly one size fits all. “One big issue facing scientists is a lack of SCLC tissue to use for research,” notes Carl Gay, M.D., Ph.D., assistant professor in the Department of Thoracic/Head and Neck Medical Oncology at The University of Texas MD Anderson Cancer Center. While researchers have identified three subtypes of SCLC, none of these three subtypes is particularly sensitive to immunotherapy. However, in the clinical trials there is a subset of SCLC patients who are sensitive. The team set out to identify the subset of SCLC patients who can be successfully treated with immunotherapy. Using a computational approach, Dr. Gay and his collaborators input all the relevant gene expression data to determine how many subtypes were likely to be found. The answer was four. The next step is to conduct the phase II clinical trial that tests the safety and efficacy of a promising drug combination (an immunotherapy to encourage immune activity combined with a PARP1 inhibitor to impede DNA repair). Patients enrolled in the trial will provide robust biopsy samples before and after the treatment, so the researchers can study the effects of the treatment and conduct a retrospective analy-

sis to determine which of the four known SCLC subtypes was the most sensitive to this treatment. The University of Texas MD Anderson Cancer Center received a $1.5 million CPRIT Early Clinical Investigator grant (RP210159) in 2021.

73. In mammals, body temperature, cognitive performance, blood pressure, hormone levels and response to therapy seem to follow a 12-hour cycle. Altered 12-hour cycles have been associated with human diseases and hundreds of genes have been identified that are activated in 12-hour cycles. In this study, Bert W. O'Malley, M.D., chancellor and professor, Department of Molecular and Cellular Biology, Baylor College of Medicine, and his colleagues found out how the 12-hour clock is regulated. In mammals, 12-hour biological rhythms are regulated by X-box-binding proten-1 (XBP1). The steroid receptor coactivator SRC-3 is a known coactivator of XBP1. As reported in *Cell Reports* in March 2022, the researchers showed that SRC-3 coactivation of XBP1 is key in regulating the 12-hour rhythms of the expression of hundreds of genes in the mouse liver. When the team studied human data, they found that SRC-3 coactivation of lipid metabolic genes is associated with conditions such as diabetes, obesity, fatty liver disease, cardiovascular diseases and human cancers such as those of the liver, colon/rectum, cervix and kidney. The availability of selective small molecule stimulators and inhibitors of steroid receptor coactivators such as SRC-3, provides new opportunities for treating and/or preventing these diseases. Baylor College of Medicine received 2 CPRIT Core Facility Support Awards grants (RP170005, RP210227) in 2016 and 2021, for a total of $9 million. The University of Texas MD Anderson Cancer Center received a $5 million CPRIT Core Facility Support Awards grant (RP170002) in 2016.

74. Providers currently rely on universal screening to identify health-related social needs (HRSNs). A team of researchers from The University of Texas Health Science Center at Houston proposed an alternative approach to universal screening; to utilize patient risk scores or risk prediction models to identify and prioritize patients who are most likely to have HRSNs. Luca Giancardo, Ph.D., assistant professor at the Center for Precision Health, and team hypothesized that using a combined dataset would outperform any single data source alone. As reported in *Nature* March 2022, they evaluated the predictive performance of HRSN status from electronic health records (EHR) and community-level social determinants of health (SDOH) data for Medicare and Medicaid beneficiaries using machine learning models. The team indicated that the relationship of social needs to insurance status may be more sensitive than previous literature has been able to detect without screening tools. Predicting HRSNs could reduce the need for additional data collection, EHR infrastructure, staff time, and training needed to offer the screening. The University of Texas Health Science Center at Houston received a $5.85 million CPRIT Core Facility Support Awards grant (RP170668) in 2017.

75. A new computational approach developed by researchers at The University of Texas MD Anderson Cancer Center successfully combines data from parallel gene-expression profiling methods to create spatial maps of a given tissue at single-cell resolution. The study was published in March 2022 in *Nature Biotechnology* and presented at the 2022 American Association for Cancer Research (AACR) Annual Meeting. Co-first authors Runmin Wei, Ph.D., Department of Genetics, and graduate student Siyuan He, led the efforts to develop CellTrek as a tool to combine the unique advantages of scRNA-seq and ST assays and create accurate spatial maps of tissue samples. The researchers collaborated with Savitri Krishnamurthy, M.D., professor, Department of Pathology, to apply CellTrek to study ductal carcincoma in situ (DCIS) breast cancer tissues. In an analysis of 6,800 single cells and 1,500 ST regions from a single DCIS sample, the team learned that different subgroups of tumor cells were evolving in unique patterns within specific regions of the tumor. The researchers presented findings from analysis of kidney and brain tissues as well as samples of DCIS breast cancer. "Pathology really drives cancer diagnoses and, with this tool, we're able to better guide treatment approaches," said senior author Nicholas Navin, Ph.D., professor, Departments of Molecular Biology and Genetics. The University of Texas MD Anderson Cancer Center received a $4.9 million CPRIT

Core Facility Support Awards grant (RP180684) in 2018.

76. Research led by The University of Texas Southwestern Medical Center scientists suggests that an investigational drug could restore the ability of some non-small cell lung cancers (NSCLCs) to respond to an immune checkpoint blockade (ICB), a therapy that harnesses the immune system to fight malignant tumors. The findings, derived from a preclinical lab model, were published on March 15, 2022, in *Cell Reports Medicine*. Study leader, Rolf Brekken, Ph.D., professor of surgery, explained that about 20% of NSCLC tumors also carry mutations in a gene known as STK11/LKB1, which is associated with poor response to ICB therapy. The key finding from the study came when the researchers found that inhibiting a protein called AXL boosted the numbers of TCF1-expressing $CD8^+$ T cells. This intervention restored the ability of mice harboring STK11/LKB1-mutated NSCLC tumors to respond to PD-1/PD-L1 inhibitors. CPRIT Scholar Yang-Xin Fu, Ph.D., Departments of Pathology and Immunology, reported that this discovery provides an important clue and path forward to enhance the benefits of immunotherapy for more patients with lung cancer. The University of Texas MD Anderson Cancer Center received a $6 million CPRIT Multi-Investigator Research Awards grant (RP160652) in 2016. The University of Texas Southwestern Medical Center recruited Dr. Fu in August 2015 from the University of Chicago with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR150072) and received two Research Awards grant (RP180725, RP210041) in 2018 and 2021, for a total of $9.75 million.

77. Mohammad A. Karim, M.D., formerly of the Department of Epidemiology at the University of Texas MD Anderson Cancer Center, and colleagues reported that nonalcoholic fatty liver disease (NAFLD) is linked to lower early-stage detection and poorer survival in patients with hepatocellular carcinoma (HCC) compared with other HCC etiologies. NAFLD is the leading cause of HCC among Medicare beneficiaries in the United States. With limited data available on NAFLD-associated HCC in a more recent population, the team used multivariable logistic regression to identify factors associated with surveillance receipt, early-stage tumor detection, and curative treatment in a cohort of 5098 HCC patients from the SEER–Medicare database between 2011 and 2015. According to study results published in March 2022 in *Clinical Gastroenterology and Hepatology*, 1,813 HCC patients had NAFLD, the most common etiology in the cohort, which was associated with lower HCC surveillance receipt, lower early-stage HCC detection and modestly worse overall survival compared with patients with hepatitis C-related HCC. Multifaceted interventions for improving surveillance uptake are needed to improve prognosis of patients with NAFLD-related HCC. The University of Texas MD Anderson Cancer Center received a $2.65 million CPRIT Research Training grant (RP170259) in 2016.

78. The use of adjuvant chemotherapy has a dramatic impact decreasing the risk of cancer recurrence and improving survival; however, delays in the administration of adjuvant chemotherapy significantly reduce this benefit. Mariana Chavez-MacGregor, M.D., Department of Health Services Research, The University of Texas MD Anderson Cancer Center, explained that the purpose of this investigation was to garner a better understanding of the challenges patients experience as they navigate the process of initiating chemotherapy treatment, particularly those at an increased risk for experiencing delays, with the goal of reducing disparate health outcomes. The researchers designed Project Start using a semi-structured interview guide. As reported in the open-access article published in March 2022 in *Dovepress*, the team enrolled (N=22) participants with median age at diagnosis 53.5 years (range 27– 70) who identified as Latina (n=8), Black (n=5), and non-Latina White (n=9). The overarching themes of these results included logistical, emotional, financial, and social sources of support and the relationship of these sources of support to perceived self-efficacy of the participants to move toward initiating treatment. The University of Texas Medical Branch at Galveston received a $6 million CPRIT Multi-Investigator Research Awards grant (RP160674) in 2016.

79. A team at Baylor College of Medicine and the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital identified a missing piece of the puzzle of how memory and mood are sustained and regulated in the brain. The study, published in March 2022 in the *Proceedings of the National Academy of Sciences*, reveals that oleic acid produced in the brain is an essential regulator of the process that enables learning and memory and supports proper mood regulation. The finding that oleic acid regulates TLX activation has paved the path to discovering potential new therapeutic strategies to counteract cognitive and mood decline in patients with neurological disorders. "TLX has become a 'druggable' target, meaning that knowing how it is activated naturally in the brain helps us to develop drugs capable of entering the brain and stimulating neurogenesis," said co-corresponding author Damian Young, Ph.D., associate professor, Department of Pharmacology and Chemical Biology and Pathology at Baylor College of Medicine. Baylor College of Medicine recruited Dr. Venken in January 2014 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (R1313) in 2014 and received a $5.17 million CPRIT Core Facility Support Awards grant (RP180672) in August 2018.

80. In 2020, the CDC reported 7,174 cases of tuberculosis and 13 million people living with a latent tuberculosis infection in the United States. In this study, published in *Aging* in March 2022, researchers at Baylor College of Medicine found that the cells of humans and animals that have recovered from tuberculosis (TB) had prematurely aged up to 12 to 14 years. Co-senior author Andrew DiNardo, M.D., assistant professor, Department of Medicine–Infectious Diseases, and colleagues looked at the cells' epigenetic clock to measure the aging of the cells affected by TB. As we age, how the DNA is coiled changes, and severe infection changes DNA to increase premature aging. The researchers studied multiple cohorts and multiple tissue types, and discovered that tuberculosis induced perturbations in epigenetic regulation, specifically in the regulation mediated by DNA methylation. These epigenetic changes were associated with premature cellular aging. "A multi-omic epigenetic clock assay could become part of the standard of care for infectious diseases and further inform about increased risk for other diseases after chronic conditions or environmental exposure," said co-senior author Cristian Coarfa, Ph.D., associate professor, Department of Molecular and Cellular Biology. Baylor College of Medicine received three CPRIT Core Facilities Support Awards (RP170005, RP200504, RP210227) in 2016, 2020, and 2021, respectively, for a total of $13 million.

81. Dry eye is a prevalent disease affecting tens of millions of individuals worldwide. Clinical trial results and animal models provide evidence that inflammation contributes to the pathogenesis of ocular surface disease in dry eye. Dry eye with corneal and conjunctival epithelial disease develops in systemic vitamin A deficiency; however, the pathogenic mechanisms had not been clarified. Stephen Pflugfelder, M.D., professor and chair in ophthalmology, Baylor College of Medicine, and colleagues investigated the mechanism for dry eye development in the RXRα loss of function mutant mouse. The findings, published in March 2022 in *Frontiers in Medicine*, indicate that RXRα suppresses generation of dry eye disease-inducing IL-17 producing lymphocytes s in the conjunctiva and identifies RXRα as a potential therapeutic target in dry eye. Strategies that maintain the ocular surface retinoid axis in dry eye may prevent IL-17 induced epithelial pathology. Baylor College of Medicine received a $5.2 million CPRIT Core Facility Support Awards grant (RP180672) in 2018.

82. A variety of pathogens, including viruses, bacteria and parasites, target cellular lipid droplets for their replication. Rotaviruses (RVs) infect the villous epithelium of the small intestine and are a major cause of acute gastroenteritis in infants and young children worldwide. Sue E. Crawford, Ph.D., assistant professor, Virol and Micro: Estes, Baylor College of Medicine, set out to review the role of lipid droplets in RV replication. Dr. Crawford and fellow researchers at Baylor College of Medicine examined studies that support the hypothesis that rotavirus infection induces and requires lipid droplets for replication. The results, published in March 2022 in *Frontiers in Physiology*, demon-

strate that RV is an excellent model to dissect the cellular process of lipid droplet formation and to determine how RV induces and usurps lipid droplet biogenesis to form viroplasm/lipid droplets for virus replication. Lipid droplets are now recognized as playing diverse roles in cellular lipid metabolism, energy metabolism and cell signaling, and are implicated in multiple human infectious diseases including hepatitis, chlamydia, tuberculosis, and metabolic diseases such as diabetes and atherosclerosis. Texas A&M University System Health Science Center received a $5.9 million CPRIT Core Facility Support Awards grant (RP150578) in 2015.

83. Glioblastoma multiforme (GBM) is a highly invasive and devastating primary form of brain cancer. The complexity and molecular heterogeneity of GBM pose the challenge for accurate diagnosis and therapy, and because of this the molecular mechanisms of GBM tumorigenesis are not clear. Zhongming Zhao, Ph.D., M.S., professor, School of Biomedical Informatics at The University of Texas Health Science Center, and researchers reported that accurate pathological subtype diagnosis is pivotal for optimal patient management. The team developed a biologically interpretable and highly efficient deep learning framework based on a convolutional neural network for subtype identification. The results, published in *Frontiers in Genetics* in March 2022, show that the deep learning model outperforms the traditional machine learning algorithms. Furthermore, they identified the genotype–phenotype relationship of GBM subtypes and the subtype-specific predictive biomarkers for potential diagnosis and treatment. The University of Texas Health Science Center at Houston received a $4.4 million CPRIT Core Facility Support Awards grant (RP180734) in 2018.

84. Researchers have identified a four-protein complex that appears to play a key role in generating ribosomes – organelles that serve as protein factories for cells – as well as a surprising part in neurodevelopmental disorders. These findings, published in March 2022 in *Cell Reports*, could lead to new ways to manipulate ribosome production, which could impact a variety of conditions that affect human health. CPRIT Scholar Jun Wu, Ph.D., assistant professor, Department of Molecular Biology, The University of Texas Southwestern Medical Center, and colleagues developed a "Ribo-SNAP" technique that researchers used to track and quantify the level of old and new ribosomes, and the maturation rate of pre-ribosomes across different human cells. Using the gene editing tool called CRISPR, the researchers identified four genes known as *CINP*, *SPATA5L1*, *C1orf109*, and *SPATA5*. This work revealed unexpected variability in ribosome assembly rates across different cell types. Michael Buszczak, Ph.D., professor, Department of Molecular Biology, The University of Texas Southwestern Medical Center, noted that he and his colleagues plan to study why the central nervous system appears to be more sensitive than other cell types to ribosomal disruptions. The University of Texas Southwestern Medical Center recruited Dr. Wu in August 2017 from Salk Institute for Biological Studies with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR170076).

85. Respiratory Syncytial Virus (RSV) is a major global health burden as it is a leading cause of acute lower respiratory infection (ALRI) in young children and the elderly. RSV causes approximately 22% of all severe ALRI worldwide resulting in over 30 million annual cases and 3 million hospitalizations. Pedro A. Piedra, M.D., professor, Department of Molecular Virology and Microbiology, Baylor College of Medicine, noted that immune responses to the initial and subsequent RSV exposures are non-sterilizing, as evidenced by re-infection throughout life. This inadequate immune response is not caused by the viral evasion of the immune system seen with other respiratory viruses, including influenza. In this study, published in *Frontiers in Immunology* in March 2022, the team evaluated the RSV-specific memory T cell responses to the F protein in healthy adult subjects over the course of a single RSV season. They found that memory T cell responses followed the three distinct antibody kinetic profiles that are associated with their RSV infection status: uninfected, acutely infected, and recently infected. The results expand their understanding of the longevity of the adaptive immune response to the RSV fusion and are vital for developing an efficacious RSV vaccine, particularly in

older adult populations. Baylor College of Medicine received a $5.17 million CPRIT Core Facility Support Awards grant (RP180672) in 2018.

86. Researchers at The University of Texas MD Anderson Cancer Center have discovered that two distinct classes of cancer-associated fibroblasts (CAFs) accumulate in the pancreatic tumor microenvironment and play opposing roles to promote and restrain pancreatic cancer development. CPRIT Scholar Raghu Kalluri, M.D., Ph.D., Chair Department of Cancer Biology, and team performed single-cell RNA sequencing (scRNA-seq) to analyze gene expression and clarify the types of CAFs present in pancreatic tumors. They focused on two distinct subsets of CAFs marked by expression of fibroblast activation protein (FAP) and alpha-smooth muscle actin (αSMA). As reported in *Cancer Discovery* in June 2022, researchers found that expression of these proteins in treatment-naïve human tumor samples correlated with patient outcomes. Using novel mouse models, the researchers next demonstrated that FAP+ and αSMA+ CAFs play distinct and opposing roles in the tumor microenvironment. "This is a new discovery that helps move the field forward, with a new appreciation of the biology of pancreatic cancer and possible strategies for therapeutic interventions," Dr. Kalluri said. The University of Texas MD Anderson Cancer Center recruited Dr. Kalluri from Harvard Medical School in August 2012 with the support of a $3.5 million CPRIT Recruitment of Established Investigators grant (R1227) and received a $900,000 CPRIT Individual Investigator grant (RP150231) in 2015.

87. Primary prostate cancer is androgen receptor (AR) signaling dependent; metastatic disease is treated with some form of androgen deprivation therapy (ADT). Some tumors develop resistance and are termed castration resistant prostate cancer (CRPC). The constitutively AR splice variant, AR-V7, plays an important role in resistance to androgen deprivation therapy in castration resistant prostate cancer (CRPC). In this study published in *Nature* in March 2022, researchers used LNCaP and VCaP cell lines in which AR-V7 expression can be induced to match the level of AR, to compare the activities of AR and AR-V7. Nancy L. Weigel, Ph.D., professor of molecular and cell biology, Baylor College of Medicine, and colleagues reported that their studies utilizing inducible models are unique in that the levels of AR-V7 were comparable to LNCaP AR levels to determine the capacity of AR-V7 to bind to chromatin and regulate gene transcription. This preclinical foundation supports the concept that the AR isoforms have unique actions with the potential to serve as biomarkers or novel therapeutic targets. Baylor College of Medicine received a $6.15 million CPRIT Multi-Investigator Research Awards grant (RP150648) in 2015.

88. A recent study published by researchers at Baylor College of Medicine and colleagues identified two main subtypes or endotypes of tuberculosis according to the person's immune response to the infection. They found that one subtype had a better prognosis for curing tuberculosis than the other. Their findings, published in the *European Respiratory Journal* in February 2022, could improve personalized treatment options for the deadliest of all bacterial infectious diseases. The team conducted this research under the assumption that tuberculosis is not a uniform disease, and that the outcome depends on the immune response produced by the infected person. Led by Cristian Coarfa, Ph.D., associate professor of molecular and cellular biology, Baylor College of Medicine, the team applied cutting-edge, unbiased bioinformatic techniques to analyze large patient datasets to look at immune responses to tuberculosis and identified two main clusters or endotypes of the disease. "When we compared different drugs as potential personalized therapy, we found that one therapy could be inconsequential or detrimental to one TB subtype, but beneficial to the other," said co-first author Andrew DiNardo, M.D., assistant professor of medicine–infectious diseases, Baylor College of Medicine. Researchers will now implement clinical trials to treat tuberculosis following a stratified personalized therapy approach. Baylor College of Medicine was awarded three CPRIT Core Facility Support Awards grants (RP170005, RP200504, RP210227) in 2016, 2020, and 2021, respectively, for a total of $13 million.

89. Acquired chemoresistance is a common cause of treatment failure in cancer. The scheduling of a multi-dose course of chemotherapeutic treatment may influence the dynamics of acquired chemoresistance, and drug schedule optimization may increase the duration of effectiveness of a particular chemotherapeutic agent for a particular patient. CPRIT Scholar Thomas Yankeelov, Ph.D., professor, Director of the Center for Computational Oncology, The University of Texas at Austin, and team presented a method for experimentally optimizing an *in vitro* drug schedule through iterative rounds of experimentation and computational analysis and demonstrate the method's ability to improve the performance of doxorubicin treatment in three breast carcinoma cell lines. As reported in *PLOS Computational Biology* in March 2022, researchers found that the interval between drug exposures can be optimized while holding drug concentration and number of treatments constant, suggesting that this may be a key variable to explore in future drug schedule optimization efforts. They also used this method's model calibration and selection process to extract information about the underlying biology of the doxorubicin response and found that the incorporation of delays on both cell death and regrowth are necessary for accurate parameterization of cell growth data. The University of Texas at Austin recruited Dr. Yankeelov in September 2015 from Vanderbilt University with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR160005).

90. Major depressive disorder (MDD) is one of the top two causes of disability in the world. Current treatments are only partially effective; about one third of patients with MDD fail to achieve remission with first- or second-line treatments. CPRIT Scholar Can Cenik, Ph.D., assistant professor, Department of Molecular Biosciences at The University of Texas at Austin, and colleagues asserted that a promising and topical approach to this problem is the discovery and validation of depression biomarkers. The team previously found that lower concentrations of the cholesterol precursor desmosterol and higher concentrations of another precursor, 7-dehydrocholesterol (7DHC), were predictive of moderate to severe depressive symptoms. Since the publication of the previous study, it has become increasingly apparent that several psychotropic medications interfere with cholesterol synthesis, including trazadone. In the current study, published in *Nature* in April 2022, the team tested the hypothesis that desmosterol and 7DHC would be altered in postmortem brains from people with depression and these changes may be explained by psychotropic medication use. According to the researchers, this is the first demonstration of sterol abnormalities in human brains due to trazodone use. This is a previously unappreciated potential risk of this commonly used medication. The University of Texas at Austin recruited Dr. Cenik in August 2018 from Stanford University School of Medicine with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR180042).

91. STING, stimulator of interferon genes, is a central part of the innate immune system, which serves as the body's first line of defense against viruses, bacteria, and cancers. The study, published in April 2022 in *Nature*, reported that STING-mediated immunity could be exploited in the development of vaccines or cancer immunotherapies. CPRIT Scholar Xiaochen Bai, Ph.D., associate professor, Department of Biophysics and Cell Biology at The University of Texas Southwestern Medical Center, and colleagues mixed purified STING protein with cGAMP and used cryo-EM to image the resulting product. However, the researchers saw few activated STING molecules, and those that were present were unstable. Scientists then added an investigational drug known as compound 53 (C53) that's currently being tested as a STING activator for anti-cancer therapy. The combination of cGAMP and C53 produced significantly more activated STING molecules. The fact that STING seems to need both cGAMP and C53 to become strongly and stably activated suggests that an unknown molecule akin to C53 may exist in cells to fill the same role. Someday drugs that attach to or block this newly discovered binding site could be used to strengthen or dampen immunity to fight infectious or autoimmune diseases. The University of Texas Southwestern Medical Center recruited Dr. Bai in September 2016 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track

Faculty Members grant (RR160082).

92. In a breakthrough discovery, scientists from The University of Texas Health Science Center at San Antonio reported that inhibiting a liver enzyme in obese mice decreased the rodents' appetite, increased energy expenditure in adipose (fat) tissues and resulted in weight loss. The finding, published in *Cell Metabolism* in April 2022, provides a potentially desirable drug target to treat metabolic issues such as obesity and diabetes. The researchers' first-in-class CNOT6L inhibitor, dubbed iD1, stabilized liver GDF15 and FGF21 mRNAs in obese mice, increasing levels of the two proteins in the blood. Senior author Masahiro Morita, Ph.D., assistant professor, Department of Molecular Medicine in UT Health San Antonio, reported that after 12 weeks, treated rodents ate 30% less food and exhibited 30% reduced body weight. Energy expenditures in the adipose tissues increased by about 15% and liver fat decreased 30%. Mice treated with iD1 showed improved insulin sensitivity and lower blood glucose levels. Their next step is to refine this mechanism and identify new drugs that may be more specific and more potent. The University of Texas Health Science Center at San Antonio received a $1 million CPRIT Individual Investigator grant (RP220267) in February 2022.

93. Researchers at the Houston Methodist Research Institute have identified the genetic and molecular fingerprints of different cancer and immune cells in glioblastoma, the deadliest and most common type of brain cancer in adults. Kyuson Yun, Ph.D., senior author and associate professor of neurology at the Houston Methodist Academic Institute, reported that their in-depth molecular analysis of over 200,000 single cells revealed a protein, called S100A4, that could be a potential therapeutic target for restoring antitumor action of immune cells toward glioblastomas that have otherwise tricked the immune system into protecting it. The study, published in February 2022 in *Nature Communications*, noted that the strategy was to spare "good" immune cells that are associated with better survival and selectively target "bad" immune cells that promote tumor growth and immune evasion. They discovered that the S100A4 regulator protein is produced and secreted by glioblastoma cancer cells, immunosuppressive T cells and bone marrow-derived myeloid cells. The team plans to develop antibody drugs to target this S100A4 protein and to develop small molecules that can enter the nucleus of cancer cells and inhibit the function of the S100A4 protein in glioblastoma stem cells. The Methodist Hospital Research Institute received a $200,000 CPRIT High Impact/ High Risk grant (RP180882) in 2018.

94. Dietary supplements are thought to boost immunity, but little is known about the effects of supplements on immunotherapy activity. To explore the connection, co-corresponding author, Dihua Yu, M.D., Ph.D., Department of Molecular and Cellular Oncology at The University of Texas MD Anderson Cancer Center, and colleagues performed a retrospective analysis of clinical data from MD Anderson patients treated with immunotherapy. Patients with melanoma who took vitamin E while on anti-PD-1/PD-L1 checkpoint inhibitors had significantly improved survival compared to patients who didn't take vitamin E or multivitamins. The results, published in *ScienceDaily* in April 2022, demonstrated that vitamin E directly binds and blocks the activity of the SHP1 checkpoint protein in dendritic cells, which increases antigen presentation and primes T cells for an anti-tumor immune response. Lead author, Xiangliang Yuan, Ph.D., Department of Molecular and Cellular Oncology, The University of Texas MD Anderson Cancer Center said, "This work yielded important insights on the interaction between vitamin E and SHP1 that will guide us to develop more specific allosteric SHP1 inhibitors. Compellingly, it appears that unleashing dendritic cells by inhibiting SHP1 may be an advantageous strategy to enhance antitumor immunity." The University of Texas MD Anderson Cancer Center received a $5.9 million CPRIT Multi-Investigator Award grant (RP180813) in 2018.

95. Researchers at The University of Texas MD Anderson Cancer Center have developed a new bioinformatics platform called REcurrent Features LEveraged for Combination Therapy (REFLECT). REFLECT integrates machine learning and cancer informatics algorithms to analyze biological tumor

features and identify frequent co-occurring alterations that could be targeted by multiple drugs. The findings were presented at the American Association for Cancer Research (AACR) Annual Meeting in April 2022 by principal investigator Anil Korkut, Ph.D., assistant professor of bioinformatics and computational biology, and were published in June 2022 in *Cancer Discovery*. The team built and used the REFLECT tool to develop a systematic and unbiased approach to match patients with optimal combination therapies. The researchers also retrospectively validated the approach in the clinical setting through available data from the I-PREDICT trials, which evaluated many combination therapies across diverse cancer types. Patients in this trial that received combinations predicted by REFLECT to be most beneficial had significantly longer progression-free survival and overall survival compared to other combinations. The researchers plan to expand their study to better address and predict toxicity from matched drug combinations and address the significant heterogeneity within tumors, which can affect response to targeted therapies. The University of Texas MD Anderson Cancer Center received a $200,000 CPRIT High Impact/High Risk grant (RP170640) in 2017.

96. uPARAP is a cell-surface receptor, which is involved in collagen degradation and displays a differentiated expression profile between healthy tissue and cancer tissue, with several cancer types significantly overexpressing the receptor, including soft-tissue sarcoma, osteosarcoma, mesothelioma and glioblastoma multiforme (GBM). Principal Investigator, Richard Gorlick, M.D., professor, Division Head of Pediatrics, The University of Texas MD Anderson Cancer Center, and researchers conducted a pre-clinical study in Osteosarcoma PDX models and presented these data at the 2022 American Association for Cancer Research (AACR) Annual Meeting in April 2022. The data is promising, suggesting that targeting uPARAP via ADCs could represent a novel therapeutic option for osteosarcoma patients and other underserved cancer indications. The University of Texas MD Anderson Cancer Center received a $5 million CPRIT Core Facility Support Awards grant (RP180819) in 2018.

97. Baylor College of Medicine researchers and colleagues examined changes to smoking habits and correlates of increases and decreases during the COVID-19 pandemic among participants enrolled in a tobacco cessation and lung cancer screening program. Between June and October 2020, they conducted a cross-sectional survey of a program participant sample. Demographic variables included age, sex, race/ethnicity and marital status. Results, published in March 2022 in the *Ochsner Journal,* showed statistically significant and potentially clinically important differences between those who increased and decreased tobacco use during the pandemic. Among current smokers, 28.2% reported increased tobacco use, 17.3% reported decreased tobacco use and 54.5% reported no change. In addition, there were no reports of relapse among former smokers. Roger Zoorob, M.D., MPH, professor and Chair, Department of Family and Community Medicine at Baylor College of Medicine, found correlates of increased tobacco use related to coping strategies and mental health. In contrast, those who smoked less were more likely to practice social distancing and other preventive strategies of proven benefit. These data may aid healthcare providers to identify and provide counsel to cigarette smokers at greater risk for increasing tobacco consumption during current and future stresses such as the COVID-19 pandemic. Baylor College of Medicine received a $1.5 million CPRIT Prevention grant (PP180016) in 2018.

98. OncoNano Medicine, Inc. announced positive results from the company's ON-BOARD™ pH-sensitive nanoparticle platform. The data, presented at the American Association for Cancer Research (AACR) Annual Meeting 2022, demonstrated that the clinically validated ON-BOARD™ platform has the potential to be a universal tool for tumor specific activation and the efficient delivery of proteins for an improved therapeutic index. A variety of biosimilar monoclonal antibodies including those of atezolizumab, cetuximab, pembrolizumab, trastuzumab and ipilimumab were encapsulated by the ON-BOARD™ platform. The findings indicate that ON-BOARD™ demonstrated: encapsulation of antibodies without additional modification of the original antibody, encapsulation efficiency ranging

from 50-100%, formulations characterized as uniformly distributed particles < 100nm in size with good stability, over a 100-fold activation window between the acid-activated and intact formulations based on *in vitro* assessment by cell-based reporter assays, pH-dependent activation that was further confirmed by affinity and binding assay, and tumor specific accumulation that was demonstrated by a biodistribution study. OncoNano Medicine, Inc. received a $15.4 million CPRIT Product Development Research grant (DP190066) awarded in 2019.

99. Circulating tumor cells (CTC), which are detached from primary tumors to enter the bloodstream, are particularly hard to detect. Researchers at the University of Houston have developed a new way to detect very rare and highly heterogeneous circulating tumor cells with high specificity and sensitivity. The UniPro device, which was reported in the journal *Molecular Therapy* in December 2021, can detect CTCs even after they have undergone epithelial-mesenchymal transition (EMT), and it is the first CTC detection method that can unambiguously detect live CTC. "We report a novel method that is based on a chimeric virus probe and can detect CTCs with extremely high specificity and sensitivity. Moreover, it exclusively detects live CTCs, and its detection efficacy is not impacted by the variation of epithelial cell adhesion molecule expression," said Shaun Zhang, M.D., Ph.D., professor, Department of Biology and Biochemistry and director of the Center for Nuclear Receptors and Cell Signaling. The University of Houston's Office of Technology Transfer & Innovation is currently working with industry partners to establish the best plan to commercialize this technology. University of Houston received a $700,000 CPRIT Individual Investigator grant (RP200464) in 2020.

100. The field of chimeric antigen receptor (CAR) modified T cell therapy has rapidly expanded in the past few decades. As of early 2022, there were six CAR T cell products that have been approved by the FDA. Recent evidence suggested that, apart from developing next-generation CAR T cells with additional genetic modifications, *ex vivo* culture conditions could significantly impact CAR T cell functionality – an often-overlooked aspect during clinical translation. A team of researchers from Baylor College of Medicine reported in the journal *Frontiers in Immunology* in April 2022, their investigation into the *ex vivo* manufacturing process of CAR T cells and how this impacts CAR T cell function. Norihiro Watanabe, Ph.D., instructor, Center for Gene Therapy, Baylor College of Medicine, and colleagues report that culture methods for the *ex vivo* maintenance of therapeutic T cells is a necessary step to generate CAR T cells for both preclinical research and clinical implementation, and their effects on the quality of cell products. The choice of reagents for *ex vivo* CAR T cell expansion can drastically affect the quality of therapeutic T cells, emphasizing the need for more detailed investigations. Combining the optimal manufacturing procedure with additional innovative genetic engineering approaches will allow the researchers to achieve the ultimate goal of developing an effective CAR T cell therapy for cancer patients. Baylor College of Medicine received a $250,000 CPRIT High Impact/High Risk grant (RP210158) in 2021.

101. Among children diagnosed with acute lymphoblastic leukemia, Latinos without minimal residual disease had a higher likelihood of relapse than their white counterparts. "Several studies have indicated that Latinos have worse outcomes compared with non-Latino whites, so trying to understand when during therapy that disparity begins was key to this assessment," said Philip J. Lupo, Ph.D., MPH, professor of pediatrics at Baylor College of Medicine. As reported in *Helio Hematology/ Oncology* in April 2022, the study included 1,662 children (> 60% Latino) diagnosed with ALL between 2004 and 2018 from the Reducing Ethnic Disparities in Acute Leukemia (REDIAL) Consortium, which comprises seven major pediatric cancer centers in the United States. They censored patients at date of death, last follow-up or bone marrow transplant. Results showed 237 (14.3%) experienced relapse, and 63% of those who relapsed had MRD-negative status. "Interestingly, while minimal residual disease is one of the strongest risk factors for relapse in the overall population, it did not predict relapse in Latino patients after accounting for other clinical and sociodemographic factors," Dr. Lupo said. The team plans to incorporate other critical factors into predictive models

for ALL outcomes, with the ultimate goal of eliminating disparities in outcomes among those diagnosed with ALL. Baylor College of Medicine received a $200,000 CPRIT High Impact/High Risk grant (RP180755) in 2018.

102. Weight loss through behavioral modification is central to treating non-alcoholic fatty liver disease (NAFLD). To achieve this, patients need to accurately self-perceive their health behaviors. Researchers at The University of Texas MD Anderson Cancer Center aimed to identify the demographic and clinical predictors of concordance between objective measures and self-perception of body weight status, physical activity (PA), and dietary behaviors among a predominantly Hispanic population of patients with NAFLD at their baseline hepatology clinic visit. The team used data from the Harris County NAFLD Cohort, an ongoing prospective study in a regional safety-net healthcare system. Patients completed self-administered baseline questionnaires on demographics, diet, PA, and self-perceptions. Researchers assessed concordance between actual and self-perceived body weight and energy-balance behaviors. Multivariable logistic regression identified predictors of concordance. Patients (n = 458; average age 46.5 years) were 90% Hispanic and 76% female. Most NAFLD patients accurately self-perceived their body weight. A third or more of those not meeting fruit/vegetable intake or PA guidelines had inaccurate perceptions about their behaviors. These findings highlight key areas to target in NAFLD-specific behavioral modification programs. The University of Texas MD Anderson Cancer Center received a $2.65 CPRIT Academic Research grant (RP170259) in 2016.

103. A most devastating feature of cancer is its ability to migrate and invade adjacent tissues. During invasion by carcinomas, cancer cells can undergo an epithelial-mesenchymal transition (EMT) to gain mesenchymal traits, such as increased motility and invasiveness. Emerging evidence reveals that EMT is a reversible transition process with one or multiple hybrid, or partial, epithelial/mesenchymal (E/M) states which can help coordinate the collective invasion of cancer cells. The transcription factor Nrf2, which is associated with tumor progression and resistance to therapy, appears to be central to this process. Using a combination of immunocytochemistry, single cell biosensors, and computational modeling, CPRIT Scholar José N. Onuchic, Ph.D., Chair, of the Department of Physics at Rice University, and colleagues show that Nrf2 functions as a phenotypic stability factor for hybrid E/M cells by inhibiting a complete epithelial-mesenchymal transition (EMT) during collective cancer migration. The results, published in April 2022 in *Frontiers in Molecular Biosciences,* provide direct evidence that Nrf2 acts as a phenotypic stability factor in restricting complete EMT and plays an important role in coordinating collective cancer migration. Rice University recruited Dr. Onuchic in July 2011 from the University of California, San Diego with the support of a $6 million CPRIT Recruitment of Established Investigators grant (R1110).

104. Khandan Keyomarsi, Ph.D., professor of experimental radiation oncology at The University of Texas MD Anderson Cancer Center, reported preclinical data demonstrating TTI-101 overcomes palbociclib resistance in metastatic breast cancer murine models. The study demonstrated that the upregulation of the IL-6 / STAT3 pathway plays a critical role in palbociclib (CDK 4/6) resistance in hormone receptor-positive (HR+), HER2-negative (HER2-) metastatic breast cancer. Further, the studies demonstrated that the combination of TTI-101 with palbociclib is synergistic in arresting tumor growth in murine models derived from metastatic breast cancer patients who had developed resistance to palbociclib. These findings were presented at the 2022 Annual Meeting of the American Association for Cancer Research (AACR) in April by Nicole Kettner, Ph.D., postdoctoral fellow, Department of Experimental Radiation Oncology at The University of Texas MD Anderson Cancer Center. The University of Texas MD Anderson Cancer Center and received a $900,000 CPRIT Individual Investigator grant (RP170079) in November 2016.

105. Bone health screening is recommended for patients with prostate cancer who are initiating treatment with androgen deprivation therapy (ADT); however, bone mineral density screening rates in the U.S. and their association with fracture prevention are unknown. Maria E. Suarez-Almazor, M.D., Ph.D., Department of Health Services Research, University of Texas MD Anderson Cancer Center, and colleagues set out to determine the rates of dual-energy x-ray absorptiometry (DXA) screening to assess bone mineral density among older men with prostate cancer who are beginning treatment with androgen deprivation therapy and their association with fracture development. As reported in the *JAMA Network Open* on April 1, 2022, in this cohort study of 54,953 older men with prostate cancer, bone mineral density testing was significantly associated with a decreased risk of developing major osteoporotic fractures after adjustment for covariates. This study's findings support the clinical importance of performing DXA screening for major fracture prevention among older men with prostate cancer and that implementation strategies are needed to adopt bone health screening guidelines in clinical practice. The University of Texas MD Anderson Cancer Center received a $872,000 CPRIT Multi-Investigator Research grant (RP101207-P2) in 2010. The University of Texas Medical Branch at Galveston received a $6 million CPRIT Multi-Investigator Research grant (RP160674) in 2016.

106. Pirtobrutinib is a highly selective, noncovalent (reversible) Bruton's tyrosine kinase (BTK) inhibitor. With currently available covalent BTK inhibitors, which irreversibly inhibit BTK, patients develop acquired resistance. Michael Wang, M.D., professor, Department of Lymphoma & Myeloma at The University of Texas MD Anderson Cancer Center, reported that the next-generation inhibitor of BTK may be effective in mantle cell lymphoma for patients previously treated with an older BTK inhibitor, according to results from the phase I/II BRUIN trial. These findings were reported at the 2021 American Society of Hematology (ASH) Annual Meeting & Exposition in December 2021. A total of 618 patients with advanced B-cell malignancies were enrolled in the phase I/II trial. The current analysis focused on the 134 with relapsed or refractory mantle cell lymphoma, with 111 patients included in the efficacy analysis. The response rate was 51%, and 25% were complete responses. Most patients enjoyed a tumor reduction. And, of 618 patients [in the overall study population], just 6, or 1%, permanently discontinued pirtobrutinib because of treatment-emergent adverse events. "This is a really impressive safety profile," Dr. Wang said. The University of Texas MD Anderson Cancer Center received an $842,000 CPRIT Individual Investigator grant (RP160019) in 2015.

107. Researchers are using many approaches to develop next-generation COVID-19 vaccines, including some that might be taken by mouth. From a scientific standpoint, vaccines are poised to keep winning the fight against SARS-CoV-2, the virus that causes COVID-19, said John Cooke, M.D., Ph.D., professor and Chair of the Department of Cardiovascular Sciences at the Methodist Hospital Research Institute in an April 15, 2022, article in *The HealthCast*. "I think that we have got it on the run," Dr. Cooke said. That speed might be essential in the fight against a virus that already has mutated several times and is certain to keep evolving. Dr. Cooke said future vaccines will be able to adapt quickly, too. Although people might need an annual COVID-19 vaccine, the way they do with influenza, the researchers have some tools now to defeat any evolutions of the virus as those occur. Dr. Cooke, whose center works on ways to help small developers bring RNA-based treatments to market, likens mRNA to biological software that can be adapted quickly. "You can simply write the code for the therapeutic protein that you need. And that therapeutic protein might be a vaccine for an infectious disease; it might be a vaccine for cancer," Dr. Cooke said. Although mRNA treatments had been in development for decades and had been tested in clinical trials for cancer and rabies, the COVID-19 vaccine marked the technology's first widespread use. The Methodist Hospital Research Institute received two CPRIT Academic Research Awards, a $4.8 million grant (RP150611) in 2015 and a $4 million grant (RP200619) in 2020.

108. Small cell lung cancer (SCLC) is an aggressive malignancy with no established biomarkers.

Schlafen 11(SLFN11), a DNA/RNA helicase that sensitizes cancer cells to DNA-damaging agents, has emerged as a promising predictive biomarker for several drug classes including platinum and PARP inhibitors. Carl M. Gay, M.D., Ph.D., Department of Thoracic-Head & Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, and fellow researchers' detection of SLFN11 in circulating tumor cells (CTCs) may provide a valuable alternative to tissue sampling. As reported in the April 19, 2022, issue of the *British Journal of Cancer*, SLFN11 levels can be monitored in CTCs from SCLC patients using non-invasive liquid biopsies. Analysis from patients with longitudinal samples suggest a decrease in CTC number and in SLFN11 expression that correlates with clinical response. The ability to detect SLFN11 in CTCs from SCLC patients adds a valuable tool for the detection and longitudinal monitoring of this promising biomarker. The University of Texas MD Anderson Cancer Center received a $1.5 million CPRIT Early Clinical Investigator grant (RP210159) in August 2021.

109. Many individuals with mild or moderate asthma benefit from treatment with inhaled corticosteroids. However, patients with severe asthma often do not benefit from inhaled corticosteroid treatment. In this study published on April 20, 2022, in *Science Translational Medicine*, researchers investigated the mechanism behind these poor responses. The authors, including Fen Wang, Ph.D., professor, Institute of Biosciences and Technology at Texas A&M University System Health Science Center, found that patients with severe asthma had increased corticosteroid-driven fibroblast growth factor (FGF) expression. In mice, FGF exposure increased hyaluronan production and neutrophil infiltration into the lungs, worsening allergic responses. This could be reversed by treating mice with pan-FGF receptor inhibitors, suggesting that a combination of corticosteroids and FGF inhibition may be a therapeutic option for those with severe asthma. In further proof-of-concept experiments, the team found that combination therapy with pan-FGF receptor inhibitors and corticosteroids prevented both eosinophilic and steroid-induced neutrophilic inflammation. Together, these results establish FGFs as therapeutic targets for severe asthma patients who do not benefit from ICS. Texas A&M University System Health Science Center received a $200,000 CPRIT High Impact/High Risk grant (RP190612) in August 2019.

110. Colorectal cancer (CRC) is the third leading cause of cancer death globally. A polyp's initial stage is noncancerous; however, some polyps may become cancerous over time. Several classification models have been proposed to identify polyps, but their performance has not been comparable to an expert endoscopist yet. In a study published in *Frontiers in Genetics* on April 26, 2022, researchers propose a multiple classifier consultation strategy to create an effective and powerful classifier for polyp identification. Zhongming Zhao, Ph.D., professor at the School of Biomedical Informatics (SBMI), founding director of the Center for Precision Health, The University of Texas Health Science Center at Houston, and team introduced a new Ensemble method for the classification of each individual frame of a colonoscopy video as informative or uninformative and then for predicting the classified informative frames as cancerous or noncancerous polyps. The Ensemble can fuse the fine-tuned convolutional neural network (CNN) models to derive a more powerful image classification scheme than the individual CNNs. It outperformed other state-of-the-art techniques with a performance measure greater than 95% in each of the algorithm parameters. This method will help researchers and gastroenterologists develop clinically applicable, computational-guided tools for colonoscopy screening. The University of Texas Health Science Center at Houston received a $4.42 million CPRIT Core Facility Support Awards grant (RP180734) in 2018.

111. Predicting outcomes of patients with COVID-19 at an early stage is crucial for optimized clinical care and resource management. Although multiple machine learning models have been proposed to address this issue, because of their requirements for extensive data preprocessing and feature engineering, they have not been validated or implemented outside of their original study site. Researchers at The University of Texas Health Science Center at Houston and colleagues aimed

to develop accurate and transferrable predictive models of outcomes on hospital admission for patients with COVID-19. In this study published in *The Lancet* on June 1, 2022, the team developed recurrent neural network-based models (CovRNN) to predict the outcomes of patients with COVID-19 by use of available electronic health record data on admission to hospital, without the need for specific feature selection or missing data imputation. Degui Zhi, Ph.D., associate professor at the UTHealth School of Biomedical Informatics, and one of the founding faculty members the Center for Precision Health, reported that CovRNN was designed to predict three outcomes: in-hospital mortality, need for mechanical ventilation, and prolonged hospital stay (>7 days). Trained on a large, heterogeneous, real-world dataset, the CovRNN models showed the feasibility of a COVID-19 predictive model that delivers high accuracy without the need for complex feature engineering. The University of Texas Health Science Center at Houston received two CPRIT Research Training grants, (RP160015, RP210042) in 2015 and 2021 for a total of $8.2 million, and a CPRIT Core Facility Support Awards grant (RP170668) in 2017 for $5.85 million.

112. There are cells in the body known as pluripotent stem cells that are yet to specialize in a particular biological function. These cells maintain the potential to become any of the possible cell types in an organism. Pluripotent stem cells have shown great promise in fields such as regenerative and transplant medicine for their properties, including unlimited self-renewal. The protein NANOG is the telltale marker of pluripotent stem cells and a necessary ingredient to reset specialized cells back into naïve, untrained stem cells. Researchers at The University of Texas Health Science Center at Houston and collaborating institutions reported their findings in the journal *Nature Cell Biology* on April 28, 2022, which provides insights into the mechanism of how human NANOG facilitates the activation of cell pluripotency. The team applied single molecule and fluorescence fluctuation microscopy techniques which they used to visualize whether two molecules interact with each other. "We were able to show that NANOG aggregation is actually essential to its function as a master transcription factor and a mediator of the bridging of DNAs," said co-corresponding author Allan Chris Ferreon, Ph.D., assistant professor of pharmacology and chemical biology at Baylor College of Medicine. NANOG's unique ability to form prion-like assemblies could provide a cooperative and concerted DNA bridging mechanism that is essential for chromatin reorganization and dose-sensitive activation of ground-state pluripotency. The University of Texas Health Science Center at Houston received a $4.4 million CPRIT Core Facility Support Awards grant (RP180734) in 2018 and a $4 million CPRIT Research Training grant (RP210042) in 2021.

113. Researchers at The University of Texas Health Science Center at Houston and collaborating institutions have identified a combination therapy for treating triple-negative breast cancer (TNBC) that results in durable tumor regression in an animal model of the condition. "TNBC is an aggressive subtype of breast cancer with an overall poorer prognosis than other breast cancer subtypes," said co-corresponding author Jeffrey Rosen, Ph.D., professor, Department of Molecular and Cellular Biology at Baylor College of Medicine. On one side, the chemotherapy drug cyclophosphamide eliminated tumor cells, while on the other front, another drug inhibited tumor-associated cells called macrophages, which block the body's immune response against the tumor. As reported in the journal *Cancer Research* in April 2022, this two-front strategy effectively treated several highly aggressive TNBC primary tumors and metastasis. This signature can help identify patients who might be candidates for combination therapy. The researchers are planning to conduct a clinical trial to assess the value of their approach in treating human TNBC. Baylor College of Medicine received a $4 million CPRIT Research Training grant (RP160283) in 2015. The University of Texas Health Science Center at Houston received a $5.9 million CPRIT Core Facility Support Awards grant (RP170668) in 2017.

114. The incidence of oropharyngeal cancer (OPC) is increasing at a rate of about 5% each year in the United States and according to current projections, OPC will represent about half of HNCs by 2030.

This increased incidence of OPC is attributed to the contribution of the human papillomavirus (HPV) in the etiology of HNC. Unfortunately, patients are at risk of developing substantial cancer treatment-related side-effects, including xerostomia. Corresponding author Sanjay Shete, Ph.D., Chair in Cancer Prevention, Department of Biostatistics, and fellow researchers from The University of Texas MD Anderson Cancer Center hypothesized that genetic variants are associated with cancer treatment-associated xerostomia. As reported in *Scientific Reports* on April 22, 2022, the team conducted a genome-wide association study and patient-reported cancer treatment-related xerostomia was assessed using the MD Anderson Symptom Inventory. Patient response was dichotomized as moderate to severe or none to mild symptoms. The most prominent findings in this study included potential associations of ANTXR1, RTP1, GLT1D1, NLRP9, and EGFLAM genes with xerostomia. This study provides, for the first time, preliminary evidence of genetic susceptibility to xerostomia. Further studies are needed to elucidate the role of genetic susceptibility to xerostomia. The University of Texas MD Anderson Cancer Center received a $2.65 million CPRIT Research Training grant (RP170259) in 2016.

115. The *RE1* Silencing Transcription Factor (REST) is a major regulator of neurogenesis and brain development. Medulloblastoma (MB) is a pediatric brain cancer characterized by a blockade of neuronal specification. *REST* gene expression is aberrantly elevated in a subset of MBs that are driven by constitutive activation of sonic hedgehog (SHH) signaling in cerebellar granular progenitor cells (CGNPs), the cells of origin of this subgroup of tumors. As reported in *Frontiers in Oncology* on May 6, 2022, Vidya Gopalakrishnan, Ph.D., Department of Pediatrics at The University of Texas MD Anderson Cancer Center, and colleagues identified the expression of two isoforms of *Rest* in mouse CGNPs, that differed in their transcription start site. Only one of the two isoforms (*Rest*-201) was significantly downregulated during neurogenesis, with *Rest*-202 likely facilitating the maintenance of *Rest* transcript at low levels essential for neuronal survival. This study also provides the first description of the epigenetic mechanisms underlying the downregulation of *Rest* mRNA during neurogenesis of CGNPs. Understanding the mechanism that controls the transcription of *REST* during normal neurogenesis and comparing it with disease states has identified novel opportunities for therapeutic targeting. The University of Texas MD Anderson Cancer Center received a $1.87 million CPRIT Individual Investigator Research Awards for Cancer in Children and Adolescents grant (RP150301) in February 2015.

116. The outcome of recurrent/refractory acute myeloid leukemia (AML) remains poor, and novel therapeutic approaches are urgently needed. T-cells expressing chimeric antigen receptors (CARs) have striking clinical activity against some hematological malignancies, but the clinical experience with CAR T-cells for AML has been limited. Michael Andreeff, M.D., Ph.D., professor of medicine, Department of Leukemia at the University of Texas MD Anderson Cancer Center, and colleagues have characterized in detail the phenotype and effector functions of ENG T-cell populations in vitro and in vivo. In this study published in Frontiers in Immunology on May 9, 2022, researchers demonstrated that the expansion, persistence, and anti-AML activity of CD123-ENG T-cells can be significantly improved by transgenic expression of IL15. The transgenic expression of IL15 significantly improved the ability of CD123-ENG T-cells to recursively kill target cells. They also highlight that targeting a single tumor antigen (CD123) can lead to immune escape, reinforcing the need to develop approaches to target multiple antigens. This study is among the first to demonstrate the benefit of transgenic IL15 in the setting of chronic antigen exposure and suggests that AML PDX models are ideal for modeling autologous CAR T-cell therapy for AML. The University of Texas MD Anderson Cancer Center received a $4.5 million CPRIT Core Facility Support Awards grant (RP130397) in December 2012.

117. When cells reproduce, the internal mechanisms that copy DNA get it right nearly every time. Researchers at Rice University have uncovered a tiny detail that helps understand how the process

could go wrong. Their study of enzymes revealed that the presence of a central metal ion critical to DNA replication also appears to be implicated in misincorporation, the faulty ordering of nucleotides on new strands. The observation reported in *Nature Communications* on April 29, 2022, could help develop treatments for genetic mutations and the diseases they cause, including cancer. CPRIT Scholar Yang Gao, Ph.D., assistant professor of biosciences, and colleagues used time-resolved crystallography to analyze proteins crystallized at 34 intermediate stages to define the positions of their atoms before, during and after DNA synthesis. "We've never known how the atoms move together because the spatial information was missing. Freezing the proteins and a small molecule substrate lets us capture this catalytic reaction for the first time," Dr. Gao said. Rice University recruited Dr. Gao in May 2019 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR190046).

118. Homologous recombination DNA repair (HR) is a complex DNA damage repair pathway and an attractive target of inhibition in anti-cancer therapy. To help guide the development of efficient HR inhibitors, it is critical to identify compensatory HR sub-pathways. In this study, CPRIT Scholar Patrick Sung, Ph.D., professor, Department of Biochemistry & Structural Biology at The University of Texas Health Science Center at San Antonio, and colleagues describe a novel synthetic interaction between RAD51AP1 and RAD54L, two structurally unrelated proteins that function downstream of the RAD51 recombinase in HR. Based on the results published in *Frontiers in Cell and Developmental Biology* on May 16, 2022, they concluded that the simultaneous inactivation of both RAD51AP1 and RAD54L could be a viable strategy to treat cancer in the context of induced DNA damage. Targeting RAD51AP1 together with RAD54L may be particularly effective against tumors with overactive HR, cancerous cells maintaining their telomeres by the ALT pathway and BRCA1/2-mutant tumors that have regained HR proficiency and are resistant to PARPi. The University of Texas Health Science Center at San Antonio recruited Dr. Sung in May 2018 from Yale University with a $6 million CPRIT Recruitment of Established Investigators grant (RR180029).

119. Researchers at The University of Texas Southwestern Medical Center examined the effectiveness of patient navigation to improve linkage to hepatitis C virus (HCV) treatment receipt in a socioeconomically disadvantaged, racially diverse patient population. Mamta Jain, M.D., professor of internal medicine, and colleagues performed a pre-post analysis evaluating the effectiveness of a patient navigation program among baby boomers who tested positive for HCV in a safety-net health system. The usual care group and patient navigation group were balanced using a stabilized inverse probability of treatment weighting approach. As reported in the journal *Clinical Gastroenterology and Hepatology* on May 13, 2022, the team found patient navigation helped baby boomers come to treatment sooner, and more patients were treated. This is the first study to demonstrate that patient navigation compared with usual care increases the proportion of patients linked to care among an underserved HCV population. The net impact of this type of program is to help move the needle towards HCV elimination. Patient navigation programs can be used to promote HCV elimination among traditionally difficult-to-reach patient populations. The University of Texas Southwestern Medical Center received a $2.6 million CPRIT Expansion of Cancer Prevention Services to Rural and Medically Underserved Populations grant (PP180091) in 2018. The University of Texas Medical Branch at Galveston received a $6 million CPRIT Multi-Investigator Research grant (RP160674) in 2016.

120. Inactivation of adenomatous polyposis coli (*APC*) is common across many cancer types and serves as a critical initiating event in most sporadic colorectal cancers. APC deficiency activates WNT signaling, which remains an elusive target for cancer therapy, prompting researchers at The University of Texas MD Anderson Cancer Center to apply the synthetic essentiality framework to identify druggable vulnerabilities for APC-deficient cancers. CPRIT Scholar Di Zhao, Ph.D., assistant professor, Department of Experimental Radiation Oncology, and colleagues reported that APC-deficient col-

orectal cancer models were susceptible to TDO2 depletion or pharmacologic inhibition, which impaired cancer cell proliferation and enhanced antitumor immune profiles. Thus, APC deficiency activates a TCF4–TDO2–AhR–CXCL5 circuit that affects multiple cancer hallmarks via autonomous and nonautonomous mechanisms and illuminates a genotype-specific vulnerability in colorectal cancer. This study, published in *Cancer Discovery* on July 6, 2022, identifies critical effectors in the maintenance of APC-deficient colorectal cancer and demonstrates the relationship between APC/WNT pathway and kynurenine pathway signaling. It further determines the tumor-associated macrophage biology in APC-deficient colorectal cancer, informing genotype-specific therapeutic targets and the use of TDO2 inhibitors. Ronald A. DePinho, M.D., professor, department of cancer biology. The University of Texas MD Anderson Cancer Center and Dr. Zhao received a CPRIT Recruitment of First-Time, Tenure-Track Faculty Members and $2 million CPRIT grant (RR190021) in 2019 and The University of Texas MD Anderson Cancer Center received a $4 million CPRIT Research Training grant (RP170067) in 2016.

121. Therapy-related myeloid neoplasms (t-MNs) represent one of the most devastating consequences of cancer therapy. These cancers arise from selective pressure introduced by chemo- and radiation therapies (CRTs) and are often treatment-resistant with a median overall survival (OS) of 7-14 months and a 5-year OS of 10-20%. They typically present in a form of acute myeloid leukemia (t-AML) or myelodysplastic syndromes (t-MDS) and develop 3 to 7 years after treatment with CRTs. Little is known about how specific CRT exposures shape the somatic mutation profiles in t-MNs. CPRIT Scholar Andrew Futreal, Ph.D., professor and Chair, Department of Genomic Medicine at The University of Texas MD Anderson Cancer Center, and colleagues systematically analyzed the mutational profiles of 416 t-MN patients and their associated clinical characteristics including prior cancer therapy exposures. The researchers identified a significant association between TP53-mutated t-MN and prior exposure to thalidomide analogs, especially lenalidomide. As reported in *Blood* on May 5, 2022, using in vitro and in vivo mouse models, the researchers demonstrated that lenalidomide treatment promotes selective outgrowth of Trp53-mutant HSPCs. Thus, it appears that TP53-CHIP may represent a uniquely high-risk lesion with increased pre-leukemic potential and risk for transformation especially in the setting of cytotoxic therapy. These findings highlight the role of lenalidomide treatment in promoting TP53-mutated t-MNs and offer a potential alternative strategy to mitigate the risk of t-MN development. Comprehensive understanding of these heterogeneous interactions will help advance a personalized approach to risk reduction and early intervention. The University of Texas MD Anderson Cancer Center recruited Dr. Futreal from the Wellcome Trust Sanger Institute in 2011 with the support of a $7 million CPRIT Recruitment of Established Investigators grant (R1205).

122. Despite the ground-breaking advances in single-cell technologies including multiomics technologies, there exists a need to computationally integrate multiple data matrices of different modalities sampled from the same biological population to derive a more comprehensive characterization of cellular identities and functions. Ken Chen, Ph.D., professor, Department of Bioinformatics and Computational Biology, The University of Texas MD Anderson Cancer Center, and colleagues presented a novel mathematical solution named bi-order canonical correlation analysis (bi-CCA), which extends the widely used CCA approach to iteratively align the rows and the columns between data matrices. As reported in *Genome Biology* on May 9, 2022, this method bi-CCA and an associated tool bindSC have addressed this important analytical challenge without compromising biological complexity in the data. In these experiments, bindSC successfully integrated data obtained from a wide variety of vastly different technologies covering transcriptomes, epigenomes, and proteomes and clearly outperformed existing tools. Taken together, the researchers believe that bindSC is likely the first tool that has achieved de novo bi-order integration of data matrices generated by different technologies and can be applied in broad settings. In the single-cell domain,

bindSC can clearly be applied to align cells and features simultaneously, which are important for ongoing investigations. Further, bindSC can potentially be applied to other domains, such as integrating patient sample mRNA profiles with cell-line drug-sensitivity data. The University of Texas MD Anderson Cancer Center received a $900,000 CPRIT Individual Investigator Research Awards for Computational Biology grant (RP180248) in 2019.

123. Ewing sarcoma is the second most common malignant bone tumor among children, adolescents, and young adults. Management of relapsed disease mostly consists of different combinations of the same agents used as prior therapy. Failure on second-line therapy is very common, and the agents used are associated with short- and long-term toxicity. Vivek Subbiah, M.D., associate professor, Department of Investigational Cancer Therapeutics at The University of Texas MD Anderson Cancer Center, and a global team of researchers reported that in preclinical models it was shown that lurbinectedin was effective in suppressing the activity of the oncogenic transcription factor EWS-FLI1 through relocalization to the nucleolus and delayed tumor growth in mice bearing Ewing sarcoma xenografts. In this open-label, single-arm, Basket phase II trial published in *Clinical Cancer Research* on July 1, 2022, researchers evaluated the monotherapy activity of lurbinectedin in terms of response rate, PFS, clinical benefit rate (CBR), and disease control rate (DCR) in a cohort of patients with relapsed Ewing sarcoma. The results showed that lurbinectedin was active in the treatment of relapsed Ewing sarcoma and had a manageable safety profile. Lurbinectedin could represent a valuable addition to therapies for Ewing sarcoma and is currently being evaluated in combination with irinotecan in advanced Ewing sarcoma in a phase Ib/II trial. The University of Texas MD Anderson Cancer Center received an $830,000 CPRIT Academic Research grant (RP110584).

124. Immune checkpoint therapy (ICT) using antibody blockade of programmed cell death protein 1 (PD-1) or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) can provoke T cell–dependent antitumor activity that generates durable clinical responses in some patients. The epigenetic and transcriptional features that T cells require for efficacious ICT remain to be fully elucidated. CPRIT Scholar Matthew Gubin, Ph.D., assistant professor, Department of Immunology, The University of Texas MD Anderson Cancer Center, and colleagues reported in the journal *Cancer Immunology Research* on May 3, 2022, that single-cell RNA sequencing (scRNAseq) analysis revealed that ICT-treated tumor-bearing BHLHE40-deficient mice have altered remodeling of intratumoral lymphoid and myeloid cells, including a profound absence of a shift from a $CX3CR1^{+}CD206^{+}$ macrophage subpopulation to an $iNOS^{+}$ subpopulation that is typically observed in wild-type (WT) mice during effective ICT. These results reveal a crucial role for BHLHE40 in effective ICT and suggest that BHLHE40 may be a predictive or prognostic biomarker for ICT efficacy and a potential therapeutic target. The University of Texas MD Anderson Cancer Center recruited Dr. Gubin from Washington University in 2018 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR190017).

125. The University of Texas Southwestern Medical Center researchers have discovered a molecular pathway that allows cells to sense when their lipid supplies become depleted, prompting activity that prevents starvation. Searching for a mechanism that cells might generally apply to sense lipid levels, the researchers starved *Caenorhabditis elegans*, a roundworm species that serves as a common lab model and shares many genes with humans. When these animals were deprived of food for 24 hours, the researchers saw that a protein known as nuclear hormone receptor 49 (NHR-49) moved from the cytosol – the liquid component of cells – to the nucleus, where it set off a cascade of gene activity that prompted transport of other proteins to the cell surface to gather extracellular nutrients. “Lipids are critical for supplying energy and serving as components for membranes and other cellular structures,” said CPRIT Scholar Peter Douglas, Ph.D., assistant professor, Department of Molecular Biology. “The mechanism we discovered appears to be a way for cells to universally

gauge lipid levels without having to distinguish between the vast variety of different lipid types." The findings, reported in *Nature* on May 18, 2022, might someday lead to new ways to combat metabolic disorders and a variety of other health conditions. The University of Texas Southwestern Medical Center recruited Dr. Douglas from University of California, Berkeley with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR150089) in 2015.

126. Skin is the largest organ in the human body, harboring a plethora of cell types and serving as the organismal barrier. Skin aging such as wrinkling and hair graying is graphically pronounced, and the molecular mechanisms behind these phenotypic manifestations are beginning to unfold. In this study, two researchers from The University of Texas MD Anderson Cancer Center focused on skin aging, especially in the context of stem cell function and the origin and consequence of lineage deregulation. CPRIT Scholar Yejing Ge, Ph.D., assistant professor, department of cancer biology, reviewed recent studies that proposed molecular mechanisms that drive the degeneration of hair follicles, a major appendage of the skin. By focusing on skin while comparing it to model organisms and adult stem cells of other tissues, she and her colleague summarized literature on genotoxic stress, nutritional sensing, metabolic rewiring, mitochondrial activity, and epigenetic regulations of stem cell plasticity. As reported in Frontiers in *Cell Developmental Biology* on May 19, 2022, RNA sequencing (RNA-seq) and assay for transposase-accessible chromatin with sequencing (ATAC-seq) at single cell level, and together with spatial transcriptomics provided unprecedented throughput and resolution of cell type, lineage trajectory, and tissue-level crosstalk in many biological contexts, and are likely to be powerful technologies in aging research. Of significance, aged HFSCs can be rejuvenated by resident cell types and niche components of the young skin, suggesting that the tissue microenvironment drives stem cell function during aging. The University of Texas MD Anderson Cancer Center recruited Yejing Ge, Ph.D., assistant professor, department of cancer biology, in 2018 from The Rockefeller University with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR180060).

127. Low-grade serous carcinoma (LGSOC) is a rare epithelial ovarian/peritoneal cancer characterized by younger age at diagnosis, relative chemoresistance, prolonged overall survival (OS), and mutations in the mitogen activated protein kinase (MAPK) pathway compared to high-grade serous carcinoma. Researchers from The University of Texas MD Anderson Cancer Center, including CPRIT Scholar Robert Hillman, M.D., Ph.D., assistant professor, Department of Gynecologic Oncology and Reproductive Medicine, described the genomic profile of LGSOC by next generation sequencing (NGS) and evaluated its potential relationship to clinical outcomes. As reported in Science Direct on May 20, 2022, this study included 215 women with LGSOC. Median age at diagnosis was 46.6 years and the majority had a stage III ovarian primary. One or more mutations were identified in 140 cases; 75 had none. The results showed that patients with MAPK-mutated tumors have a significantly improved OS compared to those without MAPK-mutated tumors. The University of Texas MD Anderson Cancer Center recruited Dr. Hillman with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR200045) in 2020.

128. Pancreatic intraepithelial neoplasia (PanIN) is a precursor of pancreatic ductal adenocarcinoma (PDAC), which commonly occurs in the general populations with aging. Selective, peroxisome proliferator-activated receptor-delta (PPARδ), a lipid nuclear receptor, agonists were initially developed and tested clinically to treat non-cancerous metabolic disorders (e.g., obesity). However, large pharmaceutical companies abandoned the development of PPARδ agonists because of concerns regarding their carcinogenic effects. Nonetheless, PPARδ agonists such as GW501516 are still illicitly being sold to athletes to enhance muscle endurance via websites claiming a lack of evidence for harmful effects. Given the availability of and uncertainty around these PPARδ agonists, Xiangsheng Zuo, M.D., Ph.D., Department of Gastrointestinal Medical Oncology, The University of Texas MD An-

derson Cancer Center, and team set out to show that PPARδ upregulated in PanINs in humans and mice. Published in *Nature Communications* on May 12, 2022, this study also reported that PPARδ ligand activation by a high-fat diet or GW501516 in mutant KRASG12D pancreatic epithelial cells strongly accelerates PanIN progression to PDAC. These findings demonstrated that activation of upregulated PPARδ in PanINs can strongly promote progression of asymptomatic PanIN to PDAC and provide a strong rationale for targeting PPARδ signaling to prevent the progression of PanIN to PDAC. The University of Texas MD Anderson Cancer Center received two CPRIT Individual Investigator Award grants (RP150195, RP140224) in 2014 and 2015 for a total of $1.8 million and a $6 million CPRIT Core Facility Support Awards grant (RP120348) in 2011.

129. A study published in *Cancer Cell* June 2, 2022, provides new insight into how the mammalian immune system, designed to attack foreign invaders like bacteria, can also recognize cancer cells as abnormal. Researchers from The University of Texas MD Anderson Cancer Center collaborated with researchers at NYU Grossman School of Medicine and Perlmutter Cancer Center and reported that exercise-induced increases in levels of the hormone adrenalin cause changes to the immune system, including in the activity of cells that respond to signaling protein interleukin-15 (IL-15). The current study found that exercise promotes the survival of CD8 T cells sensitive to IL-15 and doubles the number of them homing to pancreatic ductal adenocarcinoma (PDAC) tumors in mice. Authors then found that human patients – enrolled in their "Preoperative Rehabilitation During Neoadjuvant Therapy for Pancreatic Cancer" clinical trial – who exercised before surgery to remove their pancreatic tumors had more CD8 effector T cells that expressed a protein called granzyme B, which confers tumor-cell killing ability. In this trial, which opened in 2017, researchers found that patients who exercised and had more of these cell types had 50% percent higher overall survival over five years than patients with fewer of them. These novel findings show how aerobic exercise affects the immune microenvironment within pancreatic tumors. The University of Texas MD Anderson Cancer Center received a $2.6 million CPRIT Cancer Prevention Research Training Program grant (RP170259) in 2016.

130. Triple-negative breast cancer (TNBC) has a poor clinical outcome, due to a lack of actionable therapeutic targets. Co-corresponding author, Ratna Vadlamudi, Ph.D., professor, Department of Obstetrics and Gynecology at The University of Texas Health San Antonio, and colleagues report that their study implicates a targeted strategy for solid tumors, including breast, brain, pancreatic and ovarian, whereby small, orally bioavailable molecules targeting LIPA block protein folding, induce estrogen receptor (ER) stress and result in tumor cell death. The team tested a novel compound synthesized by co-corresponding author, Jung-Mo Ahn, Ph.D., associate professor, Department of Chemistry and Biochemistry, The University of Texas at Dallas, and called ERX-41 for its effects against breast cancer cells, both those that contain ERs and those that do not. "The ERX-41 compound did not kill healthy cells, but it wiped out tumor cells regardless of whether the cancer cells had estrogen receptors," said Dr. Ahn. "In fact, it killed the triple-negative breast cancer cells better than it killed the ER-positive cells." As reported in *Nature Cancer* on June 2, 2022, the researchers discovered that ERX-41 binds to a cellular protein called lysosomal acid lipase A (LIPA). The molecule also proved effective at killing cancer cells in human tissue gathered from patients who had their tumors removed. This targeted vulnerability has a large therapeutic window, with no adverse effects either on normal mammary epithelial cells or in mice. The University of Texas Health Science Center at San Antonio received a $2 million CPRIT Bridging the Gap: Early Translational Research Awards grant (DP150096) in 2014.

131. A new study led by the global Cancer Grand Challenges PRECISION team, including researchers from The University of Texas MD Anderson Cancer Center, was designed to determine whether subsequent invasive breast cancers are connected to the original ductal carcinoma *in situ* (DCIS).

As many DCIS lesions will never progress to invasive disease, some women may receive intensive treatment without any clinical benefit. Therefore, there is a great unmet clinical need to develop treatment strategies that avoid overtreatment. Nicholas E. Navin, Ph.D., professor, Department of Genetics and Director of the CPRIT Single Cell Genomics Center, The University of Texas MD Anderson Cancer Center, and colleagues applied genomic profiling methods to systematically and comprehensively investigate genomic concordance of pure DCIS and recurrent invasive tumors, using exome sequencing, targeted mutation panels and copy number profiling. The results, published on June 9, 2022, in *Nature Genetics*, demonstrate that roughly one in five invasive cancers were genetically unrelated to the original DCIS. The findings provide a deeper understanding of the biology of DCIS, serving as a foundation for future studies to better identify cases of DCIS most likely to progress and to determine appropriate intervention strategies for women with DCIS. The University of Texas MD Anderson Cancer Center received a $4.9 million CPRIT Core Facility Support Awards grant (RP180684) in 2018.

132. Iterion Therapeutics, Inc., announced that results from a Phase 1 study of tegavivint in patients with desmoid tumors was featured in a poster presentation and discussion session at the 2022 American Society of Clinical Oncology Annual Meeting on June 5, 2022. Tegavivint's targeting of TBL1 prevents TBL1/beta-catenin complex formation, specifically inhibiting beta-catenin's oncogenic transcriptional activity without disrupting key cell membrane functions that have been linked to toxicity common to other drugs in this pathway. The primary objectives of the study were to evaluate safety and to determine the maximum tolerated dose (MTD), the recommended Phase 2 dose (RP2D), and exploratory efficacy. No dose-limiting toxicities were observed and a maximum tolerated dose (MTD) was not determined. Treatment related adverse events were mostly Grade 1-2 with none resulting in treatment discontinuation. The RP2D was declared at 5 mg/kg based on pharmacologically relevant plasma concentrations and preliminary efficacy. Responses were observed at all dose levels with an overall response rate of 25% at the RP2D. Additionally, the 9-month progression free survival rate was 79% among those treated at the RP2D. Overall, these data demonstrated that tegavivint is well tolerated, does not appear to have the toxicity historically associated with WNT inhibition, and has promising clinical activity. Iterion is the recipient of a $15.9 million CPRIT Product Development grant (CP130058) in 2014.

133. Treatment with therapy targeting BRAF and MEK (BRAF/MEK) has revolutionized care in melanoma and other cancers; however, therapeutic resistance is common and innovative treatment strategies are needed. Androgen receptor (AR) signaling may affect response to BRAF/MEK inhibitor therapy in both male and female patients with melanoma. The report provides a new target to combat therapeutic resistance and one possible answer to why men face a poorer prognosis than women when diagnosed with melanoma. The findings, published in *Nature* on June 15, 2022, were validated in several additional cohorts of patients with unresectable metastatic melanoma who were treated with BRAF- and/or MEK-targeted therapy (n = 664 patients in total). The AR is a type of nuclear receptor that is activated by the male sex hormone testosterone. Females have lower levels of androgens, including testosterone. This research confirms the impact of sex on response to BRAF/MEK targeted therapy and shows—for the first time—that these inhibitors increase AR signaling, leading to therapeutic resistance and poor response to treatment. "This study has enormous implications for the field," said senior corresponding author Jennifer Wargo, M.D., professor of genomic medicine and surgical oncology at The University of Texas MD Anderson Cancer Center. "We know males and females get cancer at different rates and have different mortality. Our research raises the possibility that the AR and testosterone may be at play and offers a new target to improve response to treatment in both sexes." The University of Texas MD Anderson Cancer Center received a $5 million CPRIT Core Facility Support Awards grant (RP170002) in 2016.

134. Significant improvements have been made in metastatic colorectal cancer (mCRC) therapy and have almost exclusively been through randomized phase 3 trials. The trials have a key limitation of addressing a single hypothesis during constantly evolving management paradigms that concomitantly contribute to improvements in survival. In a study reported in *JAMA Network Open* on May 24, 2022, researchers studied data from 150 phase III trials of systemic therapy including a total of 77,494 patients reported between 1986 and 2016, and from 67,126 patients in the Surveillance, Epidemiology, and End Results (SEER) database from 1986 to 2015. Arvind Dasari, M.D., Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, and colleagues found that data from both phase III trials and the SEER database indicate significant improvements in overall survival for patients with metastatic colorectal cancer over a 30-year period. These findings translate into meaningful benefits outside the clinical trial setting; however, although significant cumulatively, they are largely incremental individually. These data should be a call to aim for larger gains from future trials with novel drugs, building on the increasing understanding of the biology of metastatic colorectal cancer and sophisticated translational research tools. The University of Texas MD Anderson Cancer Center received a $2.4 million CPRIT Individual Investigator Research Awards for Clinical Translation grant (RP200356) in 2020.

135. Metastasis is the major cause of mortality in cancer patients. In recent years, there is growing evidence that WNK1 is a critical kinase involved in various types of cancer, but the exact mechanisms by which WNK1 modulates tumor progression are not well understood. Melanie Cobb, Ph.D., professor, Department of Pharmacology, The University of Texas Southwestern Medical Center, and team reported that analyses of mouse models and patient data have implicated the protein kinase WNK1 as one of a handful of genes uniquely linked to a subset of invasive cancers. As reported in *Frontiers in Cell Development Biology* on June 22, 2022, WNK1 signaling pathways are widely implicated in the regulation of ion co-transporters and in controlling cell responses to osmotic stress. WNK1 has related actions in angiogenesis and cancer, however, how many of these related actions are shared by other WNK family members is not clear. The researchers highlighted four points that may be considered in future analyses of the actions of WNK1 and other WNK family members in cancers, including why and when does WNK1 switch from being a homeostatic housekeeper to instead promoting EMT. The University of Texas Southwestern Medical Center received a $3.75 million CPRIT Research Training grant (RP210041) in 2021.

136. Nonalcoholic fatty liver disease (NAFLD) raises the risk of developing hepatocellular carcinoma (HCC), but this risk can be difficult to quantify. CPRIT Scholar Yujin Hoshida, M.D., Ph.D., associate professor, Department of Internal Medicine, The University of Texas Southwestern Medical Center, and team developed hepatic transcriptome and serum secretome–derived signatures to predict NAFLD-related HCC in patients over 15 years of observations. Published in *Science Translational Medicine* on June 22, 2022, the researchers, including CPRIT Scholar Zhenyu Zhong, Ph.D., assistant professor, Department of Immunology, The University of Texas Southwestern Medical Center, analyzed samples from 409 NAFLD patients to reveal a set of 133 genes that were expressed at levels higher or lower than average in the livers of patients who developed HCC. Most of the genes and proteins found to be predictive of HCC risk were immune and inflammatory molecules, which points toward the importance of inflammation in HCC development. Moreover, the researchers showed that levels of the molecules changed in conjunction with therapies known to decrease liver inflammation and HCC risk, including bariatric surgery, cholesterol drugs, and an immunotherapy. In the future, blood tests could be developed to measure cancer risk in other major liver diseases such as hepatitis B and alcoholic liver disease. The University of Texas Southwestern Medical Center recruited Dr. Hoshida from the Icahn School of Medicine at Mount Sinai with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR180016) in 2018 and recruited Dr. Zhong from the University of California, Davis with a $2 million CPRIT Recruitment of First-Time, Tenure-Track

Faculty Members grant (RR180014) in 2018. The University of Texas Southwestern Medical Center received a $900,000 CPRIT Individual Investigator grant (RP200197) in 2020.

137. Researchers co-led by CPRIT Scholar Julian West, Ph.D., assistant professor, Department of Chemistry, Rice University, have developed a successful catalytic process to simultaneously add two distinct functional groups to single alkenes. Dr. West, whose lab designs synthetic chemistry processes, said the initial inspiration came from an enzyme, cytochrome P450, that the liver uses to eliminate potentially harmful molecules. "These enzymes are sort of buzzsaws that grind up molecules before they can get you into trouble," Dr. West said. "They do this through an interesting mechanism called radical rebound." West said P450 finds carbon-hydrogen bonds and removes the hydrogen, leaving a carbon-centered radical that includes an unpaired electron. "That electron really wants to find a partner, so the P450 will immediately give back an oxygen atom (the 'rebound'), oxidizing the molecule," Dr. West said. This helps deactivate these molecules in the body so you can get rid of them. The researchers then enabled what they call radical ligand transfer, a general method that uses manganese to catalyze the "radical rebound." Graduate student Kang-Jie (Harry) Bian also came up with the idea of adding a photocatalyst to the mix. The chemical pathway detailed in the *Journal of the American Chemical Society* on June 21, 2022, could simplify the creation of a library of precursors for the pharmaceutical industry and enhance the manufacture of polymers. Rice University recruited Dr. West from the California Institute of Technology with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR190025).

138. Researchers at The University of Texas Southwestern Medical Center have found protein complexes that could lead to new interventions to regulate immunity in individuals with overactive or underactive immune responses. More than two decades ago, Zhijian Chen, Ph.D., professor, Department of Molecular Biology and director of the Center for Inflammation Research at The University of Texas Southwestern Medical Center, discovered that a protein called ubiquitin assembles into chains inside cells when the cells are exposed to inflammatory molecules. Dr. Chen and his colleagues showed that the chains are key for promoting an immune response and can activate a group of proteins known as the IκB complex (IKK), which includes a component known as NEMO. As reported in *Molecular Cell* on July 7, 2022, experiments in human cells showed that NEMO and the polyubiquitin chains displayed the same "phase separation" behavior after the cells were exposed to IL-1 β or TNF α. When IKK entered these droplets, it became activated and triggered NF- κ B to move to the nucleus. The longer the polyubiquitin chains, the larger the droplets they formed with NEMO and the stronger the immune response they triggered. Dr. Chen noted that better understanding of this liquid phase separation phenomenon could eventually lead to treatments for NEMO deficiency syndrome and interventions to counteract overactive or underactive immunity, the root cause of autoimmune disorders and increased susceptibility to infection, respectively. The University of Texas Southwestern Medical Center received a $6 million CPRIT Multi-Investigator Research Awards grant (RP180725) in 2018 and a $3.75 million CPRIT Research Training grant (RP210041) in 2021.

139. Parents who decline HPV vaccination is a challenge for providers and leads to low adolescent HPV vaccination initiation. In 2018, 65% of adolescent girls and 56% of adolescent boys in Texas initiated HPV vaccination. Gaps between HPV vaccination rates and those for Tdap (83%) and meningococcal vaccines (87%) among 13–17-year-olds highlights missed opportunities to prevent HPV-related cancers. In 2015, Lara Savas, Ph.D., associate professor, Department of Health Promotion and Behavioral Sciences, The University of Texas Health Science Center, and colleagues surveyed pediatricians in a large Texas pediatric clinic network to assess physician knowledge, beliefs, attitudes and behaviors regarding adolescent HPV vaccination. The results of this study were published in June 2022 in the *Journal of Applied Research on Children: Informing Policy for Children at Risk*. Among 226 physicians, 59.8% completed the emailed survey. Controlling for patient and physician

demographics, odds of HPV vaccination initiation were significantly increased if physicians used a bundled approach to recommend the HPV vaccine: "Your child is due for three vaccines: Tdap, HPV, and meningococcal vaccine." This study links physician HPV vaccine recommendation wording and outcomes, showing the significant effect of bundling HPV vaccination for adolescent patients. The University of Texas Health Science Center received a $1.5 million CPRIT Individual Investigator Research Awards for Prevention and Early Detection grant (RP150014) in 2015 and a $1.5 million CPRIT Evidence-Based Prevention Programs and Services grant (PP140183) in 2018.

140. Breast cancers with HER2 mutations respond to the drug neratinib, but the responses are variable and often not durable. CPRIT Scholar Matthew Ellis, Ph.D., professor, Departments of Medicine and Molecular and Cellular Biology, Baylor College of Medicine, and team investigated whether different HER2 mutations drove different responses to therapy. The researchers conducted laboratory experiments in which the HER2 L755S gene was introduced into cells. Then, they treated the modified cells with drugs approved to treat the human cancer. The results, published in June 2022 in *Cancer Research*, a journal of the American Association for Cancer Research, found that the HER2 L755S mutation was more common among patients with metastatic lobular breast cancer than in ductal breast cancer patients. "We found that having the HER2 L755S mutation conferred the cells' resistance to treatments, including neratinib – the cells continued to grow," said Rashi Kalra, Ph.D., first author and postdoctoral research associate at Baylor College of Medicine. Of all the drugs the team tested, poziotinib was able to completely inhibit both tumor growth and metastasis in experimental models. The team is actively working on the development of a phase II clinical trial to determine the value of poziotinib in the treatment of patients with HER2 mutations. Baylor College of Medicine recruited Dr. Ellis from Washington University with the support of a $6 million CPRIT Recruitment of Established Investigators Award grant (RR140033) in 2014.

141. As solid tumors grow, they surround themselves with a thick, hard-to-penetrate wall of molecular defenses. Scientists at The University of Texas Southwestern have developed nanoparticles that can break down the physical barriers surrounding tumors to reach cancer cells. The new nanoparticles, described in *Nature Nanotechnology* May 12, 2022, effectively stopped the growth and spread of ovarian and liver tumors in mice. The system offers a new path forward for the use of the gene editing tool known as CRISPR-Cas9 in cancer treatment, said study leader Daniel Siegwart, Ph.D., associate professor of biochemistry. The researchers began with the nanoparticles that they had already optimized to travel to the liver. They added a small piece of RNA (called short interfering RNA or siRNA) that could shut off focal adhesion kinase (FAK), a gene that plays a central role in holding together the physical defenses of a number of tumors. The researchers tested the new nanoparticles in four mouse models of ovarian and liver cancer. They first showed that by adding siRNA to shut off FAK, the matrix of molecules around the tumors was less stiff and easier to penetrate than normal. Then, they analyzed the tumor cells and found that many more nanoparticles had reached the cells, effectively altering the *PD-L1* gene. Finally, they found that tumors in mice treated with the nanoparticles that targeted both FAK and *PD-L1* shrank to about one-eighth the size of tumors treated only with empty nanoparticles. In addition, more immune cells infiltrated the tumors and the treated mice survived, on average, about twice as long. The University of Texas Southwestern Medical Center received a $900,000 CPRIT Individual Investigator grant (RP190251) in 2019 and a $4 million CPRIT research Training grant (RP160157) in 2015.

142. Head and neck cancer is the 6th most common cancer worldwide and surgical resection is one of the primary interventions used in managing tumor progression. However, there remains a considerable need for accurate identification of tumor boundaries and the accurate identification of surgical margins to mitigate local recurrence. Fluorescence image-guided surgery (IGS) using antibody conjugates of the fluorophore IRDye800CW have revolutionized the surgical debulking of tumors.

Kenneth Hoyt, Ph.D., associate professor, Department of Bioengineering at The University of Texas at Dallas, and colleagues proposed that a pre-operative photodynamic priming (PDP) regimen can expedite and augment the accuracy of IGS-mediated surgical debulking of head and neck tumors and reduce the time-to-IGS. The results were published in *Frontiers in Oncology* on June 28, 2022. Seeing the potential synergy between PDT with IGS, the researchers proposed Photodynamic IGS (P-IGS), whereby a pre-operative sub-therapeutic PDT protocol (PDP), augments and expedites the delivery of Cet-IRDye800, and also increases its accuracy of tumor tissue detection. This P-IGS regimen can also enable a forward-looking post-operative protocol for the photodestruction of unresectable microscopic disease in the surgical bed. Beyond this scope, the role of PDP in the homogenous delivery of diagnostic, theranostic and therapeutic antibodies in solid tumors is of considerable significance to the wider community. The University of Texas at Dallas received a $3.5 million CPRIT Core Facility Support Awards grant (RP180670) in 2018.

143. The heart, the first organ to develop in the embryo, undergoes complex morphogenesis that when defective results in congenital heart disease (CHD). With current therapies, more than 90% of patients with CHD survive into adulthood, but many suffer premature death from heart failure and non-cardiac causes. To gain insight into this disease progression, James Martin, M.D., Ph.D., vice chairman/professor, Departments of Molecular Physiology and Biophysics, Baylor College of Medicine, and colleagues performed single-nucleus RNA sequencing on 157,273 nuclei from control hearts and hearts from patients with CHD. As reported in *Nature* on June 22, 2022, the team observed CHD-specific cell states in cardiomyocytes, which showed evidence of insulin resistance and increased expression of genes associated with FOXO signalling and *CRIM1*. Imaging mass cytometry uncovered a spatially resolved perivascular microenvironment consistent with an immunodeficient state in CHD. Peripheral immune cell profiling suggested deficient monocytic immunity in CHD, in agreement with the predilection in CHD to infection and cancer. This comprehensive phenotyping of CHD provides a roadmap towards future personalized treatments for CHD. The University of Texas MD Anderson Cancer Center received a $1.2 million CPRIT Shared Instrumentation Awards grant (RP121010) in 2012 and Baylor College of Medicine received a $5.2 million CPRIT Core Facility Support Awards grant (RP180672) in 2018.

144. Development of genome-wide CRISPR screening five years ago facilitated robust determination of genes required for in vitro proliferation across cancer types. Ongoing efforts to identify tumor-specific vulnerabilities encompass hundreds of cancer cell lines across dozens of tissue types. Researchers from The University of Texas MD Anderson Cancer Center addressed one of the key questions arising from the use of coessentiality, to predict gene co-functionality. CPRIT Scholar Traver Hart, Ph.D., assistant professor, Department of Bioinformatics and Computational Biology, and colleagues developed a framework of identifying dynamic relationships in cancer dependency data associated with differing functional contexts such as variations in tissue of origin and/or genomic lesions. As reported in *Genome Biology* on June 29, 2022, using genetic mutation information and cell line metadata, the team investigated contexts that cause emergent essentiality by analyzing coefficients obtained from a logistic regression model trained using CRISPR screen data. They developed a strategy which compares the strength of interaction between two genes, to the correlation derived from samples that exclude a specified context, or a “leave-one-out” test. These methods offer a powerful approach for predicting gene function, identifying disease genes, and reducing the search space of potential combinatorial gene effects to tractable levels. The University of Texas MD Anderson Cancer Center recruited Dr. Hart in 2016 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160032) and received a $250,000 CPRIT High Impact/High Risk grant (RP210173) in 2021.

145. Trials of neoadjuvant endocrine therapy (NeoET) in cStage II–III breast cancer have established that

early pharmacodynamic and subsequent pathologic response to NeoET are prognostic, so some patients may avoid chemotherapy. But there is still a need for pretreatment biomarkers to identify the most appropriate patients to begin NeoET. CPRIT Scholar Matthew Ellis, MB BChir, Ph.D., faculty Lester and Sue Smith Breast Center, Baylor College of Medicine, and colleagues set out to examine whether SET2,3 could identify patients who are more likely to experience tumoral response to NeoET. In this blinded analysis of the sensitivity to endocrine therapy (SET2,3) index in the American College of Surgeons Oncology Group Z1031 trial of NeoET published in *Clinical Cancer Research* on August 1, 2022, the team demonstrated that higher SET2,3 from diagnostic tumor biopsy was associated with greater odds of early pharmacodynamic response in the tumor and longer event-free survival (EFS). These results also indicate the potential for SET2,3 as an integral biomarker to enrich for patients with endocrine-sensitive breast cancer to consider neoadjuvant endocrine-based therapy. The University of Texas MD Anderson Cancer Center a $6 million CPRIT grant (RP180712) in 2018 and Baylor College of Medicine recruited Dr. Ellis from Washington University with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR140033) in 2014.

146. Cell surface proteins play essential roles in various biological processes and are highly related to cancer development. They also serve as important markers for cell identity and targets for pharmacological intervention. However, comprehensive functional analysis of cell surface proteins remains scarce. With a de novo designed library targeting cell surface proteins, Junjie Chen, Ph.D., professor and Chair of the Department of Experimental Radiation Oncology, The University of Texas MD Anderson Cancer Center, and colleagues performed in vivo CRISPR screens to evaluate the effects of cell surface proteins on tumor survival and proliferation. Published in the *Proceedings of the National Academy of Sciences* on June 15, 2022, this study revealed that Kirrel1 loss markedly promoted tumor growth in vivo. Further studies revealed that KIRREL binds directly to SAV1 to activate the Hippo tumor suppressor pathway. CPRIT Scholar Matthew Ellis, MB BChir, Ph.D., faculty Lester and Sue Smith Breast Center, Baylor College of Medicine, noted that together, their integrated screens reveal a cell surface tumor suppressor involved in the Hippo pathway and highlight the potential of these approaches in biomedical research. The University of Texas MD Anderson Cancer Center received two CPRIT Multi-Investigator Research Awards grants (RP160667, RP180813) in 2016 and 2018 for a total of $11 million and Baylor College of Medicine recruited Dr. Ellis from Washington University with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR140033) in 2014.

147. Research has shown that BD-inhibitors can help control cancer growth; however, when tested in clinical trials some had side effects and limited efficacy, halting further clinical development. To identify novel BD1-inhibitors, researchers at Baylor College of Medicine took advantage of an innovative, faster and more cost-effective drug discovery tool called DNA-Encoded Chemistry Technology (DEC-Tec) developed at Baylor's Center for Drug Discovery (CDD). As reported in *Proceedings of the National Academy of Sciences* on May 27, 2022, the team was able to screen 4 billion DNA-encoded molecules all in one test tube against BD1. "The molecules that 'stick' to the protein (in this case BD1) are identified by sequencing of their attached DNA barcode," said corresponding author Martin Matzuk, M.D., Ph.D., professor and Chair the Department of Pathology and Immunology at Baylor College of Medicine. The findings of BET BD1-specific inhibitors allow the researchers to dissect the role of this bromodomain specifically in spermatogenesis and in cancer. The series of selective and highly potent bromodomain and extraterminal (BET) inhibitors identified in the DEC-Tec screening platform, highlights the strength of DECL screening to rapidly find potent and specific inhibitors of even structurally different targets. Baylor College of Medicine received a $6 million CPRIT Core Facility Support Awards grant (RP160805) in 2016.

148. According to the U.S. Centers for Disease Control and Prevention (CDC), more than 37 million Ameri-

cans have diabetes. In Texas, approximately 2.7 million people have diagnosed diabetes and another 7 million people in Texas have prediabetes. Obesity-related diseases include heart attack, stroke, type 2 diabetes and some cancers. Researchers from The University of Texas Health Science Center at San Antonio are part of a team that have identified a CNOT6L inhibitor enhancing GDF15 and FGF21 hepatokine levels, which dramatically improves diet-induced metabolic syndrome. The liver enzyme, called CNOT6L deadenylase, turns off messenger ribonucleic acids (mRNAs) that ordinarily carry genetic instructions from the nucleus to sites in the cell where two liver proteins are made. Using small-molecule screening, senior author Masahiro Morita, PhD, assistant professor, Department of Molecular Medicine at The University of Texas Health San Antonio, and colleagues found that inhibiting a liver enzyme in obese mice decreased the rodents' appetite, increased energy expenditure in adipose (fat) tissues and resulted in weight loss. The researchers' first-in-class CNOT6L inhibitor, dubbed iD1, stabilized liver GDF15 and FGF21 mRNAs in obese mice, increasing levels of the two proteins in the blood. After 12 weeks, mice treated with iD1 showed improved insulin sensitivity and lower blood glucose levels. The finding, published in *Cell Metabolism* on April 5, 2022, provides a potentially desirable drug target to treat metabolic issues such as obesity and diabetes. The University of Texas Health Science Center at San Antonio received a $1 million CPRIT Individual Investigator grant (RP220267) in 2022.

149. Congestive heart failure typically occurring as a result of myocardial infarction remains the leading cause of mortality from cardiovascular disease. After a heart attack, the parts of the heart muscle that die do not regenerate into new heart tissue; instead, they are replaced by a scar that does not help the heart to beat. "The idea behind cell reprogramming is to coach the heart to heal itself by inducing the scar tissue, which is made mostly of fibroblasts, to change into functional heart muscle," said Todd Rosengart, M.D., FACS, professor and Chair of the Department of Surgery, Baylor College of Medicine. Direct cellular reprogramming represents a novel strategy whereby resident cardiac fibroblasts in areas of myocardial infarction or fibrosis can be transdifferentiated into functional cardiomyocyte-like cells (iCMs) that can in turn enhance myocardial contractile function. Different combinations of cardio-differentiating factors can transdifferentiate rodent and human cardiac fibroblasts into iCMs but human cells appear resistant to reprogramming compared to rodent cells. Researchers from Baylor College of Medicine and colleagues hypothesized that modulation of the epigenetic regulator gene p63 could improve the efficiency of human cell cardio-differentiation. These findings, published in *Nature* on July 6, 2022, suggest that p63 acts as an epigenetic barrier in human cardiac reprogramming and that p63-TID offers a new potential strategy to target epigenetic regulation of cardiogenic gene activation as a means to enhance human cardiac reprogramming. Texas A&M University System Health Science Center received two CPRIT Core Facility Support Awards grants (RP150578, RP170719) in 2015 and 2018 for a total of $11.8 million.

150. Researchers from Baylor College of Medicine and colleagues have found that DNA methylation plays a role in regulating virulence, reproduction and gene expression in bacteria. In other organisms, including humans, DNA methylation is essential in regulating tissue-specific gene expression. "The study of DNA methylation is part of the field of epigenetics. It is important because it helps us understand why one particular type of bacteria causes a more severe disease than another or how a normal cell can change and give rise to diseases, such as cancer," said CPRIT Scholar Tao Wu, Ph.D., assistant professor of molecular and human genetics at Baylor College of Medicine. As reported in *Genome Biology* on May 30, 2022, the team developed a method (NT-seq) to simultaneously map all three major types of DNA methylation in prokaryotic genomes which allows accurate detection of methylation motifs in both single species and microbial community samples. By coupling methyl DNA immunoprecipitation (DIP), the researchers showed that NT-seq could accurately profile 6mA at single-base resolution in bacterial genomes, which could also be applied to eukaryotic genomes to help in eliminating the non-specific signals in 6mA DIP-seq in eukaryotes. Compared to SMRT-seq, NT-seq provides a cost-efficient solution for bacterial methylation mapping

and paves the way for further epigenetic study on genomic DNA 6mA in eukaryotes. Baylor College of Medicine recruited Dr. Wu from Yale University in 2018 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR180072).

151. Almost all pediatric liver cancers have been classified as either hepatoblastoma or hepatocellular carcinoma. However, pediatric pathologists have noted that certain liver tumors have histological characteristics that do not readily match either of these two carcinoma models. The outcomes for patients with these tumors are poor and the tumors are less likely to respond to chemotherapy. Pavel Sumazin, Ph.D., associate professor of pediatrics, Baylor College of Medicine, and colleagues sought to better understand this high-risk cancer. The researchers compared the molecular features of hepatocellular neoplasm not otherwise specified (HCN NOS), with those in other pediatric hepatocellular neoplasms, including hepatoblastomas (HB) and hepatocellular carcinomas (HCC). Published in the *Journal of Hepatology* on May 13, 2022, the study found that molecular profiles of HCN NOS and HB FPAs revealed common underlying biological features that were previously observed in HCCs. Consequently, the researchers designated these tumor types collectively as HBs with HCC features (HBCs). These tumors were associated with high mutation rates and were enriched with mutations and alterations in key cancer genes and pathways. "Our findings highlight the importance of molecular testing to accurately classify these tumors to optimize treatment recommendations at the time of initial diagnosis," said Dolores López-Terrada, M.D., Ph.D., corresponding author of the paper, professor of pathology, immunology, and pediatrics at Baylor College of Medicine and chief of the division of genomic medicine at Texas Children's Hospital. Based on their findings, the team proposed a diagnostic algorithm to stratify HBCs and guide specialized treatment. Baylor College of Medicine received a $6 million CPRIT Multi-Investigator Research Awards grant (RP180674) in 2018.

152. A team led by CPRIT Scholar Isaac Hilton, Ph.D., assistant professor of bioengineering & biosciences, Rice University, used deactivated Cas9 (dCas9) proteins to target key segments of the human genome and synthetically trigger the transcription of human genes. Only around 2% of our genome contains protein-coding genes, and the remaining 98% is so-called noncoding DNA. "Genetic variation in noncoding DNA is also strongly correlated with many diseases, and even subtle differences in these regions can be linked to pathologies," Dr. Hilton said. "A pressing challenge is that it is often very difficult to pinpoint how these differences influence disease onset and treatments." This study in Nucleic Acids Research and reported on in *ScienceDaily* on July 28, 2022, highlights the growing potential of CRISPR-Cas9-based tools for synthetic gene control and cellular engineering. By using dCas9 to recruit proteins that can naturally turn genes on, the Rice team was able to reveal important details about human promoters and enhancers -- the pieces of our DNA that coordinate when, and to what extent, our genes are turned on -- which in turn controls the behaviors of our cells. The results of this study will contribute to better gene and cell therapies and biotechnologies. Rice University recruited Dr. Hilton from Duke University in 2017 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR170030).

153. The human papillomavirus (HPV) vaccine was approved in 2006 and has been shown to decrease vaccine-related HPV types in the oropharynx. Its impact on the incidence of HPV-related oropharyngeal squamous cell carcinoma (OPSCC) has not been examined. Abbey Berenson, M.D., Ph.D., professor, Departments of Obstetrics & Gynecology and Pediatrics, Director of the Center for Interdisciplinary Research in Women's Health, and fellow researchers from The University of Texas Medical Branch in Galveston investigated the impact of HPV vaccination on the incidence of HPV-related OPSCC in the U.S. among male and female adults from different age groups. The US Cancer Statistics 2001–2018 database and the National Cancer Institute's (NCI) Surveillance Epidemiology and End Results (SEER) program were used in this study. Cause-specific 5-year survival probability was

calculated using 60 monthly intervals in SEER*Stat software. As reported in *Frontiers in Oncology* on July 18, 2022, this study demonstrated a decline in the incidence of HPV-related OPSCC among young males and females during the vaccination era (2014–2018) compared with the pre-vaccination era (2002–2006). Data from SEER indicate that increasing trends in HPV-related OPSCC were primarily observed in middle-aged individuals and elders, particularly within recent years. Additional efforts are needed to improve HPV vaccination coverage in young girls and boys to further reduce the burden of HPV-related OPSCC in the U.S. The University of Texas Medical Branch at Galveston received a $2 million CPRIT Prevention grant (PP200005) in 2020.

154. Acute myeloid leukemia (AML) is a heterogeneous group of aggressive hematological malignancies commonly associated with treatment resistance, high risk of relapse, and mitochondrial dysregulation. Researchers from Rice University and The University of Texas MD Anderson Cancer Center identified six mitochondria-affecting compounds (PS compounds) that exhibit selective cytotoxicity against AML cells in vitro. In previous studies, these researchers screened around 45,000 small molecule compounds to find a few that targeted the mitochondria. In this study, they chose eight of the most promising compounds, identified between five and 30 closely related analogues for each and conducted tens of thousands of tests to systematically determine how toxic each analogue was to leukemia cells, both when administered individually or in combination with existing chemotherapy drugs. As reported in *Leukemia* on June 7, 2022, the team found that the eight compounds targeted the mitochondria by inducing mitophagy. During times of extreme stress, cells can temporarily forgo mitophagy. The researchers reasoned that mitophagy-inducing drugs might weaken leukemia cells and make them more susceptible to chemotherapy. CPRIT Scholar Natalia Kirienko, Ph.D., assistant professor, Department of Biosciences, Rice University and corresponding author, noted that these compounds are promising leads for development of future combinatorial therapeutic approaches for mitochondria-driven hematologic malignancies such as AML, ALL, and CML. Rice University recruited Dr. Kirienko in 2015 from Massachusetts General Hospital and Harvard Medical School with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR150044).

155. Researchers from The University of Texas MD Anderson Cancer Center and colleagues showed cancer cells produce a unique form of collagen that protects them from immune responses. CPRIT Scholar Raghu Kalluri, M.D., Ph.D., professor and Chair, Department of Cancer Biology, and Director Metastasis Research Center, reported that in contrast to normal type I collagen (Col1) heterotrimer (α1/α2/α1) produced by fibroblasts, pancreatic cancer cells specifically produce unique Col1 homotrimer. As reported in the journal *Cancer Cell* on July 21, 2022, deletion of Col1 homotrimers increases overall survival of mice with pancreatic ductal adenocarcinoma (PDAC). Deletion of Col1 homotrimers enhances T cell infiltration and enables efficacy of anti-PD-1 immunotherapy. "Cancer cells make an atypical collagen to create their own protective extracellular matrix that helps their proliferation and their ability to survive and repel T cells," said Dr. Kalluri. "Uncovering and understanding this unique adaptation can help us target more specific treatments to combat these effects." This study implicates Col1 homotrimer-α3β1 integrin signaling axis as a cancer-specific therapeutic target. The University of Texas MD Anderson Cancer Center recruited Dr. Kalluri from Harvard University in 2012 with the support of a $3.5 million CPRIT Recruitment of Established Investigators grant (R1227) and received a $900,000 CPRIT Individual Investigator grant (RP150231) in 2015.

156. Conventional cancer treatments tend to non-specifically kill tumor cells. Cancer immunotherapy is a treatment strategy that uses a patient's own immune system to fight the cancerous cells and has become a promising alternative cancer treatment after surgery, radiotherapy, and chemotherapy in recent years because of its mild side effects and significant therapeutic benefits. Peptide-based

cancer vaccines have been shown to boost immune systems to kill tumor cells in cancer patients. However, designing an effective T cell epitope peptide-based cancer vaccine still remains a challenge and is a major hurdle for the application of cancer vaccines. In this study, Chao Cheng, Ph.D., associate professor, Department of Medicine, Institution of Clinical and Translational Research, Baylor College of Medicine, and colleagues constructed for the first time a library of peptide-based cancer vaccines and their clinical attributes, named CancerVaccine. To investigate the association factors that influence the effectiveness of cancer vaccines, these peptide-based cancer vaccines were classified into high (HCR) and low (LCR) clinical responses based on their clinical efficacy. Results published in *Frontiers in Immunology* on July 27, 2022, highlight that modified peptides derived from artificially modified proteins are suitable as cancer vaccines, especially for melanoma. Together, these findings illustrate that a high clinical response following peptide-based cancer vaccination is correlated with the right type of peptide, the appropriate adjuvant, and a matched HLA allele, as well as an appropriate treatment regimen. This study would allow for enhanced development of cancer vaccines. Baylor College of Medicine recruited Dr. Cheng from the Geisel School of Medicine at Dartmouth in 2018 with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR180061).

157. Pancreatic ductal adenocarcinoma (PDAC) remains a challenging disease with few effective treatment options. With limited success from immunotherapy, there is a need to further understand the tumor immune microenvironment in order to develop effective therapeutic strategies. In a new study co-led by Nicholas Navin, Ph.D., professor, Department of Bioinformatics, The University of Texas MD Anderson Cancer Center, researchers used single-cell RNA sequencing and T cell receptor analysis to profile 80,000 T cells from 57 pancreatic tumor samples, 22 matched normal samples and cultured tumor-infiltrating lymphocytes (TILs). According to the results published in *Cancer Discovery* on August 23, 2022, the researchers identified 20 unique T cell states defined by different gene expression profiles and discovered that certain states, such as dysfunctional and inhibitory T cells, often were found together. Analysis of cultured TIL revealed that high-frequency clones from effector populations were preferentially expanded. These data provide a framework for understanding the PDAC TIL landscape for future TIL use in immunotherapy for PDAC. The University of Texas MD Anderson received a $4.9 million CPRIT Core Facility Support Awards grant (RP180684) in 2018.

158. Early gene expression profiling of metastatic melanoma tumors demonstrated that melanoma cells display distinct gene expression signatures, corresponding broadly with either a “proliferative” or an “invasive” in vitro phenotype, but the molecular pathways regulating these gene expression signatures and corresponding therapeutic outcomes are not well understood. A team of performed comprehensive molecular profiling on 68 patient-derived melanoma cell lines, including analyses of genomic, transcriptomic, proteomic and non-coding RNA features. The researchers, including Jianjun Shen, Ph.D., professor, Department of Epigenetics and Molecular Carcinogenesis, The University of Texas MD Anderson Cancer Center, defined molecular programs underlying three distinct classes of cell types and demonstrated these programs are conserved between tumors and laboratory cell lines as reported in the journal *Nature Communications* on July 9, 2022. They identified defining gene expression signatures that can be used to categorize both cell lines and tumors and showed these cell types are associated with outcomes to immunotherapy and cellular therapy. These data confirm the utility of performing parallel ‘omics’ analyses to identify multi-modal molecular regulatory features and relating these to observable clinical outcomes. The University of Texas MD Anderson Cancer Center received a $5 million CPRIT Core Facilities Support Award grant (RP170002) in 2016.

159. The GNASR201 gain-of-function mutation is the single most frequent cancer-causing mutation

across all heterotrimeric G proteins, driving oncogenesis in various low-grade/benign gastrointestinal and pancreatic tumors. Activating mutations in the GNAS gene — which encodes a signaling protein called Gαs — leads to the activation of pathways associated with cancer cell proliferation, but the mechanisms involved have remained unclear. Researchers from The University of Texas MD Anderson Cancer Center, including CPRIT Scholar John Paul Shen, M.D., assistant professor, Department of Gastrointestinal Medical Oncology, looked at peritoneal models of colorectal cancer with specific activating GNAS mutations in order to determine the tumors' dependence on the GNAS pathway and to identify downstream targets. Using gene knockouts, they showed that these mutant tumors relied on GNAS to proliferate. The researchers were able to identify several downstream targets of GNAS signaling, including the PKA and Wnt pathways. The results published in *Oncogene* on July 25, 2022, showed that blocking PKA and Wnt signaling reduced the growth of GNAS mutant tumors, suggesting they could be potential therapeutic targets. These findings demonstrate oncogene addiction to GNAS mutations and offer potential new therapeutic strategies in patient with GNAS-mutant cancers. The University of Texas MD Anderson Cancer Center recruited Dr. Shen from the University of California, San Diego in 2018 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR180035).

160. CPRIT Scholar Christopher Amos, Ph.D., Associate Director of quantitative science, Baylor College of Medicine, and global researchers set out to identify new susceptibility loci to lung cancer among diverse populations. The team performed cross-ancestry genome-wide association studies in European, East Asian and African populations and discovered five loci that have not been previously reported. As reported in *Nature Genetics* on August 1, 2022, the team replicated 26 signals and identified 10 new lead associations from previously reported loci. Rare-variant associations tended to be specific to populations, but even common-variant associations influencing smoking behavior, such as those with CHRNA5 and CYP2A6, showed population specificity. Fine-mapping and expression quantitative trait locus colocalization nominated several candidate variants and susceptibility genes such as IRF4 and FUBP1. DNA damage assays of prioritized genes in lung fibroblasts indicated that a subset of these genes, including the pleiotropic gene IRF4, potentially exert effects by promoting endogenous DNA damage. Baylor College of Medicine recruited Dr. Amos in in 2017 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR170048) and received a $5.2 million CPRIT Core Facility Support Awards grant (RP180672) in 2018.

161. Aerobic exercise is associated with decreased cancer incidence and cancer-associated mortality. However, little is known about the effects of exercise on pancreatic ductal adenocarcinoma (PDA), a disease for which current therapeutic options are limited. The research, published in the journal *Cancer Cell* on July 11, 2022, highlights how the human immune system, which is built to combat external invaders like bacteria, can also identify cancer cells as abnormal. Florencia McAllister, M.D., associate professor, Department of Clinical Cancer Prevention, The University of Texas MD Anderson Cancer Center, and team, discovered that exercise increases the number of CD8 T cells that are sensitive to IL-15 that survive and doubles the number of them homing to pancreatic ductal adenocarcinoma (PDAC) tumors in mice. IL-15 signaling is involved in biological systems that prevent illness and repair tissue and depending on the situation, it may intensify the immune system's assault on pancreatic cancer cells. These findings highlight the therapeutic potential of an exercise-oncology axis and identify IL-15 activation as a promising treatment strategy for this deadly disease. The University of Texas MD Anderson Cancer Center received a $2 million CPRIT Individual Investigator Research Awards for Clinical Translation grant (RP200173) in 2020.

162. About 50% of all cancer patients are medically or surgically unfit to have their tumors resected and require treatment with radiation therapy. Ionizing radiation directly or indirectly causes DNA damage to induce cancer cell death and cancer cells can develop resistance to radiation therapy

and threaten treatment failure. Intriguingly, proton pump inhibitors (PPIs), FDA-approved for the treatment of gastric reflux, have been evaluated for their anticancer and chemosensitizing effects at preclinical and clinical levels. Research has demonstrated that PPIs such as pantoprazole, lansoprazole, omeprazole, and esomeprazole possess anticancer and chemosensitizing activity. In this study, Yohannes T. Ghebre, Ph.D., associate professor, Director of Radiation Biology Research and Education, Baylor College of Medicine, and colleagues outlined six molecular pathways that confer resistance of cancer cells to ionizing radiation and described how PPIs may be used to overcome radioresistance induced by alteration of one or more of these signaling pathways. As reported in *Frontiers in Oncology* on August 5, 2022, the inflammatory, adaptive, hypoxia, DNA damage repair, cell adhesion, and developmental pathways are all linked to the resistance of cancer cells to ionizing radiation. The team described the molecular link between alteration of these pathways in cancer cells and development of resistance to ionizing radiation. Such an intervention with PPIs is expected to increase the therapeutic index by reducing radiation-induced normal tissue toxicity and improving tumor control. Given that PPIs are FDA-approved drugs, they have the potential to be fast-tracked into the clinic. Baylor College of Medicine received a $200,000 CPRIT High Impact/High Risk grant (RP190497) in 2019.

163. A University of Texas at Arlington electrical engineering researcher is creating a portable, wearable device for rapid gas analysis that could detect illness immediately. Yuze "Alice" Sun, associate professor, Department of Electrical Engineering, said the device will play an important role in health care, industrial and workplace safety, environmental monitoring and defense and national security sectors. The title of the project is: PFI-RP: Portable integrated photonic micro-gas chromatography system for rapid gas analysis. The team will also work closely with its industrial partner, ams Sensors USA Inc. Advancements in micro-gas chromatography in the past 20 years have demonstrated great potential for the development of powerful portable gas analysis devices. But it remains a challenge to achieve efficient separation and rapid detection for effective gas analysis in a highly integrated and cost-effective platform, as well as in a mobile device. According to the team, the key to the project is system-level integration, including creating new micro-gas chromatography architecture and using photonic integrated circuits to achieve rapid and comprehensive volatile organic compounds gas analysis. Dr. Sun said her project will create technology to transform a powerful gas analysis instrument traditionally used in research labs into portable and wearable devices that are easily accepted and accessible by the public. The University of Texas at Arlington received a $200,000 CPRIT High Impact/High Risk grant (RP170747) in 2017.

164. Only about 1% of human DNA encodes instructions for making proteins. Research in recent decades has shown that much of the remaining noncoding genetic material holds regulatory elements — such as promoters, enhancers, silencers, and insulators — that control how the coding DNA is expressed. To better understand these regulatory components, study author and CPRIT Scholar Jian Zhou, Ph.D., assistant professor, Department of Bioinformatics, The University of Texas Southwestern Medical Center, and colleagues developed a deep learning model they named Sei, which accurately sorts these snippets of noncoding DNA into 40 "sequence classes." These 40 sequence classes cover more than 97% of the human genome. In May, Dr. Zhou reported the development of a different tool, called Orca, which predicts the 3D architecture of DNA in chromosomes based on its sequence. Dr. Zhou trained the model to make connections and evaluated the model's ability to predict structure at various length scales. The findings, published in *Nature Genetics* in May 2022, showed that Orca predicted DNA structures both small and large based on their sequences with high accuracy, including for sequences carrying mutations associated with various health conditions including a form of leukemia and limb malformations. The team plans to use Sei and Orca, which are both publicly available on web servers and as open-source code, to further explore the role of genetic mutations in causing the molecular and physical manifestations of diseases — re-

search that could eventually lead to new ways to treat these conditions. The University of Texas Southwestern Medical Center recruited Dr. Zhou with the support of a $2 million CPRIT Recruitment of First-time, Tenure-Track Faculty Members grant (RR190071) in 2019.

165. Hexametric helicase is a central component in DNA replication and many replicative helicases have been proposed as drug targets for disease treatment. Rice University researchers have modeled a key mechanism by which DNA replicates. Combining structural experiments and computer simulations, CPRIT Scholar Yang Gao, Ph.D., assistant professor, Department of Biosciences, and colleagues have uncovered details about how helicases, a family of ringlike motor proteins, wrangle DNA during replication. The researchers noted that because the helicase-DNA complex is so large, there have been only a few attempts to simulate translocation of the helicase from one end of the strand to the other. The Rice hybrid of coarse-grained protein–single-stranded DNA force field techniques provided the opportunity to study the process from beginning to end and recapitulated the large-scale translocation of the gp4 subunit with limited computational cost and revealed numerous mechanistic details about gp4 helicase translocation. The synergy between the experiments and large-scale simulations they described in the *Proceedings of the National Academy of Sciences* on August 1, 2022, could become a paradigm for modeling of the mechanisms of many complex biological systems and could reveal new targets for disease-fighting drugs. "These computational models can make a big contribution and they will, for sure, be adapted to other large systems to examine rather important questions," Dr. Gao said. Rice University received a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR190046) in 2019.

166. Researchers from The University of Texas MD Anderson Cancer Center and colleagues reviewed the impact of the 2021 lung cancer screening recommendations from the United States Preventive Services Task Force (USPSTF) to lower screening thresholds from 55 to 50 years of age and cumulative smoking exposure from 30 to 20 pack years. Corresponding author Robert Volk, Ph.D., professor, Department of Health Services Research, and colleagues compared lung cancer screening eligibility estimates after 2013 recommendations from the USPSTF to eligibility estimates after the 2021 recommendations from USPSTF. The researchers noted an overall 81.4% increase in eligibility for lung cancer screening. The results published in *Cancer Medicine* on July 24, 2022, also noted significant socioeconomic disparities that didn't appear to change after the lowered screening thresholds from the 2021 USPSTF recommendations. In 2013, people with less than a high school diploma (20%) were four times less likely than those with a high school diploma or higher educational level (80%) to have lung cancer screening. For people under the age of 65, they estimated that in 2013, people with no health care insurance were over 5.5 times less likely to have lung cancer screening in comparison to people with private insurance (10.9% versus 57.6%). "Our findings show potential gaps, particularly among non-Hispanic Black individuals who have lower levels of education, income, and employment. These factors are important to consider within the context of exacerbating disparities that may compound upon one another," Dr. Volk noted. The University of Texas MD Anderson Cancer Center received a $1.5 million CPRIT Individual Investigator Research Awards for Prevention and Early Detection grant (RP190210) in 2019.

167. In a study published on August 10, 2022, in *Cancer Research*, a team of researchers led by C. Patrick Reynolds, M.D., Ph.D., Cancer Center Director for the School of Medicine, Texas Tech University Health Sciences Center (TTUHSC), sought to expand upon his lab's previous research that showed ALT tumors identified by a biomarker known as C-circles share a common biology that confers vulnerabilities to be exploited for cancer therapy. Cancer cells must maintain their telomeres using telomere maintenance mechanisms (TMM) to continue growing and multiplying. However, some cancer cells are able to grow continuously without turning on telomerase. Instead, they grow by using an alternate lengthening of telomeres (ALT) mechanism that can repair telomeres without

telomerase. The team employed the C-circle assay to evaluate a variety of childhood and adult cancers. They found ALT positivity in pediatric cancers (neuroblastoma and sarcoma) and in adult cancers (breast, colon and lung cancers). The team demonstrated that ALT cancer cells have high amounts of activated ATM (ataxia-telangiectasia mutated) kinase, which promotes chemotherapy resistance in ALT cancers. Data from this project can be an aid in developing clinical trials for patients whose ALT cancer is readily identifiable with the C-circle biomarker. Texas Tech University Health Science Center received two CPRIT Academic Research grants (RP200432, RP210154) in 2020 and 2021 for a total of $7.2 million.

168. Genetic information is stored in double-helix–structured DNA molecules. During DNA replication, topoisomerase proteins (TOPs) play the critical role of making temporary DNA-strand breaks so they can be untangled and made accessible to the replication machinery. Some chemotherapies, such as camptothecin, work by trapping TOPs on the DNA, causing sustained breaks and cell death. The TDP1 protein can help repair this damage, but it is not clear what other players may be involved in this process. A study led by Junjie Chen, Ph.D., professor and Chair of the Department of Experimental Radiation Oncology, and colleagues at The University of Texas MD Anderson Cancer Center used a whole-genome CRISPR screen to identify MUS81 as a key protein in repairing damage from topoisomerase 1 (TOP1) in the absence of TDP1. They clarified the mechanism for MUS81's activity and showed that loss of both TDP1 and MUS81 enhanced cancer cell sensitivity to camptothecin. These findings, published in *Nature Communications* on July 22, 2022, suggest that MUS81 could be an alternate target to improve activity of certain cancer therapies. The University of Texas MD Anderson Cancer Center received a $5.1 million CPRIT Multi-Investigator Research Awards grant (RP160667) in 2016.

169. Engineered oncolytic viruses can provoke anti-tumor immune responses in glioblastoma, as shown by a 20% response rate in a phase I study. However, immunosuppressive signals in the tumor microenvironment can limit the efficacy of these therapies. Researchers, including W. Jim Zheng, Ph.D., professor, School of Biomedical Informatics, The University of Texas Health Science Center at Houston, demonstrated that an oncolytic virus carrying a T cell activator (Delta-24-RGDOX) combined with targeted inhibitors of IDO – a suppressive immune signal – can effectively reshape the microenvironment to enhance anti-tumor immune responses. Published on July 28, 2022, in *Journal for ImmunoTherapy of Cancer*, the results show that Delta-24-RGDOX alone led to activation of IDO pathways but adding IDO inhibitors increased anti-tumor T cells and decreased suppressive immune cells. The combination also improved the survival of laboratory glioma models, suggesting this therapeutic approach warrants further clinical evaluation for patients with glioblastoma. The University of Texas Health Science Center at Houston received a $5.8 million CPRIT Core Facility Support Awards grant (RP170668) in 2017 and The University of Texas Medical Branch at Galveston received a $3.5 million CPRIT Core Facility Support Awards grant (RP190682) in 2019.

170. Colorectal cancer remains the second leading cause of cancer-related mortality in the United States. Most patients with metastatic colorectal cancer (mCRC) will develop liver metastases, which account for almost two-thirds of all colorectal cancer (CRC) deaths. Approximately 75% of patients with mCRC who undergo resection of liver metastases will develop disease recurrence. CPRIT Scholar, John Paul Shen, M.D., assistant professor, Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, and team hypothesized that prevention of TGF-β–induced immune exclusion along with immune checkpoint blockade may eliminate colorectal cancer micrometastases still present after resection of all evident disease. They conducted a pilot study in patients to determine if bintrafusp alfa treatment led to clearance of ctDNA (and presumably, of micrometastatic disease). This study, accepted in July 2022 in *Cancer Research Communications,* reported that while bintrafusp alfa was overall well-tolerated, the rapid onset of

clinical progression and the acquisition of new mutations raised concern among investigators for loss of equipoise, leading to premature discontinuation of the study. This study demonstrates the feasibility of hypotheses for future study of treatment strategies of colorectal cancer which may be better informed by the observed complexity of potential compensatory signaling of multiple TGF-β isoforms. The University of Texas MD Anderson Cancer Center recruited Dr. Shen from the University of California, San Diego in 2018 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR180035) and received two CPRIT Individual Investigator grants (RP200356, RP220416) in 2020 and 2022 for a total of $3.4 million.

171. B cell malignancies, in particular multiple myeloma (MM) and diffuse large B cell lymphoma (DLBCL), represent some of the most common hematological cancers worldwide. Patients have seen success using genetically modified CAR T cells to target and destroy cancerous B cells, but this immunotherapeutic strategy often has serious side effects and is unsuitable for older individuals who often have MM and DLBCL. CPRIT Scholar Can Cenik, Ph.D., assistant professor, Department of Molecular Biosciences, The University of Texas at Austin, and a team of researchers investigated whether a soluble version of BCMA, unattached to the B cell surface, would act as a "decoy receptor" to mop up excess APRIL and BAFF and prevent these proteins from driving the growth of cancerous B cells. APRIL and BAFF regulate the growth of healthy B cells, but increased levels encourage the development and survival of malignant B cells, promoting the spread of blood cancer and the development of treatment resistance. In this study published in the *Journal of Experimental Medicine* (JEM) on Jul 26, 2022, the researchers engineered a mutant version of soluble BCMA that binds strongly to both APRIL and BAFF. Dubbed V3sBCMA-Fc V3, this decoy receptor reduced the activity of APRIL and BAFF in mice and cynomolgus monkeys without causing any significant side effects. The University of Texas at Austin recruited Dr. Cenik from Stanford University School of Medicine in 2018 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR180042).

172. Hexametric helicase is a central component in DNA replication and many replicative helicases have been proposed as drug targets for disease treatment. CPRIT Scholar Yang Gao, Ph.D., assistant professor, Department of Biosciences, Rice University, and colleagues combined structural experiments and computer simulations to uncover details about how helicases, a family of ringlike motor proteins, wrangle DNA during replication. The synergy between the experiments and large-scale simulations described in the *Proceedings of the National Academy of Sciences* in August 2022, could become a paradigm for modeling of the mechanisms of many complex biological systems. "These are dynamic processes that cannot be captured well with experimental methods alone," said Dr. Gao. "But it's important to show the mechanisms of these helicases, because they're essential for DNA replication, and also possible drug targets." Until now, researchers have been unable to pin down how the helicase steps along as it unzips the double strand. The team found that ATP tightly binds the helicase subunits, but that hydrolysis significantly lowers the energy barrier for subunit disassociation, allowing the protein to step forward. The coarse-grained protein–single-stranded DNA force field provides a transferable model with top-down parameterization, which can be easily applied to other giant protein–nucleic acid systems. With the emergence of many cryo-EM structures of giant protein–nucleic acid complexes, the researchers believe their novel system can greatly aid the mechanistic understanding of essential physiological processes in molecular biology. Rice University and Dr. Gao received a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR190046) in 2019.

173. Clinical trial sponsors rely on eligibility criteria to control the characteristics of patients in their studies, promote the safety of participants, and optimize the interpretation of results. However, in recent years, complex and often overly restrictive inclusion and exclusion criteria have created substantial

barriers to patient access to novel therapies, hindered trial recruitment and completion, and limited generalizability of trial results. A LUNGevity Foundation working group developed a framework for lung cancer clinical trial eligibility criteria. The goals of this framework are to simplify eligibility criteria, facilitate stakeholders' (patients, clinicians, and sponsors) search for appropriate trials, and harmonize trial populations to support intertrial comparisons of treatment effects. David Gerber, M.D., professor, Department of Internal Medicine, The University of Texas Southwestern Medical Center, and clinicians and representatives from the pharmaceutical industry, the National Cancer Institute, the U.S. FDA, the European Medicines Agency, and the LUNGevity Foundation undertook a process to identify and prioritize key items for inclusion in trial eligibility criteria. The group generated a prioritized library of terms to guide investigators and sponsors in the design of first-line, advanced non–small cell lung cancer clinical trials intended to support marketing application. This effort forms the basis for a forthcoming FDA draft guidance for industry. Going forward, by connecting diverse stakeholders and providing formal opportunity for public input, the emerging FDA draft guidance may also provide an opportunity to revise and simplify long-standing approaches to trial eligibility. This work serves as a prototype for similar efforts now underway for other cancers. The University of Texas Southwestern Medical Center received a $1.5 million CPRIT Texas Clinical Trials Participation Program Award grant (RP210115) in 2021.

174. The increasing prevalence of Alzheimer's disease (AD) has wide-ranging implications for patients with AD, their families, and the health care system as a whole. Mounting evidence indicates that systemic immune responses can have lasting effects on the brain and can influence AD risk and/or progression. A diverse range of microorganisms and infectious diseases have been associated with an increased risk and/or rate of cognitive decline, particularly among older adults, including influenzal respiratory infections, pneumonia, herpes infections, chronic periodontitis, urinary tract infections, gastrointestinal infections, sepsis, and most recently, COVID-19. Prevention or attenuation of microbe-related inflammation may therefore represent a rational strategy to delay or reduce the risk of neurodegenerative disease. Researchers from The University of Texas Health Science Center, including CPRIT Scholar Xiaoqian Jiang, Ph.D., professor and Director of Center for Secure Artificial intelligence For hEalthcare (SAFE), compared the risk of Alzheimer's disease incidence between patients with and without prior flu vaccination in a large nationwide sample of U.S. deidentified claims data spanning September 1, 2009 - August 31, 2019. Eligible patients were free of dementia during the 6-year look-back period and≥65 years old by the start of follow-up. The results published in the *Journal of Alzheimer's Disease* on August 2, 2022, reported that people who received at least one influenza vaccine were 40% less likely than their non-vaccinated peers to develop Alzheimer's disease over the course of four years. The University of Texas Health Science Center recruited Dr. Xiaoqian from the University of California, San Diego in 2018 with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR180012).

175. ARROW is a phase 1/2 study of the highly selective RET inhibitor pralsetinib in patients with medullary thyroid cancer, RET-altered non-small cell lung cancer (NSCLC) and other RET-altered solid tumors. After recent approvals of pralsetinib in patients with RET-altered NSCLC and thyroid cancers and respective publications of these data, here corresponding author Vivek Subbiah, M.D., associate professor, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, and fellow researchers presented interim data on the efficacy and safety of pralsetinib in prospectively identified patients with diverse RET fusion–positive tumors. The study results, published on August 12, 2022, in *Nature Medicine*, showed an overall response rate of 57% and a disease control rate of 83% in 23 patients with a range of cancer types. These findings build upon positive results previously reported in RET-altered NSCLC and thyroid cancer, suggesting the targeted therapy may offer tissue-agnostic benefits to patients with RET fusions. "We've had an explosion in clinical next-generation sequencing that allows us to understand shared biomarkers

across multiple tumor types, and this study was important to determine if RET fusions are actionable across cancer types," said Dr. Subbiah. "We observed responses regardless of tumor type, prior therapy or gene fusion partner. These data validate RET as a tissue-agnostic target with sensitivity to RET inhibition." The University of Texas MD Anderson Cancer Center received an $830,000 CPRIT Academic Research grant (RP110584).

176. Scientists have long known that members of the Wnt family of proteins are pivotal for embryonic development, kicking off signaling pathways necessary for functions such as axis formation, cell fate specification, and cell proliferation and migration. Aberrant Wnt signaling is known to contribute to pancreatic cancer, melanoma, triple-negative breast cancer, and other types of malignancies. Xiaochun Li, Ph.D., associate professor of molecular genetics and biophysics, The University of Texas Southwestern Medical Center, explained that to perform their signaling functions, Wnt proteins must first be activated by the addition of a lipid molecule, a job performed by an enzyme called Porcupine (PORCN). How this occurs structurally and the mechanism by which investigational drugs inhibit this activity have been unknown. Using UT Southwestern's Cryo-Electron Microscopy Facility, Dr. Li and his colleagues gathered cryo-EM images, which freezes proteins in place to get atomic-resolution microscopic images, of four structures. The findings, reported in *Nature*, shed light on the mechanisms behind this activity and could eventually lead to new drugs to treat various malignancies. Dr. Li noted that LGK974 is one of several drugs that affect Wnt signaling that is currently in clinical trials against various cancers. Knowing the atomic structures of Wnt, PORCN, palmitoleoyl-CoA, and their complexes could lead to drugs better designed to block these interactions. The University of Texas Southwestern Medical Center received a $5.5 million CPRIT Core Facility Support Awards grant (RP170644) in 2017.

177. Higher levels of tumor-infiltrating T cells in ovarian cancer are correlated with improved patient survival, suggesting these T cells are capable of mounting an anti-tumor immune response. However, immune suppression from signaling in the tumor microenvironment can dampen this response. A new study from researchers at The University of Texas MD Anderson Cancer Center, including Chantale Bernatchez, Ph.D., associate director, cell therapy process development, department of biologics development, and Amir Jazaeri, M.D., Vice Chair for Clinical Research and the Director of the Gynecologic Cancer Immunotherapy program, reports the successful development of genetically engineered tumor-infiltrating lymphocytes (TILs) that are resistant to TGF-β, a major immunosuppressive signal. Their methods build upon previous work to optimize expansion of isolated TILs in culture. Using CRISPR/Cas9 gene editing, the researchers removed the gene encoding TGF-β receptor 2 (TGFBR2) in isolated TILs prior to expansion. In pre-clinical studies, these engineered TILs had enhanced cell-killing ability in the presence of TGF-β compared to controls. The study, published in July 2022 in the *Journal for ImmunoTherapy of Cancer*, suggests this approach may provide opportunities to improve TIL therapies for ovarian cancers and other solid tumors. The University of Texas MD Anderson Cancer Center received a $4 million CPRIT Research Training grant (RP170067) in 2016.

178. Engineered oncolytic viruses can provoke anti-tumor immune responses in glioblastoma, as shown by a 20% response rate in a Phase I University of Texas MD Anderson study. However, immunosuppressive signals in the tumor microenvironment can limit the efficacy of these therapies. Researchers led by Candelaria Gomez-Manzano, M.D., professor, Department of Neuro-Oncology - Research, and Juan Fueyo, M.D., professor, Department of Neuro-Oncology - Research, The University of Texas MD Anderson Cancer Center, demonstrated that an oncolytic virus carrying a T cell activator (Delta-24-RGDOX) combined with targeted inhibitors of IDO – a suppressive immune signal – can effectively reshape the microenvironment to enhance anti-tumor immune responses. The results published in the *Journal for ImmunoTherapy of Cancer* in July 2022, reported that Delta-24-RGDOX alone led to activation of IDO pathways but adding IDO inhibitors increased anti-tumor T cells and

decreased suppressive immune cells. Specifically, the IDO-Kyn-AhR activity was responsible for the resurface of local immunosuppression and resistance to therapy, which was ablated through IDO inhibition. Our data indicate that combined molecular and immune therapy may improve outcomes in human gliomas and other cancers treated with virotherapy. The University of Texas Health Science Center at Houston received two CPRIT Core Facility Support Awards grants (RP170668, RP190682) in 2017 and 2019 for a total of $9.3 million.

179. The p53 gene has long been a focus of cancer research because it is mutated in most human malignant tumors, covering more than half of all human cancers. It appears to activate a variety of "downstream" genes when cells become stressed from factors that damage their DNA. When researchers individually disabled cellular programs known to be activated by p53, the gene appeared to still suppress tumor development, suggesting that stress-induced gene activation isn't its only job. Researchers from The University of Texas Southwestern Medical Center, led by John Abrams, Ph.D., professor of cell biology, reported that p53 also keeps potential tumor-driving genes turned off. The new study published in *Developmental Cell* on July 11, 2022, builds on a 2020 report from the Abrams lab. Together, the two papers suggest that beyond turning on genes when cells are stressed, p53 appears to have a second role in which it acts directly on other genes to keep them turned off. Notably, these include many not currently known to contribute to cancer. By individually deleting specific p53 protein isoforms in their model system – the lab model Drosophila melanogaster, or fruit fly – Dr. Abrams and his colleagues demonstrated that previously silent gene programs became activated. Ongoing efforts to discover drugs that can replace p53 activity when it becomes impaired by mutations should not only focus on p53's role as a gene activator but also replicate its role as a gene silencer and genes that healthy p53 keeps inactivated may play currently unrecognized roles in promoting cancer. The University of Texas Southwestern Medical Center received a $4 million CPRIT Research Training grant (RP160157) in 2015 and an $816,000 CPRIT Individual Investigator grant (RP170086) in 2017.

180. For years, the nucleus within a cell was thought to be elastic like a rubber ball, deforming and snapping back into shape as the cell navigated through pores and between fibers inside the human body. Researchers at Texas A&M University and colleagues have discovered that the nucleus is more complex than originally believed, behaving more like a liquid drop than a rubber ball. CPRIT Scholar Tanmay Lele, Ph.D., professor, Department of Biomedical Engineering, said that understanding how nuclei become misshapen may help uncover a way to aid cell nuclei in regaining their normal shapes, leading to new approaches for treating cancer. The findings from this study, published in *Advanced Science* in June 2022, are critical to understanding how a protective layer surrounding the nucleus, called the lamina, helps preserve nuclear shape while cells crawl through the tortuous paths through pores and around tissue fibers. Dr. Lele reported, "Our work points to a fundamental mechanism by which the nucleus preserves its shape and protects its genome. Our discovery also helps us better understand how misshapen nuclei arise in cancer and how to potentially make them normal again." The team is now studying the implications of the drop model for the abnormal nuclear shapes commonly observed in cancer. Texas A&M Engineering Experiment Station recruited Dr. Lele from the University of Florida in 2020 with the support of a $5 million CPRIT Recruitment of Established Investigators grant (RR200043) in 2020.

181. Rice University and Baylor College of Medicine researchers have shown they can eradicate advanced-stage mesothelioma tumors in mice in just a few days with a treatment combining Rice University's cytokine "drug factory" implants and a checkpoint inhibitor drug. Mesothelioma refers to any cancer that occurs in the tissue linings that surround and protect internal organs. Research team leader, CPRIT Scholar Omid Veiseh, Ph.D., assistant professor of bioengineering, Rice University, explained that they place the beads, which are just 1.5 millimeters wide, beside tumors and inside the thin layer of tissue known as the pleura, which covers the lungs and lines the interior

wall of the chest. Once placed, the beads produce continuous, high doses of interleukin-2 (IL-2), a natural compound that activates white blood cells to fight cancer. In this study, published in *Clinical Cancer Research* on August 22, 2022, researchers found the drug factory implants eliminated tumors in more than 50% of the treated animals when used by themselves. Tumors were destroyed completely in all seven mice that were treated with both the drug factory implants and PD-1 checkpoint inhibitor. The results also suggested that the combination of IL-2-producing implants and anti-PD-1 checkpoint inhibitors could be effective at training "memory T cells" that can reactivate the immune system to fight mesothelioma if it recurs. Rice University recruited of Dr. Veiseh from the Massachusetts Institute of Technology with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160047) in 2016.

182. COX-1 and COX-2 are enzymes which produce prostaglandins that promote inflammation, pain, and fever. Ming Hu, Ph.D., professor, Department of Pharmacological and Pharmaceutical Sciences, University of Houston College of Pharmacy, and colleagues developed an approach to determine the relative contribution of COX-1 and COX-2 to the production of prostaglandin E_2 (PGE_2), an important lipid mediator, in inflammation in different tissues and cells with the aid of the newly developed and validated LC-MS method. The team found that both COX-1 and COX-2 are inducible during inflammation and reported that COX-1 plays an unexpectedly but more important role than COX-2 in abnormal PGE_2 production since COX-1 expression is much higher than COX-2 in human oral cancer tissues and cells as well as Pirc rat colon. As reported in *Dovepress* on August 4, 2022, the absolute amount of COX-1 and COX-2 proteins were determined for the first time in the current study. These results indicate that targeted suppression of local COX-1 should be considered to reduce colon-specific PGE_2-mediated inflammation. The University of Houston College of Pharmacy received a $200,000 CPRIT High Impact/High Risk grant (RP180863) in 2018.

183. Researchers at Baylor College of Medicine and colleagues have identified biological markers in triple negative breast cancer (TNBC) that are associated with resistance to chemotherapy treatment. Ten to 15% of breast cancers are designated TNBC because of low expression of HER2, the estrogen receptor (ER) and the progesterone receptor. TNBC exhibits high mortality and frequent chemotherapy resistance and the majority of TNBC cases do not have an obvious hereditary explanation, and therefore the underlying DNA repair defects are more obscure. The research team, including CPRIT Scholars Gloria Echeverria, Ph.D., assistant professor, and Bing Zhang, Ph.D., professor, both from the Department of Molecular and Human Genetics, used an innovative analytic approach called "microscaled proteogenomics" that they previously developed to analyze tumor biopsies taken from TNBC patients prior to treatment with chemotherapy. Data from standard DNA and RNA sequencing approaches were integrated with mass spectrometry-based proteomics and phosphoproteomic analyses to derive more complete molecular portraits of treatment-responsive versus treatment-resistant tumors. The study, published on August 24, 2022, in the journal *Cancer Discovery*, reported that when the team considered both proteomics and gene expression data together, they observed that sensitivity to chemotherapy was marked by higher DNA repair signatures, interferon gamma signaling and immune checkpoint components. The team then conducted analyses that triangulated treatment response, chromosomal deletion or gain and concordant decreases or increases in mRNA and protein expression. This led the team to determine that a deletion on chromosome 19 was associated with resistance to chemotherapy treatment. Of the hundreds of genes deleted in this location, expression of the DNA ligase gene LIG1 was one of the mostly consistently suppressed genes at both the mRNA and protein level. Baylor College of Medicine recruited Dr. Echeverria from The University of Texas MD Anderson Cancer Center in 2019 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR200009), received a $4.7 million CPRIT Core Facility Support grant (RP170691) in 2017, and recruited Dr. Zhang, from the Vanderbilt University School of Medicine in 2016 with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR160027).

184. Diffuse midline glioma (DMG) is a uniformly fatal pediatric cancer driven by oncohistones that do not readily lend themselves to drug development. With median survival of less than a year, DMGs are the leading cause of brain cancer deaths in children. These mutant histone oncoproteins function to reconfigure chromatin and are essentially undruggable. To identify druggable targets for DMG, CPRIT Scholar Sam McBrayer, Ph.D., assistant professor at Children's Medical Center Research Institute at The University of Texas Southwestern Medical Center, and colleagues conducted an unbiased genome-wide CRISPR screen to identify DMG vulnerabilities. This revealed a DMG selective dependency on the de novo pathway for pyrimidine biosynthesis. A clinical stage inhibitor of DHODH diminishes uridine-50-phosphate (UMP) pools, generates DNA damage, and induces apoptosis through suppression of replication forks—an "on-target" effect. The results, published in *Cancer Cell* on August 18, 2022, demonstrated that this DHODH inhibitor (BAY2402234) accumulates in the brain at therapeutically relevant concentrations, suppresses de novo pyrimidine biosynthesis in vivo, and prolongs survival of mice bearing intracranial DMG xenografts, highlighting BAY2402234 as a promising therapy against DMGs. The University of Texas Southwestern Medical Center recruited Dr. McBrayer from the Dana-Farber Cancer Institute and Harvard Medical School in 2019 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR190034).

185. Researchers from the University of Houston and The University of Texas MD Anderson Cancer Center are altering T cells from the immune system in the lab to attack cancer cells. This form of immunotherapy, called chimeric antigen receptor (CAR) T-cell therapy, can be a life-saving treatment resulting in tumor control lasting ten years or longer. Navin Varadarajan, Ph.D., Department of Chemical and Biomolecular Engineering, the University of Houston, and colleagues have found a way to determine which patients are likely to respond to CAR T-cell therapy, saving precious time in treating lymphoma, which is most responsive to this form of immunotherapy. To determine the best patient prospects, the team studied the dynamic interactions between T cells and tumor cells. Their findings published July 26, 2022, in *The Journal of Clinical Investigation*, point to the relationship between a ligand molecule on a cancer cell (CD58) and a protein on a T cell (CD2) which work together to communicate and activate the CD2, turning it into a cancer cell killer. Dr. Varadarajan and colleagues profiled the dynamic interactions between T cells that comprise patient infusion products and tumors, using the TIMING (Timelapse Imaging Microscopy In Nanowell Grids) method, developed in Dr. Varadarajan's lab at the University of Houston. TIMING is high-throughput single-cell technology that merges artificial intelligence with a nanowell imaging platform to simultaneously evaluate how individual cells move, activate, interact, kill and survive. By interrogating thousands of individual interactions between T cells and tumor cells, the research revealed how patients whose tumors expressed CD58 are much more likely to respond to CAR T-cell therapy compared to patients whose tumors did not express CD58. The University of Houston received a $1.17 million CPRIT Individual Investigator Research Awards for Clinical Translation grant (RP180466) in February 2018.

186. Malignant pleural mesothelioma (MPM) is a lung pleural cancer with very poor disease outcome. With limited curative MPM treatment available, it is vital to study prognostic biomarkers to categorize different patient risk groups. Researchers from the Baylor College of Medicine defined gene signatures to separately characterize intrinsic and extrinsic features and investigated their interactions in MPM tumor samples. The team calculated gene signature scores to capture the downstream pathways of major mutated driver genes as tumor-intrinsic features. CPRIT Scholars Christopher Amos, Ph.D., professor of medicine, Director of the Institute for Clinical and Translational Research, and Chao Cheng, Ph.D., associate professor, Institute for Clinical and Translational Research, inferred the infiltration levels for major immune cells in the tumor microenvironment to characterize tumor-extrinsic features. They integrated these features with clinical factors to predict prognosis in MPM. The results published in the *British Journal of Cancer* on August 23, 2022,

reported that the gene signature scores were more prognostic than the corresponding genomic mutations, mRNA and protein expression. High immune infiltration levels were associated with prolonged survival. The team concluded that by using an integrative model that combines intrinsic and extrinsic features, doctors can more correctly predict the clinical outcomes of patients with MPM. Baylor College of Medicine recruited Dr. Amos in in 2017 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR170048), recruited Dr. Cheng from the Geisel School of Medicine at Dartmouth in 2018 with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR180061), and received a $900,000 CPRIT Individual Investigator grant (RP200443) in 2020.

187. Chimeric antigen receptor (CAR) T cell therapy targeting CD19 is a breakthrough advance, but over half of patients with relapsed or refractory large B-cell lymphomas do not benefit from treatment. Pretreatment prognostic measures are needed to identify patients unlikely to have durable responses to CART19 and/or who may benefit from consolidative or alternative treatment strategies. Low-pass whole genome sequencing (lpWGS) is a quick and effective DNA-sequencing technology used to detect genetic variations by sequencing small amounts from multiple samples. Researchers led by Michael Green, Ph.D., associate professor and Director of Translational and Laboratory Research, Department of Lymphoma/Myeloma, and Jason Westin, M.D., associate professor, and Director of Lymphoma Clinical Research, both of The University of Texas MD Anderson Cancer Center, performed lpWGS on cell-free DNA in blood samples from 122 patients at time of leukapheresis prior to CAR T cell therapy to study copy number alterations (CNA) and develop prognostic markers of poor outcomes. As reported in the journal *Blood* on August 4, 2022, the team discovered that a high focal CNA score — a measure of genomic instability — was the most significant variable associated with poor outcomes. Combining a focal CNA score with traditional markers of increased tumor bulk provides a valuable risk model to help prioritize patients that may benefit from alternate treatment strategies. The University of Texas MD Anderson Cancer Center received a $900,000 CPRIT Individual Investigator grant (RP200385) in 2020.

188. NASA's planned mission to Mars will result in astronauts being exposed to 350 mSv/yr of Galactic Cosmic Radiation (GCR). A growing body of data from ground-based experiments indicate that exposure to space radiation doses (approximating those which astronauts will be exposed to on a mission to Mars) impairs a variety of cognitive processes, including cognitive flexibility tasks. In this study, researchers from around the U.S., including William K. Russell, Ph.D., associate professor, Department of Biochemistry & Molecular Biology, UTMB Mass Spectrometry Director, University of Texas Medical Branch – Galveston, have employed a robust label-free mass spectrometry (MS) -based untargeted quantitative proteomic profiling approach to characterize the composition of the medial prefrontal cortex (mPFC) proteome in rats that have been exposed to 15 cGy of 600 MeV/n28Si ions. A variety of analytical techniques were used to mine the generated expression data. As reported in *Frontiers in Physiology* on August 26, 2022, the team identified several pathways and proteins whose expression alters as a result of space radiation exposure, including decreased mitochondrial function, and a further subset of proteins differs in rats that have a high level of cognitive performance after SR exposure in comparison with those that have low performance levels. Carbohydrate metabolism, lipid metabolism, and detoxification were the most suppressed in samples from irradiated animals. The correct balance for the OXPHOS complexes in the mPFC is essential for maintaining the bioenergetics needed to prevent cognitive issues. The identified list of proteins and biological pathways from the mPFC is the first database of low dose space specific radiation. In combination with previous publications by the team on hippocampal proteins affected by low dose radiation, this publication adds to NASA's GeneLab open science database of specific peptides that show dysregulation from different areas of the brain directly related to space relevant dose effects. The University of Texas Medical Branch at Galveston received a $3.5 million CPRIT Core Facility Support Awards grant (RP190682) in 2019.

189. For years, researchers have struggled to fill clinical trials and enroll sufficiently diverse groups of patients for results to reflect the broader population, in part because of stringent guidelines on who can participate. Patients, clinicians, and regulators struggle to evaluate trials when inclusion/exclusion criteria are difficult to understand, assess, and compare. To address this challenge, the multistakeholder group developed a framework for standardizing the approach to defining and presenting trial protocol eligibility criteria. The process involved leveraging prior efforts to reform clinical trial eligibility criteria (including expanding eligibility by eliminating overly restrictive criteria) and rigorous consensus-building steps through multiple meetings focused on definition and presentation of criteria involving regulators, clinicians, and clinical trial sponsors. The group was co-led by David Gerber, M.D., professor of internal medicine, hematology/oncology, The University of Texas Southwestern Medical Center and co-director of the Experimental Therapeutics Program, along with representatives from the Food and Drug Administration (FDA), National Cancer Institute, European Medicines Agency, pharmaceutical companies, and the LUNGevity Foundation. The recommendations, published on August 4, 2022, in *JAMA Oncology*, offer the first publicly available outline of upcoming FDA draft guidance on lung cancer clinical trials that are expected to make it easier to include more patients. The researchers hope that the FDA's interest in addressing these topics will prompt investigators and sponsors to evaluate study protocols critically and with an eye toward standardization of eligibility criteria, ultimately leading to trials that are easier to evaluate and compare. The University of Texas Southwestern Medical Center and Dr. Gerber received a $1.5 million CPRIT Texas Clinical Trials Participation Program Award grant (RP210115) in 2021.

190. Texas A&M University researchers, including Vladislav Yakovlev, Ph.D., professor, Department of Biomedical Engineering, accomplished what was once considered impossible—they created a device capable of squeezing the quantum fluctuations of light down to a directed path creating enhanced contrast imaging. This one-of-a-kind "flashlight" was built to increase the signal-to-noise ratio present in Brillouin microscopy spectroscopic measurements that visually record the mechanical properties of structures inside living cells and tissues. As reported in *Optica* on August 18, 2022, after nearly two years of vigorous explorations, the device grew into a tabletop-sized mechanism of complex optical configurations and measuring instruments that allowed the researchers to adjust, direct and efficiently manipulate and detect light. During that time, Tian Li, Ph.D., associate research scientist, Department of Biological and Agricultural Engineering, gained a better understanding of biology, and Dr. Yakovlev and Girish Agarwal, Ph.D., professor, Department of Biological and Agricultural Engineering, developed a mechanism to create the proper state and matter of light needed for noise reduction without damaging live cells. The test results reveal the new source significantly increases image clarity and accuracy and the use of quantum light may pave the way for significantly improved sensitivity that cannot be achieved classically. The team is enhancing the capabilities of Brillouin microscopy to identify the viscous or elastic materials in biological systems, which control the physical properties of cells and cell structures and define everything from cell development to cancer progression. Texas A&M Engineering Experiment Station received an $897,000 CPRIT Individual Investigator Research Awards for Prevention and Early Detection grant (RP180588) in February 2018.

191. T cell receptor (TCR)-based immunotherapy has emerged as a promising therapeutic approach for the treatment of patients with solid cancers; however, the lack of shared neoantigens across patients limits the use of this technique. A key requirement for safe and efficacious TCR-based therapies is identifying peptide–human leukocyte antigen (pHLA) complexes highly presented on tumors and rarely expressed on healthy tissue in combination with high-affinity TCRs that when introduced into T cells can redirect T cells to eliminate tumor but not healthy tissue. Steffen Walter, Ph.D., Chief Technology Officer of Immatics, Inc., and colleagues employed population-scale immunopeptidomics using quantitative mass spectrometry across ~1500 tumor and normal tissue

samples and identified an HLA-A*02:01-restricted pan-cancer epitope within the collagen type VI α-3 (COL6A3) gene that is highly presented on tumor stroma across multiple solid cancers due to a tumor-specific alternative splicing event that rarely occurs outside the tumor microenvironment. Published in *Science Translational Medicine* on August 31, 2022, the results reported that the researchers created affinity-enhanced T cell receptor T (TCR-T) cells and treated mice *in vivo* to show regression in tumors that expressed physiological levels of the targeted pHLA without toxicity to normal cells. The enhanced TCR variants exhibited a favorable safety profile with no detectable off-target reactivity, paving the way to initiate clinical trials using COL6A3-specific TCRs to target an array of solid tumors. Immatics, Inc. received a $19.7 million CPRIT Product Development Research grant (DP150029) in 2015.