CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Published Research Findings

A summary of research findings published by CPRIT grantees
September 1, 2022 – August 31, 2023.

For Fiscal Year 2023

1. Small cell lung cancer (SCLC) accounts for approximately 15% of lung cancer and is a highly malignant and nearly uniformly fatal disease. SCLC rapidly becomes resistant to conventional chemotherapy, leaving patients with no alternative treatment options. In this study, CPRIT Scholar Pawel K. Mazur, Ph.D., assistant professor, Department of Experimental Radiation Oncology at The University of Texas MD Anderson Cancer Center, and colleagues performed pharmacologic screening of 285 clinically approved and experimental small-molecule inhibitors to facilitate the potential implementation of promising combination therapeutic strategies. The results, published in *Cancer Discovery* on September 1, 2022, identified the lysine methyltransferase SMYD3 as a major regulator of SCLC sensitivity to alkylation-based chemotherapy. The team uncovered the molecular mechanisms that drive therapeutic resistance necessary to develop and improve novel therapies effective for SCLC. The University of Texas MD Anderson Cancer Center recruited Dr. Pawel from Stanford University in August 2016 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160078).

2. Imaging RNA of interest (ROI) has become a crucial strategy to understand many cellular pathways and physiological processes. Fluorescent light-up aptamers (FLAPs) are well-performed biosensors for cellular imaging and the detection of different targets of interest, including RNA. To explore the binding mechanisms of ROI and their cognate fluorogens, second author Chengwen Liu, Ph.D., Department of Biomedical Engineering at The University of Texas at Austin, and colleagues performed computational simulations to obtain information about FLAPs at atomic resolution. The study, published in *Frontiers in Molecular Biosciences* on September 2, 2022, reported that the researchers used an AMOEBA polarizable force field, with the capability of handling the highly charged and flexible RNA system, for the simulation of Mango-II with TO1-Biotin and TO3-Biotin. This work is the first attempt to simulate RNA ligand binding using advanced electrostatic and polarizable models. The University of Texas at Austin received a $4 million CPRIT Core Facility Support Awards grant (RP210088) in 2021 to support the Targeted Therapeutic Drug Discovery & Development Program.

3. In 2018, Americans aged 50-54 were 30.4% less likely to meet recommended colorectal cancer screening guidelines than Americans aged 70-75 and faced higher screening disparities based on race, ethnicity, household income, educational attainment, and insurance coverage. Because younger individuals face unique barriers to screening, Caitlin Murphy, Ph.D., MPH, associate professor, Department of Health Promotion and Behavioral Sciences at The University of Texas Health Science Center at Houston, and colleagues sought to predict screening disparities by looking at screening patterns. The team estimated prevalence of colorectal cancer screening (by colonoscopy, sigmoidoscopy, CT colonography, or stool-based tests) in adults ages 50 to 75 years using data from the National Health Interview Survey gathered during eight discontinuous years between 2000 and 2018. The results, published on September 2, 2022, in *Cancer Epidemiology, Biomarkers & Prevention*, report that colorectal cancer screening participation increased over time, but the increase was smallest among individuals aged 50-54. In contrast, screening for individuals aged 70-75 years increased from 2000 to 2018. The University of Texas Southwestern Medical Center received a $1.5 million CPRIT Prevention grant (PP160075) in 2016 to support the CRC screening outreach program.

4. Drugs that target the androgen receptor (AR), a key protein for prostate development and maintenance, have revolutionized prostate cancer management in recent decades. However, study leader and CPRIT Scholar Ping Mu, Ph.D., assistant professor, Department of Molecular Biology at The University of Texas Southwestern Medical Center (UTSW), explained that these therapies fail over time as prostate tumors develop resistance through lineage plasticity. Using different analytical methods including single-cell RNA sequencing, CPRIT Scholar Bo Li, Ph.D., assistant professor, Departments of Bioinformatics and Immunology, and fellow researchers from UTSW searched for key molecular pathways that separated the resistant cells from the sensitive ones. The results, published in *Nature Cancer* on September 5, 2022, revealed that when resistant prostate cancer cells were treated with both JAK1 and STAT1 inhibitors along with an AR-targeting drug, these cancer cells lost their ability to divide and survive. Using a similar strategy could offer a new way to overcome resistance in human prostate cancer patients. The University of Texas Southwestern Medical Center recruited Dr. Mu in August 2017 with the support of a $2 million Recruitment of First-Time, Tenure-Track Faculty Members (RR170050), and

recruited Dr. Li in August 2017 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members (RR170079), and received three CPRIT Academic Research grants totaling $5.9 million (RP220473, RP190208, RP160157) in February 2022, August 2019, and November 2015, respectively.

5. The receptor TREM2 TVD-Ig (TREM2) plays an important role in the pathophysiology of Alzheimer's disease (AD), and recent data suggests that increasing TREM2 activation could have therapeutic effects. Research led by senior author, professor and chair, Department of Chemistry at The University of Texas Health Science Center at Houston, reported that the newly developed agonistic antibody reduced the amyloid pathology (the buildup of abnormal proteins) in mice with Alzheimer's disease. The study, published on September 7, 2022, in *Science Translational Medicine*, reported that raising TREM2 activation decreased amyloid burden, eased neuron damage, and alleviated cognitive decline in mice with AD. The results suggest that this antibody engineering approach enables the development of effective TREM2-targeting therapies for AD. The University of Texas Health Science Center at Houston received two CPRIT Core Facility Support Awards (RP150551, RP190561) in 2015 and 2019 for a total of $11.2 million to support innovative antibody engineering technologies.

6. Glioma is the most common primary malignant brain tumor in adults and is often fatal. Despite efforts to develop novel treatments, no new medical therapies have been approved for adult patients with glioma in the last decade. Although mutant isocitrate dehydrogenase (IDH) inhibitors are effective against leukemia, they seem to be less active in aggressive glioma. CPRIT Scholar Samuel McBrayer, Ph.D., assistant professor, Children's Medical Center Research Institute at The University of Texas Southwestern Medical Center, and team identified a metabolic pathway that researchers can target to stop glioma. As reported in *Cancer Cell* on September 12, 2022, the researchers developed a genetically engineered mouse model of mutant IDH1-driven astrocytoma and discovered that IDH1-mutant brain tumor cells are extremely sensitive to drugs that target enzymes involved in the production of building blocks for DNA. This work outlines a therapeutic strategy that is poised for clinical translation. The University of Texas Southwestern Medical Center recruited Dr. McBrayer in May 2019 from Dana-Farber Cancer Institute and Harvard Medical School with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR190034).

7. Scientists have discovered that by targeting an enzyme, stearoyl CoA desaturase-1 (SCD1), they can inhibit the growth of tumors and trigger programmed cell death. Since SCD1 is a key regulator in fat metabolism and is required for survival of cancer cells, it is a validated drug target for many types of cancers, neurodegenerative diseases, and metabolic diseases. CPRIT Scholar Ming Zhou, Ph.D., professor, Department of Biochemistry and Molecular Biology at Baylor College of Medicine, and colleagues demonstrated that ultimately obtaining structures on stable binary or ternary complexes of electron transfer partners is relevant in developing novel strategies to inhibit SCD1 or other membrane-bound oxidoreductases. The results of this study, published in *Communications Biology* on September 12, 2022, reported that by studying the structures of stable pairs or groups of molecules involved in electron transfer, researchers can gain insights into how SCD1 and similar enzymes function. This knowledge is crucial for developing new strategies to inhibit the activity of SCD1 and other membrane-bound oxidoreductases. Baylor College of Medicine recruited Dr. Zhou in August 2012 from Columbia University Medical Center with a $4.5 million CPRIT Recruitment of Rising Stars grant (R1223).

8. Through extensive single-cell analysis, researchers have created a spatial map of tumor-infiltrating B cells and plasma cells in early-stage lung cancers, highlighting previously unappreciated roles these immune cells play in tumor development and treatment outcomes. Humam Kadara, Ph.D., associate professor, Department of Translational Molecular Pathology, and Linghua Wang, M.D., Ph.D., associate professor, Department of Genomic Medicine at The University of Texas MD Anderson Cancer Center, and fellow researchers performed single-cell analysis on 16 tumors and 47 matched normal lung tissues. They identified 12 different cell subsets, with more differentiated states being highly enriched in the tumors relative to adjacent normal tissue. "Our data reveal the importance of environmental factors, such as exposure to cigarette smoke, and molecular features of the tumor in contributing to the landscape of infiltrating B cells and plasma cells," Dr. Kadara said. The study, published in *Cancer Discovery* on September 13, 2022, represents the largest and most

comprehensive single-cell atlas on tumor-infiltrating B cells and plasma cells to date, which can be used to develop novel immunotherapy strategies. The University of Texas MD Anderson Cancer Center received two CPRIT Academic Research grants (RP160668, RP220101) in May 2016 and February 2022 for a total of $5.4 million to further understanding of how KRAS-mutant lung cancer evolves.

9. In clear cell renal carcinoma (ccRCC), the most common form of kidney cancer, new metastatic lesions often develop well after the primary tumor has been removed. This process, called metachronous metastasis, can occur months or years later, when many patients and their physicians believe they are cancer-free. To find out why this happens, CPRIT Scholar Srinivas Malladi, Ph.D., assistant professor of pathology at The University of Texas Southwestern Medical Center, and his colleagues created a mouse model of metachronous metastasis by implanting human ccRCC cells that carried extra genes to make them glow and resist an antibiotic called hygromycin. Although none of the mice developed metastatic tumors over the next five months, the researchers found living cells in the animals' lungs that glowed and resisted hygromycin. Further investigation identified a gene called SPARC that appeared to play a key role in both latent metastatic cell displacement and establishment at distal organs. The findings, published in *Cancer Discovery* on September 13, 2022, could lead to better ways to treat or even prevent metastasis in ccRCC. Dr. Malladi was recruited from Memorial Sloan-Kettering Cancer Center with a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR170003) in November 2016. UT Southwestern received a $3.7 million Core Facility Support Award grant (RP180770) in August 2018, and a $3.75 million Research Training grant (RP210041) in May 2021.

10. C. Patrick Reynolds, M.D., Ph.D., director of the Texas Tech University Health Sciences Center School of Medicine Cancer Center, and his team expanded upon their earlier research to demonstrate that many tumors share a vulnerability to reactivation of mutant TP53 protein that researchers can exploit for cancer therapy. To continue multiplying, cancer cells must maintain the integrity of their genome, particularly the telomeres, or the caps on the ends of chromosomes that serve to protect the genetic information. The most common mechanism is to turn on the telomerase enzyme that replenishes the DNA at the telomeres. However, as reported in the September 15 edition of *Cancer Research*, Dr. Reynolds and his colleagues discovered that this mechanism is inactive in 10-80% of pediatric cancers (neuroblastomas and sarcomas) and adult cancers (breast, colon, and lung cancers), which use another mechanism - alternate lengthening of telomeres (ALT) - only found in malignant cells. Uncontrolled telomere damage in ALT+ cancer cells normally activate the DNA damage and repair pathway through TP53, but cancer cells have turned off this pathway by inactivating TP53. The research team demonstrated that "normalization" of mutant TP53 protein function, using a new and promising class of TP53 targeting drug eprenetapopt (APR-246), drives the cell to undergo cell death when combined with DNA-damaging chemotherapy. Importantly, *in vivo* studies showed that the combination therapy led to the eradication of tumors in mice injected with human neuroblastomas, sarcomas, or breast cancer cells. These seminal findings indicate a potential strategy to overcome therapeutic resistance and support clinical evaluation of a combinatorial approach using APR-246 and chemotherapy in patients with ALT+ cancers, which currently lack targeted therapeutic approaches, and have a poor prognosis. Dr. Reynolds received a $1.3 million CPRIT Individual Investigator Award for Cancer in Children and Adolescents (RP220460) in February 2022 to support this discovery.

11. A clue found in the rare, crested ibis could someday help our bodies make better drugs. The species of bird is the only one known to naturally produce an enzyme able to generate a noncanonical amino acid. CPRIT Scholar Han Xiao, Ph.D., assistant professor, Departments of Chemistry, Biosciences, and Bioengineering, and his colleagues from Rice University reported that this discovery, made through computational comparison of genome databases, proves it's possible for that enzyme to work within the context of living cells. In this study, published on September 16, 2022, in *Nature Communications*, researchers found that the amino acid, sulfotyrosine (sTyr), is a key building block to program living cells that express therapeutic proteins. It could potentially allow cells to serve as sensors that monitor their environments and respond with the necessary treatment. The proof-of-concept study produced for the first time, mammalian cells that synthesize sTyr. "In nature, most of our species are made with 20 canonical building blocks," Dr. Xiao said. "If you want to

add an additional building block, you need to think about how to make it. We solved that problem: We can ask the cell to make it. But then we have to have the translational machinery to recognize it. And a special codon to encode this new building block." With this study, the team has fulfilled all three of these requirements. The researchers expect to use the combination of bioinformatics and computationally enhanced screening to produce a library of biosynthesized noncanonical amino acids. Rice University recruited Dr. Xiao in February 2017 from Stanford University with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR170014).

12. Human metapneumovirus (hMPV) is a major cause of acute respiratory infections in infants and older adults, for which no vaccines or therapeutics are available. In an article published on September 20, 2022, in *Cell Reports*, Jason McLellan, Ph.D., professor, Department of Molecular Biosciences and chair in Chemistry at The University of Texas at Austin, and researchers identified more details about sites on the hMPV protein that could be important for vaccine development. Using cryo-electron microscopy, an advanced imaging technique that allows scientists to see the molecular structure of proteins and viruses, the team identified vulnerabilities in the protein and provided a detailed map of how two antibodies manage to bind to those viral sites. These results provide insight into the humoral response to hMPV infection in older adults and will help guide vaccine development. "This is really important for a virus that, like flu and other illnesses, can cause complications in young children, in older adults and in people who are immunocompromised," Dr. McLellan said. The University of Texas at Austin received a $6 million CPRIT Recruitment of Established Investigators grant (RR160023) for Daniel Leahy, Ph.D., in February 2016.

13. COVID-19 disease has caused one of the major pandemic events in human history since COVID-19 cases were first identified in late 2019. Zhongming Zhao, Ph.D., M.S., professor, School of Biomedical Informatics at The University of Texas Health Science Center at Houston, reported that the virus can mutate quickly, and a vaccine has not been created that is fully effective for containing a novel strain. Although at present, the most reliable identifying process is reverse transcription-polymerase chain reaction (RT-PCR), this process is time-consuming and costly, and the testing kits are limited. The team proposed a model to distinguish COVID-19 patients from non-COVID-19 through chest X-rays and CT scan using a deep learning (DL) network based on the DenseNet169. This task uses transfer learning techniques and retrains a pre-trained model on a massive dataset like ImageNET to detect viral sequence and thus control the virus's spread. The experimental results reported in *Frontiers in Genetics* on September 21, 2022, found that the introduced model can achieve 99.59% accuracy for X-rays and 99.95% for CT scan images. For the COVID-19 test, this approach can save RT-PCR screening kits (and cost) and takes less time than the RT-PCR test. The University of Texas Health Science Center at Houston received two CPRIT Academic Research grants (RP180734, RP210045) in 2018 and 2021 for a total of $8.4 million to establish a unique collaborative Biomedical Informatics, Genomics, and Translational Cancer Research Training Program (BIG-TCR).

14. The breakthrough of the immune checkpoint blockade therapy has revolutionized cancer treatment. However, the existing approach is only effective in treating some cancers. Chengcheng Zhang, Ph.D., professor, Departments of Physiology and Oncology at The University of Texas Southwestern Medical Center, and colleagues reported the development of an anti-LAIR1 antagonist antibody that stimulated the activities of T cells, natural killer cells, macrophages, and dendritic cells *in vitro*. Using several functional assays, the team demonstrated that active blocking LAIR1 signaling with the LAIR1 antagonist antibody can activate anti-tumor function of multiple immune cells and inhibit tumor development. Importantly, the LAIR1 blockade inhibited the activity of immunosuppressive myeloid cells and reactivated T cells from cancer patients *in vitro* and impeded tumor metastasis in a humanized mouse model. The results published in *Frontiers in Immunology* on September 21, 2022, represent a promising strategy for development of anti-cancer immunotherapy. The University of Texas Health Science Center at Houston received two CPRIT Core Facility Support Awards (RP150551, RP190561) in 2015 and 2019 for a total of $11.2 million. The University of Texas Southwestern Medical Center received a $1.05 million CPRIT Academic Research grant (RP220032) in February 2022 to support a better understanding of the function of myeloid cells in cancer immunology.

15. Engineered living materials are inspired by naturally occurring living materials but use synthetic biology to introduce tailored, non-natural functions. The creation of autonomous engineered living materials—or ELMs—has been a long-time goal of CPRIT Scholar Caroline Ajo-Franklin, Ph.D., professor of biosciences at Rice University. This study, published on September 21, 2022, in *Nature Communications,* details how Dr. Ajo-Franklin and colleagues created flexible, adaptable ELMs using *Caulobacter crescentus* as a biological building block. The researchers modified the *C. crescentus* to express a version of that protein, which they call BUD (for bottom-up *de novo*, as in from scratch), with characteristics not only favorable to forming ELMs (dubbed BUD-ELMs) but also providing tags for future functionalization. One of the key advantages of the *C. crescentus* BUD-ELM platform is the highly reproducible, autonomous formation of engineered living materials. This work provides genetic tools, design and assembly rules, and a platform for growing ELMs with control over both matrix and cellular structure and function. Rice University recruited 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).

16. Researchers at Rice University and colleagues engineered the RNA-editing CRISPR-Cas13 system to amplify their power for detecting minute amounts of the SARS-CoV-2 virus in biological samples without the time-consuming RNA extraction and amplification step necessary in polymerase chain reaction (PCR) testing. The study, led by CPRIT Scholar Yang Gao, Ph.D., assistant professor, Department of Chemical and Biomolecular Engineering at Rice University, indicated that the new platform was highly successful compared to PCR, finding 10 out of 11 positives and no false positives for the virus in tests on clinical samples directly from nasal swabs. The results were published in *Nature Chemical Biology* on September 22, 2022. "The stability and robustness of engineered Cas13 variants make them more suitable for point-of-care diagnostics in low-resource setting areas when expensive PCR machines are not available," 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).

17. Estrogen-disrupting chemicals (EDCs) are substances found in our environment, including in water, soil, or food. EDCs are known to interfere with the endocrine system, which is responsible for growth, development, and metabolism. Exposure to these chemicals can lead to certain illnesses, including some forms of cancer. Researchers at Baylor College of Medicine have created new cell line models allowing fast, sensitive, direct observations of what happens when estrogen receptors are exposed to estrogen-disrupting chemicals at the CPRIT-funded GCC Center for Advanced Microscopy and Image Informatics. The results were published in *iScience* on September 23, 2022. "We are exposing the cell lines to a mixture of well-known toxins commonly used in testing by the Environmental Protection Agency. The data points are complex and robust and required numerous cell line-based assays that take hours or weeks to collect and process data. But now, our new models can make the call on potential estrogen-disrupting chemicals 'hits' within minutes and simultaneously report on potential mechanisms of action data," said principal investigator Michael Mancini, Ph.D., professor, Department of Molecular and Cellular Biology and director of the Integrated Microscopy Core. CPRIT awarded two Core Facility Support Awards grants (RP170719, RP150578) in 2015 and 2017 totaling $11.8 million to Texas A&M University System Health Science Center to promote highly collaborative and productive partnerships between experts in advanced imaging research and outstanding cancer researchers.

18. In cancer, innate immune cells can either promote or restrain malignant tumor growth, with outcomes depending on molecular cues received in the tumor environment. Researchers at The Watowich Lab at The University of Texas MD Anderson Cancer Center sought to improve understanding of the molecular mechanisms by which innate immune cells are regulated to inform new therapies for cancer and immune disease. Type I conventional dendritic cells (cDC1s) are a specialized subset of dendritic cells with a unique role in cancer immune control. To probe transcriptional mechanisms regulating cDC1 function, Stephanie Watowich, Ph.D., professor and deputy chair, Department of Immunology, and colleagues generated novel RNA sequencing datasets. The results, published in *The Journal of Immunology* on October

1, 2022, clarified an essential role for STAT3 in restraining autocrine IFN-I signaling in cDC1s and provided novel RNA sequencing datasets that will aid in further delineating inflammatory and anti-inflammatory mechanisms in cDC1s. The University of Texas MD Anderson Cancer Center received two CPRIT Research Training grants (RP170067, RP210028) in 2016 and 2021 for a total of $8 million in support of an innovative training program to educate exceptional postdoctoral fellows, predoctoral, and undergraduate students through an integrated, multidisciplinary approach.

19. Surgical treatment of pelvic sarcomas has improved considerably over the past few years using limb-preserving internal hemipelvectomy to achieve local control of cancerous tumors. However, the current custom prosthesis design process does not account for the patient's post-surgery prosthesis and bone loading patterns, nor can it predict how different surgical or rehabilitation decisions will affect prosthesis durability and post-surgery walking function. In this study, CPRIT Scholar Benjamin Fregly, Ph.D., professor, Department of Mechanical Engineering & Bioengineering at Rice University, and colleagues used a patient-specific neuromusculoskeletal model to predict the impact of psoas muscle strength on walking function following internal hemipelvectomy with custom prosthesis reconstruction. As reported in *Frontiers in Bioengineering and Biotechnology* in September 2022, these results suggest that when post-surgery psoas strength was increased, stance width and stride length returned to pre-surgery values. This approach may eventually influence surgical, rehabilitation, and custom prosthesis design decisions to meet the unique clinical needs of pelvic sarcoma patients. Rice University recruited Dr. Fregly in May 2017 from the University of Florida with the support of a $5.1 million CPRIT Recruitment of Established Investigators grant (RR170026).

20. Non-small cell lung cancer (NSCLC) is the deadliest form of cancer worldwide, primarily because of its propensity to metastasize, and is responsible for approximately 25% of all cancer-related deaths in the United States. Building upon their previous research implicating Impad1 as a key driver of invasion and metastasis in NSCLC, researchers at The University of Texas MD Anderson Cancer Center sought to understand the role of Impad1 in altering Golgi apparatus dynamics and exocytosis. Impad1 is found in the Golgi apparatus, a cellular organelle involved in protein transport. Led by Don Gibbons, M.D., Ph.D., professor, Department of Thoracic/Head and Neck Medical Oncology, the team reported that Impad1 interacts with a trafficking protein, Syt11, to alter the Golgi apparatus and change vesicular trafficking in a way that promotes lung cancer metastasis. The results of this study, published in *Cell Reports* on September 22, 2022, showed that inhibiting Impad1 or Syt11 reversed these effects, suggesting these proteins play an important role in regulating the tumor microenvironment and underscoring their potential as therapeutic targets. The University of Texas MD Anderson Cancer Center was awarded a $6 million CPRIT Academic Research grant (RP160652) in May 2016 and $4 million CPRIT Research Training Grant (RP170067) in November 2016 in support of a comprehensive learning environment focused solely on cancer.

21. Primary graft dysfunction (PGD) is the main cause of early morbidity and mortality after lung transplantation. Although patients can be successfully treated with supportive care, there is no cure for PGD. Corresponding author Gabriel Loor, M.D., FACC, associate professor, Department of Surgery at Baylor College of Medicine, reported that the ability to accurately map a molecular signature for detecting PGD could enhance the overall treatment of patients. In this study published in *Nature* on September 27, 2022, researchers validated the utility of protein biomarkers for detecting the severity and duration of PGD. The team used the most updated PGD grading guidelines, a contemporary cohort of lung transplant recipients, and novel statistical methods to aid in detecting a wide breadth of biomarkers. These PGD biomarker panels may improve early detection of PGD, predict its clinical course, and help monitor treatment efficacy in the current era of lung transplantation. Baylor College of Medicine received a $4 million CPRIT Core Facility Support Awards grant (RP200504) in August 2020 to support the Comprehensive Cancer Epigenomics Core (CCEC) facility.

22. Understanding the physiology of the central nervous system, particularly the brain, is one of the most pressing challenges in medicine. Since many diseases have at their origin a protein that does not function properly, researchers from Texas A&M AgriLife and Texas A&M University sought and found a way to deliver a protein quickly and efficiently to the brain. Jean-Philippe Pellois, Ph.D., professor, Department of Biochemistry and Biophysics at Texas A&M College of Agricul-

ture and Life Sciences, and colleagues mixed a protein payload with an endosomolytic peptide in solution, then injected the mixture into the brains of mice, who were bred so that the protein created a visual signal if it arrived as intended. As reported on September 28, 2022, in *Science Advances*, brain cells near the injection site began to fluoresce only after the protein and its delivery tool were injected together. "Proteins are large molecules that don't easily enter cells or cross cell membranes, but we've created a trick to achieve this," Dr. Pellois said. Both the protein and its delivery system degrade naturally after performing their role; the reagents can enter cells without disrupting them and then leave without a trace. Potential uses for the method include repairing spinal cord injuries and reducing the amount of anti-cancer drugs delivered to the patient. Texas AgriLife Research was awarded a $200,000 CPRIT High Impact/High Risk grant (RP190655) in August 2019 to help determine the basic mechanisms by which exosomes transfer signals from metastatic cancer cells to other cells.

23. Broad-spectrum antibiotics are often given during allogeneic hematopoietic stem cell transplantation (allo-HSCT), a specialized treatment for blood cancers. New CPRIT-supported research reveals that dietary supplements may improve one of the life-threatening complications of life-saving hematopoietic stem cell transplants for blood cancer, such as leukemia or lymphoma. Eiko Hayase, M.D., Ph.D., and CPRIT Scholar Robert Jenq, M.D., associate professor, Department of Genomic Medicine at The University of Texas MD Anderson Cancer Center, discovered that certain antibiotics alter the sugar composition of the gut, forcing a normally beneficial species of bacteria to consume mucin in the intestinal lining, which can lead to complications such as graft-versus-host disease (GVHD). According to the study published on September 29, 2022, in *Cell*, the team found that treating allo-HSCT laboratory models with meropenem — a commonly used broad-spectrum antibiotic — resulted in a thinned colonic mucus layer and intestinal GVHD. The researchers then administered oral xylose as a nutritional supplement and found the gut mucus layer once again thickened, as the bacteria was able to preferentially consume the sugar instead of the mucin lining. This novel, low-risk technique offers a compelling approach in helping allo-HSCT patients who need to be on broad-spectrum antibiotics. The University of Texas MD Anderson Cancer Center recruited Dr. Jenq in September 2016 from the Memorial Sloan-Kettering Cancer Center with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR160089).

24. Obesity affects more than 2 billion people worldwide, making it one of the largest contributors to poor health. According to studies, maternal obesity appears to lead to transgenerational amplification of obesity and to the increase in risk of neurodevelopmental outcomes including attention deficit hyperactivity disorder and autism spectrum disorder. In this study, corresponding author Robert Waterland, Ph.D., professor, Department of Pediatrics-Nutrition at Baylor College of Medicine, and colleagues focused on a brain region called the arcuate nucleus of the hypothalamus, which integrates satiety and hunger, physical activity, and metabolism. "One of our study's biggest strengths is that we studied the two major classes of brain cells, neurons and glia," said Harry MacKay, Ph.D., postdoctoral associate Pediatrics-Nutrition at Baylor. As reported in *Science Advances* on September 28, 2022, molecular mechanisms of brain development during early life are likely a major determinant of obesity risk and suggest that it may be useful to consider obesity as a neurodevelopmental disease. In addition, this study was the first to compare this epigenetic development in males and females and found that they are more different than they are similar. These results suggest that improved understanding of these cell type–specific developmental processes could offer insights into effective primary prevention of obesity. Baylor College of Medicine received a $5.17 million CPRIT Core Facility Support Awards grant (RP180672) in August 2018 with the goal to assist cancer researchers who study the interactions between cancer cells and their environment.

25. A team of researchers found that a new dual-chimeric antigen receptor (CAR) system improves the antitumor activity of CAR natural killer cells and makes them less susceptible to therapeutic resistance in preclinical models. Using multiple *in vivo* tumor models and clinical data, Navin Varadarajan, Ph.D., professor, Department of Chemical & Biomolecular Engineering at the University of Houston, and colleagues reported that CAR activation in natural killer (NK) cells promoted transfer of the CAR cognate antigen from tumor to NK cells. This resulted in lower tumor antigen density, impairing the ability of CAR-NK cells to engage with their target. The data, published in *Nature Medicine* on September 29, 2022, report-

ed that this system prevented trogocytic antigen-mediated fratricide, while sparing activating CAR signaling against the tumor antigen, and resulted in enhanced CAR-NK cell activity. The University of Houston received a $1.17 million CPRIT Academic Research Award grant (RP180466) in February 2018 in support of the study of immune cells directly from patients undergoing treatment within Texas to identify biomarkers of responses.

26. Colorectal cancer (CRC) is a leading cause of cancer-related death. The development of CRC can be strongly influenced by specific gut microbes. *Streptococcus gallolyticus* subspecies *gallolyticus (Sgg*) has a strong clinical association with CRC and actively promotes the development of colon tumors. However, the mechanisms *Sgg* utilizes to promote tumors are not well understood. Researchers from Baylor College of Medicine and Texas A&M University System Health Science Center showed for the first time that *Sgg* upregulates the expression of collagens, which in turn affects the interaction between *Sgg* and CRC cells and mediates CRC cell proliferation. These findings, published in *PLOS Pathogens* on October 3, 2022, report a previously unrecognized dynamic bidirectional interplay between a CRC-associated microbe and the extracellular matrix (ECM). ECM is a dynamic tissue support network that has an intricate relationship with immune cells and is important in normal homeostasis and in tumor microenvironment. Texas A&M University System Health Science Center received a $200,000 CPRIT High Impact/High Risk grant (RP170653) in August 2017 to help identify the critical Sg molecules. Baylor College of Medicine received a $4 million CPRIT Core Facility Award grant (RP210227) in August 2021 to facilitate comprehensive multiomic studies in preclinical models and clinical tumor specimens and access to cutting-edge proteomics and metabolomics technologies and computational expertise.

27. Excessive alcohol use and obesity are known to increase the risk for developing cirrhosis and liver cancer, but the risk is not the same for everyone with these factors. Researchers at Baylor College of Medicine found that a key genetic variant risk factor, PNPLA3, plays a synergistic role in increasing the risk for cirrhosis, liver cancer, and liver-related death when combined with alcohol use and obesity. The risk for liver disease increases with any one of those factors, but the findings showed a dramatically increased risk when a person had all three. As reported in *JAMA Network* on October 3, 2022, the researchers analyzed data from more than 400,000 people in the United Kingdom Biobank. CPRIT Scholars Christopher Amos, Ph.D., and Chao Cheng, Ph.D., from Baylor College of Medicine, and team reported that PNPLA3 I148M variant showed synergistic interplay with heavy alcohol intake and obesity and was associated with increased risk of developing cirrhosis, HCC, and liver disease–related death in a middle-aged population. Baylor College of Medicine recruited Drs. Amos and Cheng in August 2017 and 2018, respectively, from Dartmouth-Geisel School of Medicine with the support of $6 million CPRIT Recruitment of Established Investigators grant (RR170048) and a $4 million CPRIT Recruitment of Rising Stars grant (RR180061). Baylor College of Medicine received a $9.77 million CPRIT Multi-Investigator Research Awards grant (RP150587) in May 2015.

28. Joshua D. Wythe, Ph.D., associate professor, Department of Integrative Physiology and Neurosurgery, and Chih-Wei Logan Hsu, Ph.D., assistant professor, Department of Molecular Physiology and Biophysics at Baylor College of Medicine, and fellow researchers developed an innovative technology called EZ Clear. EZ Clear, which enables 3-D imaging of entire, intact tissues or even entire organs, is a simple, robust, and easy to adopt whole organ clearing technique that can be applied to various sample volumes and utilized across most common imaging platforms. Their new method, published in the journal *eLife* on October 11, 2022, shows successful clearing and labeling of neurons and blood vessels within the brain, as well as vessels within the eye, heart, kidney, testis and ovary, and successful whole organ clearing of mouse lung, liver and pancreas. "The beauty of this method is that you can analyze the sample from a global or macro view without physically disturbing the natural organization of the tissue or organ," Dr. Wythe said. EZ Clear is faster, less expensive, and simpler than previous clearing methods. Researchers can now learn this easier-to-complete, reproducible tissue clearing process at the Optical Imaging and Vital Microscopy Core at Baylor and then implement it in their own labs and obtain results in 48 hours. Baylor College of Medicine received a $900,000 CPRIT Individual Investigator grant (RP200402) February 19, 2020.

29. Prostate cancer is the second leading cause of death in male cancer patients in the U.S. and the fifth among men worldwide. Advanced prostate cancer is typically treated with castration therapy, and although it is initially effective, it often becomes ineffective as tumors develop resistance to it. In this study, published in the *Proceedings of the National Academy of Sciences* on October 17, 2022, Feng Yang, Ph.D., assistant professor, Department of Molecular & Cellular Biology at Baylor College of Medicine, and team discovered an approach that suppresses the growth of therapy-resistant tumors. Knowing that androgen receptor activation remained a key driver of the growth of castration-resistant tumors, the researchers focused on GATA2, a factor known to promote androgen receptor expression and activation. "We discovered that the enzyme COP1 drives GATA2 degradation, and that this was followed by striking inhibition of androgen receptor expression and activation. Importantly, when we promoted GATA2 degradation in our animal models, tumor growth as well as castration resistance were markedly suppressed," Dr. Yang said. These findings have the potential to lead to improved treatments for castration-resistant prostate cancer. Baylor College of Medicine received a $580,000 CPRIT Individual Investigator grant (RP130651) in 2012.

30. Researchers from Children's Medical Center Research Institute (CRI) at The University of Texas Southwestern Medical Center found that different skeletal stem cell (SSC) populations contribute to the repair of different kinds of bone injuries. In the study, published in *Cell Stem Cell* October 21, 2022, postdoctoral researcher Elise Jeffery, Ph.D., systematically compared 11 genetically engineered mouse lines to identify markers that could distinguish periosteal SSCs from bone marrow SSCs. The researchers found that bone marrow SSCs repair smaller, stabilized bone injuries and are responsible for new bone growth under normal conditions during adulthood. In contrast, periosteal SSCs are primarily responsible for the repair of larger, unstabilized injuries like fractures. Surprisingly, researchers found that periosteal SSCs also regenerate cells within the bone marrow at the fracture site, giving rise to new bone marrow SSCs. "The discovery that different bone-forming stem cells are responsible for different aspects of bone maintenance and repair will allow us to focus future bone regeneration efforts on the correct stem cell population," said CPRIT Scholar Sean Morrison, Ph.D., professor, Department of Pediatrics and director of CRI. The University of Texas Southwestern Medical Center recruited Dr. Morrison in July 2011 from the University of Michigan with the support of a $10 million CPRIT Recruitment of Established Investigators grant (R1109).

31. Vaccines of different classes have been approved and are in use to combat Coronavirus disease 2019 (COVID-19). However, immunocompromised (IC) patients show diminished immune response to COVID-19 mRNA vaccines (Co-mV). Researchers, led by CPRIT Scholar Srinivas Malladi, Ph.D., assistant professor, Department of Pathology at The University of Texas Southwestern Medical Center, used *in vitro*, *in vivo*, and supporting clinical data and interrogated the effect of immunosuppressants (ISs) on the translation of Co-mV, which is central to its effectiveness. Their findings, reported in *Frontiers in Immunology* on October 26, 2022, indicate that manipulating the appropriate combination of ISs during Co-mV period may contribute to long-lasting vaccine efficacy in IC patients. These findings lay a strong foundation for guiding future studies aimed at improving Co-mV responses in high-risk IC patients. The University of Texas Southwestern Medical Center recruited Dr. Malladi from Memorial Sloan-Kettering Cancer Center with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR170003).

32. Breast cancer may return or metastasize in other organs years after breast tumors have been removed. Bone is frequently affected by metastasis and in this study, researchers showed that the initiation of bone metastasis was coupled with the normal bone repair process. "As cancer progresses, a few cells may leave the primary tumor and travel to the bone, but we still don't completely understand what determines the fate of these cells – we call them metastatic seeds," said corresponding author Dr. Xiang Zhang, Ph.D., professor, Department of Molecular and Cellular Biology at Baylor College of Medicine. The team investigated the effect of triggering the bone repair process on bone metastasis in a mouse model and found that activating the process resulted in significantly more metastases. They also discovered a subset of bone stem cells that express the marker NG2, called NG2-positive (NG2+) cells, which drive normal bone turnover. As reported in *Cancer Discovery* on October 26, 2022, these cells seemed to be directly involved in the awakening of

metastatic seeds. The researchers then genetically removed the NG2 marker from these cells and the result was fewer metastases. Baylor College of Medicine received a $5.17 million CPRIT Core Facility Support Award (RP180672) in August 2018 with the goal to assist cancer researchers who study the interactions between cancer cells and their environment.

33. Real-time chemical sensing is crucial for applications in environmental and health monitoring. A team led by CPRIT Scholar Caroline Ajo-Franklin, Ph.D., and Jonathan Silberg, Ph.D., both professors of biosciences at Rice University, combined synthetic biology and materials engineering to develop biosensors to sense and report on the presence of a variety of contaminants. Their study published in *Nature* on November 2, 2022, showed that cells can be programmed to identify chemical invaders and report within minutes by releasing a detectable electrical current. The researchers' proof-of-concept bacteria was *Escherichia coli*, and their first target was thiosulfate, a dichlorination agent used in water treatment that can cause algae blooms. This living sensor was able to sense this chemical at levels less than 0.25 millimoles per liter, far lower than levels toxic to fish. Such "smart" devices could power themselves by scavenging energy in the environment as they monitor conditions in settings like rivers, farms, industry, and wastewater treatment plants and to ensure water security. These results provide design rules and a new platform for miniature, low-power bioelectronic sensors that safeguard ecological and human health. Rice University recruited Caroline Ajo-Franklin, Ph.D., from the Lawrence Berkeley National Laboratory with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR190063) in November 2019.

34. Most patients with triple-negative breast cancer (TNBC) present residual disease after chemotherapy, with high rates of metastatic recurrence and mortality. For TNBC, treatment options are largely limited to conventional cytotoxic chemotherapy. Research has shown that histone post-translational modifications (PTMs) are important for regulating various DNA-related biological processes. Researchers led by CPRIT Scholar Qing Zhang, Ph.D., associate professor of pathology at The University of Texas Southwestern Medical Center, reported the existence of a histone PTM in mammalian cells. This study, published in *Nature Genetics* on November 8, 2022, emphasizes the important role of EGLN2 in regulating the WNT pathway, which could motivate the development of EGLN2 inhibitors in the context of breast cancer treatment. The University of Texas Southwest Medical Center recruited Dr. Zhang in May 2019 from the University of North Carolina Lineberger Comprehensive Cancer Center with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR190058).

35. Researchers at Baylor College of Medicine wanted to know how ultrafine particles present in cigarette smoke impact the development and progression of lung cancer. Using two different mouse models of lung cancer, Cheng-Yen Chang, Ph.D., a postdoctoral fellow, and Farrah Kheradmand, M.D., professor, Department of Medicine-Pulmonary at Baylor College of Medicine, and colleagues were able to replicate the same type of exposure to ultrafine particles typically seen in a heavy smoker. Both mouse models showed accelerated lung cancer progression. In this study published on November 16, 2022, in *Science Advances*, the team reported that ultrafine particles changed the cell's primary energy source, creating new byproducts in the lungs. "They went from using fat, which is what is seen in the average cell, to using sugar. The new byproducts alter immune cells allowing for tumors to escape recognition," Dr. Chang said. "This exposure made tumors more aggressive and more likely to metastasize or spread throughout the body." Baylor College of Medicine received a $4 million Research Training grant (RP160283) in 2015, a $5.1 million Core Facility Support Awards grant (RP180672) in 2018, and an $897,500 CPRIT Individual Investigator grant (RP200443) in February 2020.

36. Dysfunction of inositol-1,4,5-trisphosphate receptors (IP3Rs) is associated with a multitude of human diseases such as Alzheimer's disease, hereditary ataxias, cardiac hypertrophy, heart failure, Parkinson's and Huntington's diseases, atherosclerosis, hypertension, and some migraines. Despite more than three decades since the discovery of IP3Rs, the detailed molecular and structural mechanisms underlying the complex interplay between ligands, allosteric modulators, and channel gating remains unresolved. Researchers at Baylor College of Medicine and The University of Texas Health Science Center at Houston provided a structural framework for understanding the allosteric mechanisms underlying

ligand-mediated IP3Rs activation and regulation. Principal investigator, Steven Ludtke, Ph.D., professor, Department of Biochemistry and Molecular Biology at Baylor, and colleagues used a deep-learning approach and 3D variability analysis to extract molecular motions of the key protein domains from cryogenic electron microscopy (cryo-EM) density data. The results, reported in *Nature* on November 14, 2022, highlight a key role of specific interactions in the side chain network surrounding the ion conduction path in regulating gating behavior of IP3R channels and represents a stepping-stone to developing mechanistic understanding of conformational pathways. TFS Titan Krios Equipment, used for cryo-EM imaging in this work, was subsidized by a $5.38 million CPRIT Core Facility Support Awards grant (RP190602) in 2019 to Baylor College of Medicine.

37. Triple negative breast cancer (TNBC) is a highly aggressive form of breast cancer lacking expression of the estrogen and progesterone receptors as well as the master oncogene HER2. Principal Investigator Ann M. Killary, Ph.D., professor, Department of Translational Molecular Pathology, and colleagues at The University of Texas MD Anderson Cancer Center, highlighted the role of DEAR1, a tumor suppressor, in maintaining proper luminal differentiation since most breast cancers arise from luminal cells. The cumulative results of this study, published in *Nature* on November 14, 2022, document compelling evidence that DEAR1 is an important, novel regulator of luminal cell fate and provide evidence for its potential clinical utility as a biomarker to distinguish TNBC patients for risk of metastasis or targeted therapies aimed at the pathways and cell plasticity regulated by DEAR1. The results also demonstrate that low DEAR1 expression significantly correlates with young age of onset and shorter time to metastasis, suggesting DEAR1 could serve as a biomarker to stratify early onset TNBCs for targeted stem cell therapies. The University of Texas MD Anderson Cancer Center received a $900,000 CPRIT Individual Investigator grant (RP150403) in 2015 in support of TNBC research.

38. CPRIT Scholar Liuqing Yang, Ph.D., Department of Molecular and Cellular Oncology at The University of Texas MD Anderson Cancer Center, and colleagues studied gender differences in immune checkpoint inhibitor (ICI) myocarditis and may have discovered the underlying cause. In this study, published in *Science Translational Medicine* on November 2, 2022, the researchers developed laboratory models of melanoma, breast cancer, and colorectal cancer and treated them with commonly used immune checkpoint inhibitors. These treatments repressed tumor growth but also increased immune-cell infiltration, which is necessary for the initiation and progression of cancer, especially in the hearts of female patients, causing dysfunction associated with myocarditis. "Immune checkpoint inhibitors can be lifesaving for many patients but increasing the dose or combining [them] with other therapies also increases the risk [of] myocarditis, particularly in women," said co-corresponding author Dr. Yang. "With this study, we now understand the mechanisms behind this, and we've found several potential ways to reduce this risk without compromising the antitumor effects of treatment." The University of Texas MD Anderson Cancer Center recruited Dr. Yang in 2012 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (R1218). MD Anderson also received two $900,000 Individual Investigator grants (RP180259, RP200423) in 2018 and 2020 in support of this project.

39. Brain metastases are the most common intracranial tumors. More than 9% of patients with cancer develop brain metastases. Management of brain metastases is usually palliative and can include chemotherapy, surgery, radiotherapy, or a combination of them. Researchers at The University of Texas MD Anderson Cancer Center developed a configurable auto-planning algorithm to automatically generate field-in-field whole-brain radiotherapy (WBRT) plans independent of the treatment planning system. This algorithm creates a homogeneous dose distribution by minimizing hotspots, resulting in clinically acceptable plans. As reported in the *Journal of Applied Clinical Medical Physics* on November 10, 2022, the algorithm was retrospectively tested on 17 whole-brain patients. The final auto-optimized plans were assessed for clinical acceptability by an experienced radiation oncologist. The algorithm successfully produced high-quality WBRT plans and can improve treatment planning efficiency when incorporated into an automatic planning workflow. The University of Texas MD Anderson received a $4 million CPRIT Research Training grant (RP210028) in May 2021 to instruct postdoctoral fellows for careers in translational cancer research.

40. CPRIT Scholar Xiaoqian Jiang, Ph.D., professor at The University of Texas Health Science Center at Houston, and colleagues developed an artificial intelligence (AI) guided framework to recognize tooth numbers in panoramic and intraoral radiographs without prior domain knowledge and arrange the intraoral radiographs into a full mouth series arrangement template. A panoramic radiograph provides a quick overview and diagnosis, but it is insufficient to diagnose initial and minor abnormalities. The results of this study, published in the journal *BMC Oral Health* on November 9, 2022, reported that this framework utilized image segmentation models to generate the masks of bone area, tooth, and cementoenamel junction lines from intraoral radiographs. These masks were used to detect and extract teeth bounding boxes utilizing several image analysis methods. This artificial intelligence-based tooth detection and tooth number assignment in dental radiographs can be integrated with different diseases, such as periodontitis or caries, to facilitate clinical examinations and diagnoses and will help dentists with enhanced communication, documentation, and treatment planning. Dr. Jiang was recruited by The University of Texas Health Science Center at Houston from the University of California San Diego, a $4 million CPRIT Recruitment of Rising Stars grant (RR180012) in 2018. The University of Texas Health Science Center at Houston received a $250,000 Individual Investigator grant (RP200526) in 2020.

41. Pancreatic cancer is one of the most aggressive tumor types and it accounts for 7% of all cancer-related deaths in the United States. Radiation treatment planning for pancreatic cancer is often complex with tight dose constraints because the pancreas is surrounded by highly radiosensitive and serial organs at risk (OARs) and manually delineating upper OARs is a time-consuming task. In this study researchers, including principal investigator Laurence E. Court, Ph.D., associate professor, Department of Radiation Physics at The University of Texas MD Anderson Cancer Center, trained a three-dimensional (3D) U-Net ensemble that automatically segments all organ contours concurrently with the self-configuring nnU-Net framework. Using only 40 patients, the researchers trained a nnU-Net model to generate automatic contours that was able to produce clinically acceptable results on both contrast-enhanced and non-contrast-enhanced CT images as detailed in the journal *Scientific Reports* published on November 9, 2022. The results of the presented analysis led to the clinical deployment of this tool. The University of Texas MD Anderson Cancer Center received a $900,000 CPRIT Individual Investigator grant (RP200395) in February 2020.

42. Neutropenia, a reduction in white blood cells, is a common complication of cancer therapy which often leads to infections and high fever. Previous studies suggested that patients with acute myeloid leukemia and neutropenic fever also had changes in their gut microbiome. CPRIT Scholar Robert Jenq, M.D., associate professor, Department of Genomic Medicine at The University of Texas MD Anderson Cancer Center, and colleagues studied both clinical samples and laboratory models to learn how the gut microbiome may influence febrile neutropenia after cancer treatment. The results, published on November 16, 2022, in *Science Translational Medicine,* demonstrated that higher levels of a specific mucin-degrading bacteria were associated with a higher incidence of febrile neutropenia and that treatment with antibiotics helped restore those levels to normal. Additionally, the researchers found that dietary supplementation with propionate, a metabolic end product, also suppressed these bacteria and improved outcomes. This study suggests that diet, metabolites, and colonic mucus link the microbiome to neutropenic fever and may guide future microbiome-based preventive strategies. The University of Texas MD Anderson Cancer Center recruited Dr. Jenq in September 2016 from the Memorial Sloan-Kettering Cancer Center with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR160089) and received a $4.5 million Core Facility Support Awards grant (RP130397) in 2012.

43. Immune checkpoint blockade (ICB) has revolutionized cancer treatment, yet quality of life and continuation of therapy can be constrained by immune-related adverse events (irAEs). Limited understanding of irAE mechanisms hampers development of approaches to lessen their damage. To address this, researchers, including CPRIT Scholar Matthew M. Gubin, Ph.D., assistant professor, Department of Immunology at The University of Texas MD Anderson Cancer Center, examined whether mice gained sensitivity to anti-CTLA-4 (αCTLA-4)–mediated toxicity upon disruption of gut homeostatic immunity. Corresponding author, Stephanie S. Watowich, Ph.D., professor, Department of Immunology, reported in the *Journal of Experimental Medicine* on November 12, 2022, that the team identified an immune signature of αCTLA-4–me-

diated irAEs and found that IL-6 blockade combined with antibiotic treatment reduced intestinal damage and improved αCTLA-4 therapeutic efficacy in inflammation-prone mice. Intestinal immune signatures were validated in biopsies from patients with ICB colitis. This study provides potential approaches to enhance ICB efficacy while mitigating irAEs. Dr. Gubin was recruited by The University of Texas MD Anderson Cancer Center in 2018 with a $2 million Recruitment of First-Time, Tenure-Track Faculty Members grant (RR190017). The University of Texas MD Anderson Cancer Center received two $4 million CPRIT Research Training grants (RP170067, RP210028) in 2016 and 2021.

44. Preclinical data suggest poly (ADP-ribose) polymerase (PARP) inhibitors work effectively in combination with immune checkpoint inhibitors (ICIs) to enhance antitumor response, but little is known about which patients would benefit from this combination therapy. To evaluate this approach across tumor types, principal investigator Timothy Yap, MBBS, Ph.D., The University of Texas MD Anderson Cancer Center, and colleagues evaluated the safety and efficacy of the PARP inhibitor talazoparib plus avelumab (anti-PD-L1) in two clinical trials. These studies, published on November 17, 2022, in *JAMA Oncology*, highlight the importance of considering molecular subtype when selecting treatments for future ICI and PARP-inhibitor combination strategies. The Phase IIb JAVELIN BRCA/ATM trial evaluated the combination in 200 patients with advanced BRCA1/2d or ATM-altered solid tumors and was well-tolerated, though neither cohort met the target overall response rate of 40%. The Phase Ib/II JAVELIN PARP Medley basket trial enrolled 223 patients with advanced solid tumors in multiple cohorts of different tumor types. The combination therapy achieved overall response rates comparable to PARP and ICI monotherapies, with certain cohorts showing prolonged duration of response. The treatment was well tolerated with few side effects. The University of Texas MD Anderson Cancer Center received a $6 million CPRIT Core Facility Support Awards grant (RP15053) in May 2015.

45. Genome-wide profiling of rhythmic gene expression has offered new avenues for studying the contribution of circadian clock to diverse biological processes. Sleep has been considered one of the most important physiological processes that are regulated by the circadian clock, however, the effects of chronic sleep loss on rhythmic gene expression remain poorly understood. CPRIT Scholar Wanhe Li, Ph.D., assistant professor at Texas A&M University, and researchers from The Rockefeller University, exploited *Drosophila* (fruit flies) sleep mutants as models for chronic sleep loss. The study, published in the journal *Frontiers in Physiology* on November 18, 2022, showed that analysis of gene oscillation revealed a substantial loss of rhythmicity. The team identified a subset of genes whose loss of rhythmicity was shared among animals with chronic sleep loss and old flies, suggesting a contribution of aging to chronic, sleep-loss-induced disruption of gene oscillation. The collection of genes that lost rhythmic expression in this study provides promising material for further investigation into whether the change of rhythmicity was the result of dampened oscillation of core clock genes or a direct effect of chronic sleep disruption. Texas A&M University recruited Dr. Li with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR220021) in November 2021.

46. Online image guidance (i.e. to image the patient at the treatment position) plays an important role in the success of radiation therapy (RT). Using an imaging device installed on the medical linear accelerator to acquire patient anatomy images immediately before, or during treatment delivery, allows visualization of the patient anatomy at the treatment stage and accurate alignment of the radiation beam. Principal investigator, Jie Deng, Ph.D., associate professor, and fellow researchers at The University of Texas Southwestern Medical Center developed an algorithm exploiting the patient-specific image prior to facilitate the reconstruction of Magnetic Resonance (MR) images with an undersampled data acquisition, since undersampling in MR acquisition accelerates the imaging process but unavoidably deteriorates the reconstructed image quality. The team's method, published in *Frontiers in Oncology* on November 21, 2022, outperformed others by producing reconstructions of visually improved image quality compared to the patient-generic manifold method. The University of Texas Southwestern Medical Center received a $250,000 CPRIT High Impact/High Risk grant (RP200573) in August 2020 to develop a customized compact non-conventional MRI scanner that can be installed on existing LINACs, which realizes MR-guided RT at a much-reduced cost.

47. The anthracycline drug doxorubicin (Dox) is a highly effective anti-cancer chemotherapy, but it often causes cardiotoxicity. In contrast to the general population, young adult and childhood cancer survivors are at significant risk of developing cardiac failure. Principal investigator Eugenie Kleinerman, M.D., Department of Pediatrics at The University of Texas MD Anderson Cancer Center, and colleagues reviewed the role of innate immunity in the pathogenesis of cardiovascular disease and dox-induced cardiotoxicity. As reported in the *International Journal of Molecular Sciences* in November 2022, the new therapeutic approach to improve patient outcomes with cardiac disease is immune modulation targeting neutrophils, macrophages, and cytokines to dampen inflammatory cascade and boost cardiac recovery and repair. One of the potential approaches is the liposomal formulation of Dox which has demonstrated significantly lower cardiotoxicity profiles with better cardiac safety than conventional Dox, but with well-preserved anti-tumor efficacy. The University of Texas MD Anderson Cancer Center received a $1.44 million CPRIT Individual Investigator Research Awards for Cancer in Children and Adolescents grant (RP200381) in February 2020.

48. Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal lung disease of unknown etiology. Currently, pirfenidone and nintedanib are the only FDA-approved drugs for the treatment of IPF. However, these drugs can only slow down the progression; they are unable to stop or reverse established fibrosis. Researchers at Baylor College of Medicine and colleagues found that proton pump inhibitors (PPI) might be combined with pirfenidone for enhanced antifibrotic activity. Corresponding author Yohannes Ghebre, Ph.D., Department of Radiation Oncology, reported in *Nature* on November 30, 2022, that the team used cell biological, computational, and animal models to understand how PPIs may contribute to enhanced antifibrotic efficacy in combination with pirfenidone. The *in vitro* study using IPF lung fibroblasts and the *in vivo* study in a mouse model of TGFβ-induced lung fibrosis demonstrated that combining esomeprazole, a PPI, with pirfenidone improves antifibrotic efficacy of the now standard of care drug pirfenidone. Baylor College of Medicine a $200,000 CPRIT High Impact/High Risk grant (RP190497) in August 2019.

49. Cancers cause significant mortality and morbidity in adolescents and young adults (AYAs), but their biological and genetic underpinnings are incompletely understood. In the last 30 years, survival rates for AYA patients have shown little improvement while significant improvements have been made for children and older adults (OAs). CPRIT Scholar Siyuan Zheng, Ph.D., Department of Population Health Sciences at The University of Texas Health Science Center at San Antonio, and colleagues analyzed clinical and genomic disparities using panel sequencing data between AYAs and OAs in more than 100,000 cancer patients. The results, published in *Nature Communications* on November 24, 2022, found significant differences in clinical presentation between AYAs and OAs, including sex, metastasis rates, race and ethnicity, overall survival, and cancer histology. In most cancer types, AYA tumors showed lower mutation burden and less genome instability, resulting in fewer tumor-specific alterations to proteins, a finding that has been a barrier to developing effective immunotherapies for these tumors. However, some mutations, such as CTNNB1 and BRAF mutations are overrepresented in AYAs across multiple cancer types, important findings as these pathways are amenable to targeted therapy. The University of Texas Health Science Center at San Antonio recruited Dr. Zheng with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR170055) in August 2017.

50. Clinical interpretation of genetic test results is increasingly complicated by variants of uncertain significance (VUS) which have an unknown impact on health. Since there is little empirical evidence regarding VUS reclassification in oncology care settings, including the prevalence and outcomes of reclassification and racial/ethnic differences, Zhongming Zhao, Ph.D., M.S., professor for Precision Health at The University of Texas Health Science Center at Houston, and colleagues carried out a retrospective analysis of 2,715 persons with and without a personal history of cancer carrying VUS in breast, ovarian, and colorectal cancer predisposition genes. The participants were seen at four cancer care settings (in Texas, Florida, Ohio, and New Jersey) between 2013 and 2019. The results, reported in *Cancer Medicine* on November 24, 2022, suggest that VUS reclassification alters clinical management, has implications for precision cancer prevention, and highlights the need for implementing practices and solutions for efficiently returning reinterpreted genetic test results. The University of Texas Health Science Center at Houston received two CPRIT Academic Research

grants (RP180734, RP210045) in 2018 and 2021 for a total of $8.4 million. The University of Texas MD Anderson Cancer Center received a $2.6 CPRIT Research Training grant (RP170259) in November 2016 to support a cancer prevention research training program that prepares junior cancer prevention researchers to assume leadership roles as independent investigators in cancer prevention in Texas.

51. Hepatocellular carcinoma (HCC), the most common type of liver cancer, often places a significant financial burden on patients, according to an analysis led by Amit Singal, M.D., professor, Department of Internal Medicine at The University of Texas Southwestern Medical Center. The team set out to estimate the financial burden related to HCC in a large nationally representative United States cohort. As reported in *Clinical Gastroenterology and Hepatology* on November 24, 2022, the study, which looked at costs for patients with HCC in the first year after diagnosis, found that median Medicare payments exceeded $65,000 and out-of-pocket costs were more than $10,000 – significantly more than costs for patients with cirrhosis alone. The team found that patients with early-stage liver cancer had lower costs and patients with certain co-existing conditions, such as non-alcoholic fatty liver disease, experienced higher costs. Unfortunately, most patients are found beyond an early stage, and non-alcoholic fatty liver disease is an increasingly common underlying factor for liver cancer. "There is a clear need for policy interventions and financial support systems in this patient population," said Dr. Singal. The University of Texas MD Anderson Cancer Center received a $2.6 million CPRIT Research Training grant (RP170259) in November 2016 to support a cancer prevention research training program in Texas.

52. Cellular plasticity is a phenomenon where cells acquire traits not included in their homeostatic repository. In cancers, cellular plasticity is co-opted as a method for tumor initiation, progression, and therapeutic resistance. Basal-like breast cancers are a type of cancer initiated through cell lineage plasticity. The Hippo pathway is a regulator of cell fate in numerous tissues, however, the precise roles and cellular phenotypes stimulated by Hippo have yet to be fully understood. In order to better elucidate the impact of Hippo pathway dysregulation in the mammary epithelium *in vivo*, Randy L. Johnson, Ph.D., professor, Department of Cancer Biology at The University of Texas MD Anderson Cancer Center, and colleagues demonstrated the necessity for LATS1/2 in maintaining luminal cell fate in the mammary epithelium. The results, published in *Nature Communications* on November 28, 2022, showed that conditional loss of LATS1/2 in the mature mouse luminal mammary epithelium results in the development of mammary carcinomas with basal-like traits and offers insight and clarification into the functions of Hippo pathway signaling. The University of Texas MD Anderson Cancer Center received two CPRIT Individual Investigator grants (RP180530, RP200240) totaling $1.7 million in 2018 and 2020.

53. CRISPR screening is a large-scale experimental approach used to screen a population of mutant cells to discover genes involved in a specific phenotype (an individual's observable traits). Functional interaction networks can be inferred from CRISPR knockout screens, which disrupt the DNA to prevent expression of a gene, in cancer cell lines. CPRIT Scholar Traver Hart, Ph.D., associate professor, Department of Bioinformatics and Computational Biology at The University of Texas MD Anderson Cancer Center, and team identified an optimal measure of functional interaction and tested all combinations of options at each step to identify best practices for generating a functional interaction network from CRISPR knockout data. The results, published in *BMC Bioinformatics* on November 28, 2022, describe a systematic survey of methods for generating coessentiality networks (identifying which genes are co-essential between cell lines), which provide a powerful framework for identifying functional modules in the cell and for inferring the roles of uncharacterized genes. This work reinforces studies that show that coessentiality networks are among the most powerful predictors of mammalian gene function. The University of Texas MD Anderson Cancer Center recruited Dr. Hart from the University of Toronto with a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160032) in February 2016.

54. Hearing loss is a widespread public health issue which can be treated with cochlear implants or hearing aids, but biological restoration of cochlear structure and function is not currently possible. Reprogramming of the cochlea with hair-cell-specific transcription factors such as ATOH1 is a potential therapeutic strategy for hearing loss. ATOH1 expres-

sion in the developing cochlea can efficiently induce hair cell regeneration but the efficiency of hair cell reprogramming declines rapidly as the cochlea matures. Researchers, including Russell S. Ray, Ph.D., associate professor, Department of Neuroscience at Baylor College of Medicine, developed Cre-inducible mice to compare hair cell reprogramming with ATOH1 alone or in combination with two other hair cell transcription factors, GFI1 and POU4F3. The results, published in *eLife* on November 29, 2022, show that while overexpression of multiple hair cell transcription factors in the cochlea promotes more efficient reprogramming in older animals, significant challenges to producing viable, functional hair cells still remain, shedding light on the molecular barriers that must be overcome to promote hair cell regeneration in the adult cochlea. Baylor College of Medicine received a $5.17 million CPRIT Core Facility Support Award grant (RP180672) in August 2018 with the goal to assist cancer researchers who study the interactions between cancer cells and their environment.

55. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected the lives of billions and killed millions of infected people. The identification of the molecular states related to the severity of a COVID-19 infection has become of the utmost importance to understanding the differences in critical immune response. Principal investigator Yidong Chen, Ph.D., professor, Department of Population Health Sciences at The University of Texas Health Science Center at San Antonio, and team conducted the first study to line up the characterization of macrophages to the severity of COVID-19 infections using a single-cell RNA Seq analysis. This analysis was published in *Genes* on December 1, 2022, and showed significant differences in the gene expression profiles of inflammatory response and immune cells of severely infected patients, which was evidenced by the significant increase in macrophages. To verify these findings, the team developed several artificial neural networks (ANNs) and graph convolutional neural network (GCNN) models. The novelty of this study lies in the integration of a single-cell RNA seq analysis with DL models to predict the severity of COVID-19 infection. The University of Texas Health Science Center at San Antonio received a $3.7 million CPRIT Core Facility Support Awards grant (RP160732) in May 2016 to establish the UTHSCSA Cancer Genome Sequencing and Computation Core.

56. In order to determine if Perimeter's wide-field optical coherence tomography (WF-OCT) imaging has potential as an adjunct to standard pathology for margin analysis of squamous cell carcinoma (SCC) of the oral cavity and oropharynx, researchers evaluated the utility of WF-OCT at margins of excised oral and oropharyngeal tissue. The study, conducted at Mount Sinai Icahn School of Medicine, included 53 adult patients undergoing primary ablative surgery of the oral cavity or oropharynx for SCC. Resected specimens were imaged with Perimeter S-Series OCT in the operating room prior to routine pathology to allow for post-operative comparisons. The results, published on December 1, 2022, in *JAMA Otolaryngology—Head and Neck Surgery*, validated that Perimeter's WF-OCT imaging was feasible for visualizing tissue microarchitecture at the surface of resected tissues and was not associated with changes in specimen integrity or surgical and pathology workflow. These findings suggest that formal clinical studies investigating the use of WF-OCT may be warranted. Perimeter Medical Imaging AI, Inc. received a $7.45 million CPRIT Product Development Research grant (DP190087) in August 2019.

57. The cardiac conduction system (CCS) comprises about 1%-5% of the heart cell population and coordinates a series of electrical impulses to ensure efficient heartbeat and blood circulation. Failure of this system may result in arrhythmias such as atrial fibrillation, sinus bradycardia, atrioventricular block, and ventricular tachycardia. However, little is known about the genetics and molecular makeup of this small group of heart cells. Co-first authors CPRIT Scholar Ralf Kittler, Ph.D., associate professor, Department of Molecular Biology, and Nikhil Munshi, M.D., Ph.D., associate professor, Departments of Internal Medicine and Molecular Biology, and colleagues from The University of Texas Southwestern Medical Center set out to determine the control components of the CCS. The team, using a technique previously developed by the Munshi lab (PAN-INTACT), and a second method called ATAC-Seq, identified parts of the genome that control gene expression, known as cis-regulatory elements (CREs). The researchers gathered their results to establish a CRE database that can be used to better understand the functions of these cells and how they're regulated and help to interpret human variants associated with arrhythmias. "Our study provides the first road map for all the gene-control elements in

the specialized population of cardiomyocytes responsible for cardiac rhythm," said Dr. Munshi. These results, published in *The Journal of Clinical Investigation* on December 1, 2022, illustrate several key aspects of CCS component function, provide a rich database for future mechanistic investigation, and could impact diagnosis and risk prediction for a variety of common arrhythmias. The University of Texas Southwestern Medical Center recruited Dr. Kittler from the University of Chicago in November 2009 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Member grant (R1002).

58. Mailed stool testing programs increase colorectal cancer (CRC) screening in diverse settings, but whether uptake differs by key demographic characteristics has not been well-studied. Researchers from The University of Texas at Austin examined the uptake and equity of the first cycle of a mailed stool test program implemented over a 3-year period in a Central Texas Federally Qualified Health Center system. In this retrospective cohort study, principal investigator Michael Pignone M.D., MPH, Departments of Internal Medicine and Population Health, and team mailed outreach in English/Spanish, included an introductory letter, free-of-charge fecal immunochemical test (FIT), and lab requisition with postage-paid mailer, simple instructions, and a medical records update postcard. One text and one letter reminded non-responders. Over 3 years, 33,606 patients received an initial cycle of outreach. Overall, 19.9% completed at least one mailed FIT, 5.6% tested positive during that initial cycle, and 72.5% of those with positive FIT completed a colonoscopy. Hispanic/Latinx, Spanish-speaking, and uninsured patients were more likely to complete mailed FIT compared with white, English-speaking, and commercially insured patients. Spanish-speaking patients were more likely to complete colonoscopy after positive FIT compared with English-speaking patients. The results of the Mailed FIT outreach, published in the *Journal of General Internal Medicine* on December 1, 2022, proved effective in equitably reaching patients not up to date for CRC screening. The December 5, 2022, edition of UNDARK digital magazine featured the colorectal cancer screening project directed by Dr. Michael Pignone. The University of Texas at Austin received two CPRIT Prevention grants (PP170082, PP200066) in 2017 and 2020 totaling $4.2 million for the support of the multi-faceted intervention program.

59. Prostate cancer is one of the most heritable cancers. Genome-wide association studies have identified at least 185 common prostate cancer risk alleles, or snippets, of DNA. But because the vast majority of these alleles are located in DNA's noncoding regions, how they affect prostate cancer risk has largely been a mystery. Principal investigator, Ram Mani, Ph.D., assistant professor, Departments of Pathology and Urology, and fellow researchers at The University of Texas Southwestern Medical Center, used several approaches to identify which genes serve as targets for the risk alleles. A three-dimensional mapping technique using data from 565 prostate cancer tumors showed that 87 of these risk alleles affected the activity of hundreds of genes, which produced proteins known to be involved in molecular pathways for development, apoptosis (programmed cell death), and metabolism, among other cellular processes. As Dr. Mani explains, "Traditionally, we think of regulatory elements in the genome affecting neighboring genes. But these risk variants, or risk alleles, can act like a light switch. The light is on the ceiling, but the switch is on the wall on the other side of the room." The data, published in *Cancer Discovery* on December 2, 2022, could lead to the development of new prostate cancer treatments and to better risk models for patients, particularly for especially aggressive disease and for populations at high risk, such as African American men who have an elevated risk of prostate cancer. The University of Texas Southwestern Medical Center received a $900,000 CPRIT Individual Investigator grant (RP190454) in February 2019 to help in the development of epigenetic therapies for cancer and personalized epigenomics.

60. Pelvic sarcomas account for as much as 10% of osteosarcoma cases and disproportionately affect individuals under the age of 25. Limb-salvaging internal hemipelvectomy surgery has become common for treating pelvic sarcomas; however, estimating trunk and leg muscle forces simultaneously during walking based on electromyography (EMG) data remains challenging. Researchers, including CPRIT Scholar Benjamin J. Fregly, Ph.D., professor, Departments of Mechanical Engineering and Bioengineering at Rice University, developed a computational method for estimating unmeasured trunk muscle activations during walking. EMG data were collected from each leg and using non-negative matrix factorization, muscle synergies were extracted from activations of leg muscles. The team created a custom full-body model by com-

bining two existing musculoskeletal models which were further modified and heavily personalized to represent various aspects of the pelvic sarcoma patient. This proposed method, published in *Frontiers in Bioengineering and Biotechnology* on December 13, 2022, can facilitate the prediction of post-surgery walking function and pelvic prosthesis loading, as well as provide objective evaluations for surgical and prosthesis design decisions. Rice University recruited Dr. Fregly from the University of Florida with the support of a $5.1 million CPRIT Recruitment of Established Investigators grant (RR170026) in May 2017.

61. Immune checkpoint inhibitors have revolutionized the treatment of cancer in general, but only recently have been recognized to have some efficacy in mesothelioma. CPRIT Scholar Christopher Amos, Ph.D., professor of medicine, and colleagues at Baylor College of Medicine found that treating patients who have resectable malignant pleural mesothelioma (MPM) with immunotherapy ahead of surgery resulted in favorable clinical outcomes. The immunotherapy works by activating an immune response that will persist after the tumor is resected. The results of this phase 2, randomized, window-of-opportunity trial of neoadjuvant durvalumab versus durvalumab plus tremelimumab followed by surgery were published in the journal *Clinical Cancer Research* on December 5, 2022. The data indicates that neoadjuvant durvalumab plus tremelimumab orchestrates *de novo* systemic immune responses that extend to the tumor microenvironment and correlate with favorable clinical outcomes. Baylor College of Medicine recruited Dr. Amos in August 2017 from Dartmouth – Geisel School of Medicine with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR170048). The University of Texas MD Anderson Cancer Center received a $1.22 million CPRIT Shared Instrumentation Awards grant (RP121010) in March 2012.

62. Acute cerebral stroke is a leading cause of disability and death in the industrialized world. While treatments for acute stroke exist, their efficacy is directly connected to the speed with which they can be delivered after stroke onset, with diminishing effect over time. Corresponding author Luca Giancardo, Ph.D., MSc, associate professor, the Center for Precision Health at The University of Texas Health Science Center at Houston, and colleagues set out to determine if a portable retina imaging system could identify acute stroke events and effectively act as a proxy for brain imaging, enabling prompt diagnosis during patient transportation to the hospital. These imaging modalities are non-invasive and have optics that can be made portable, which could significantly streamline stroke care by transforming any standard ambulance into a mobile stroke unit. In this study, the team compared multiple methodologies on multi-modal retina imaging and showed initial evidence of the feasibility of this approach. The results were published in *The Journal of Clinical Medicine* on December 14, 2022. The University of Texas Health Science Center at Houston received a $5.85 million CPRIT Core Facility Support Awards (RP170668) in August 2017.

63. Nonalcoholic fatty liver disease (NAFLD) is a spectrum of chronic liver disorders that start out as benign fatty liver but can progress into more advanced disease stages including NASH, cirrhosis, and hepatocellular carcinoma (HCC). Obesity-induced chronic liver inflammation is a hallmark of nonalcoholic steatohepatitis (NASH). Immunologists at The University of Texas Southwestern Medical Center discovered that dietary obesity upregulates TREM2 (a macrophage receptor) which can trigger severe forms of nonalcoholic fatty liver disease and potential liver failure. The data, published in *Immunity* on December 14, 2022, revealed that persistent obesity can damage TREM2, thereby disabling a critical function that otherwise keeps liver inflammation in check. The team led by CPRIT Scholar Zhenyu Zhong, Ph.D., and Shuang Liang, Ph.D., assistant professors, Department of Immunology, reported that blocking TREM2 cleavage to restore tissue repair may represent an effective strategy to treat NASH. The University of Texas Southwestern Medical Center recruited Dr. Zhong from the University of California, San Diego with a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR180014) in February 2018. The University of Texas Southwestern Medical Center and Dr. Liang received a $900,000 CPRIT Individual Investigator grant (RP200197) in February 2020.

64. Cyclin E1 (CCNE1) is a protein coding gene, and its amplification is frequently identified in many types of malignancies associated with resistance to chemotherapy and short survival duration. In this phase II trial, corresponding author

Siqing Fu, M.D., Ph.D., professor, Department of Investigational Cancer Therapeutics at The University of Texas MD Anderson Cancer Center, and fellow researchers assessed the antitumor activity of adavosertib in patients with CCNE1-amplified, advanced refractory solid tumors. The results, published in the *Journal of Clinical Oncology* on December 5, 2022, reported 30 patients with CCNE1 amplification, treated with adavosertib achieved a median overall survival (OS) of 9.9 months and objective response rate (ORR) of 27%. Interestingly, in 14 patients with CCNE1-amplified epithelial ovarian cancer, the ORR was 36% and median OS was 14.9 months, meriting further study in this specific population. The University of Texas MD Anderson Cancer Center received a $6 million CPRIT Multi-investigator Research Awards grant (RP180712) in August 2018.

65. Inflammatory breast cancer (IBC), the most aggressive breast cancer subtype, is driven by an immunosuppressive tumor microenvironment (TME) and current treatments have limited efficacy. Researchers led by Xiaoping Wang, Ph.D., assistant professor, Department of Breast Medical Oncology at The University of Texas MD Anderson Cancer Center, previously established the combination of anti-EGFR antibody panitumumab and neoadjuvant chemotherapy as a viable treatment strategy for patients with IBC. In this new study, the researchers sought to uncover the mechanisms regulating responses to this combination therapy. As reported in *Science Advances* on December 16, 2022, using humanized IBC mouse models, the team demonstrated that EGFR-targeted therapy remodels the TME to be more receptive to immune checkpoint inhibitors, improving the antitumor response of immunotherapy. This highlights the therapeutic potential of suppressing the EGFR pathway as a means of improving responses for patients with IBC. The University of Texas MD Anderson Cancer Center received a $4.9 million CPRIT Core Facility Support Awards grant (RP180684) in August 2018 to establish an Integrated Single Cell Genomics (SCG) Core Facility at the MD Anderson Cancer Center to provide cutting-edge technologies for single cell sequencing and bioinformatics support.

66. At the cellular level, RNA modifications regulate several cellular processes, including cell death, proliferation, migration, metabolism, and the DNA damage response. Evidence suggests that RNA modification pathways are misregulated in human cancers and may be ideal targets of cancer therapy. However, the importance of these modifications is not well understood. CPRIT Scholar David Taylor, Ph.D., associate professor, Department of Molecular Biosciences, and scientists at The University of Texas at Austin set out to show how a single nucleotide modification serves as a structural checkpoint in ribosome assembly. The data, published in *Nature* on December 19, 2022, demonstrated that a single RNA modification is a critical checkpoint in the process of making ribosomes, suggesting that such modifications can play an important role in regulation and assembly of macromolecular machines. The University of Texas at Austin recruited Dr. Taylor from the University of California, Berkeley with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160088) in September 2016.

67. Invasive breast cancer is composed of more than 20 different histological subtypes. Invasive lobular carcinoma (ILC) makes up 10-15% of invasive ductal carcinoma (IDC) cases. Although the addition of targeted therapies to endocrine therapy (ET) has improved the outcomes of patients with HR-positive, HER2-negative metastatic breast cancer (mBC), it is unknown whether patients with ILC or mixed histologies experience the same magnitude of benefit from this therapy. Researchers from The University of Texas MD Anderson Cancer Center set out to determine whether patients with IDC, ILC, and mixed HR+/HER2– mBC derive similar benefit from the addition of CDK4/6is, mTORi, and PI3Ki to ET in a retrospective observational, population-based investigation. Corresponding author, Jason A. Mouabbi, M.D., assistant professor, Department of Breast Medical Oncology, and team reported in *Nature* on December 20, 2022, that the addition of CDK4/6is, everolimus, or alpelisib to ET led to a similar magnitude of benefit, irrespective of histology. These results are reassuring for patients with lobular and mixed histologies. The University of Texas MD Anderson Cancer Center received a $6 million CPRIT Multi-Investigator Research Awards grant (RP180712) in August 2018.

68. CPRIT Scholar Han Xiao, Ph.D., Departments of Chemistry and Bioengineering at Rice University, and collaborators have developed a noninvasive brain imaging tool that can help illuminate hard-to-access structures and processes. Brain

imaging poses a particular challenge because of the blood-brain barrier, a layer of cells that shields the brain from toxic substances in the blood, supplies brain tissues with nutrients, and filters harmful compounds from the brain back to the bloodstream. The team's small-molecule dye, or fluorophore, is the first of its kind that can cross the blood-brain barrier. Using murine glioblastoma models, fluorophore allowed the researchers to differentiate between healthy brain tissue and a glioblastoma tumor in mice. These results were reported in *ACS Publications* in December 2022. "This could be very useful for imaging-guided surgery, for example," Dr. Xiao said. "Using this dye, a doctor could determine where the boundary is between normal brain tissue versus tumor tissue." Rice University recruited Dr. Xiao in 2017 from Stanford University with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR170014).

69. Ewing sarcoma is an aggressive cancer of bone and soft tissue in children. The prognosis for patients with metastatic or recurrent Ewing sarcoma cases continues to be poor. While the chimeric protein EWS::FLI1 is the major driver of Ewing sarcoma, it has been difficult to target. Principal investigator Yuzuru Shiio, M.D., Ph.D., associate professor, Department of Biochemistry & Structural Biology, and colleagues from The University of Texas Health Science Center at San Antonio reported that a promising alternative approach is to identify and target the molecular vulnerabilities created by EWS::FLI1. The results published in *Genes and Cancer* in December 2022, showed that EWS::FLI1 induces the expression of Slit2, which stimulates the Ewing sarcoma growth. Ewing sarcoma's dependence on Slit2 signaling provides an excellent opportunity for therapeutic targeting. The University of Texas Health Science Center at San Antonio received three CPRIT Academic Research grants (RP160487, RP160841, and RP190385) in 2015, 2016, and 2019, totaling $2.6 million.

70. The KRAS protein is part of a normal signaling pathway regulating growth and proliferation of cells, but activating mutations in KRAS drives abnormal growth in cancer. KRAS mutations are especially common in pancreatic cancers, occurring in about 90% of patients, while KRAS G12C mutations are present in 1-2% of cases. Researchers at The University of Texas MD Anderson Cancer Center have reported that the KRAS G12C inhibitor sotorasib achieved meaningful anticancer activity with an acceptable safety profile in heavily pretreated patients with KRAS G12C-mutated metastatic pancreatic cancer in the Phase I/II CodeBreaK 100 trial. The results of the trial, published on December 21, 2022, in the *New England Journal of Medicine*, indicated an objective response rate of 21.1% and a median time-to-response of 1.5 months, with 84% of patients experiencing disease control. Median progression-free survival was 4 months and overall survival was 6.9 months and there were no treatment-related adverse events that would lead to treatment discontinuation. "These are encouraging early data because they point toward establishing that KRAS inhibitors can work in pancreatic cancers, which have been difficult to crack from a targeted therapy standpoint," said principal investigator David S. Hong, M.D., professor, Department of Investigational Cancer Therapeutics. The University of Texas MD Anderson Cancer Center received a $6 million CPRIT Core Facility Support Awards grant (RP150535) in May 2015.

71. Great progress has been made in the design and synthesis of powerful therapeutic and diagnostic molecules for oncology; however, many compounds are impossible to synthesize using state-of-the-art organic chemistry methods. State-of-the-art methods for alkene diazidation rely on the usage of corrosive and expensive oxidants or complicated electrochemical setups, significantly limiting the substrate tolerance and practicality of these methods on a large scale. Rice University scientists, led by CPRIT Scholar Julian West, Ph.D., assistant professor, Department of Chemistry, utilized a stable, earth abundant, and inexpensive iron salt to function as both radical initiator and terminator. As reported in *Nature Communications* on December 23, 2022, this simple and general method allows for diazidation (a reaction that is commonly used to change the properties of a molecule) of a broad range of alkenes. Preliminary mechanistic studies support the radical nature of the cooperative process in the photochemical diazidation, revealing this approach to be a powerful means of olefin difunctionalization, a powerful tool for rapid formation of structurally complex building blocks from readily available starting materials. 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) in February 2019.

72. Neurodegenerative disorders, such as Alzheimer's and Parkinson's disease, result from the loss of specific types of neurons due to abnormal accumulation of mutant proteins and are characterized by region and cell-specific degeneration. Huda Yahya Zoghbi, M.D., professor, Department of Molecular and Human Genetics, and fellow researchers at Baylor College of Medicine, set out to understand why certain brain cells and regions are more sensitive to harmful mutant proteins in a condition called spinocerebellar ataxia type 1 (SCA 1). The team uncovered the diversity of molecular players and pathways that contribute to this neurodegenerative disorder. "We were quite surprised to discover that for this single gene disorder the mutant protein uses distinct partners to drive toxicity in different brain cells," Dr. Zoghbi said. "In fact, this study underscores the importance of investigating partners of other disease-driving proteins...to be in a better position to explore therapeutic interventions." The discovery, published on December 27, 2022, in *Neuron*, charts an investigative path for a better understanding of regional vulnerability in other neurodegenerative disorders. Baylor College of Medicine was awarded a $5 million CPRIT Core Facilities Support Awards grant (RP170005) in September 2016.

73. Several neurodegenerative disorders, such as Alzheimer's and Parkinson's disease, are characterized by region and cell-specific degeneration. However, the mechanisms driving this regional vulnerability are unknown. One such disease, spinocerebellar ataxia type 1 (SCA1), is an autosomal dominant neurodegenerative disorder affecting 1 in 100,000 people. A study led by Huda Y. Zoghbi, M.D., professor, Department of Molecular and Human Genetics at Baylor College of Medicine, uncovered the diversity of molecular players and pathways that contribute to this neurodegenerative disorder. The data, published in *Neuron* on December 27, 2022, demonstrate that the gene ATXN1 interacts with a host of transcription factors (proteins involved in the process of converting DNA into RNA) and that these additional factors might co-regulate genes dysregulated in SCA1 and contribute to the development of disease in mouse and human models. Dr. Zoghbi said, "This study underscores the importance of investigating partners of other disease-driving proteins...for all neurodegenerative disorders. It is only through such systematic studies that we can understand the mechanisms driving these diseases and be in a better position to explore therapeutic interventions." Baylor College of Medicine received a $5 million CPRIT Core Facility Support Awards grant (RP170005) in September 2016 in support of the BCM Mass Spectrometry Proteomics Core.

74. CPRIT Scholar David Taylor, Ph.D., associate professor of molecular biosciences at The University of Texas at Austin, and colleagues have discovered a protein that has been found to act as a multipurpose self-destruct system for bacteria, capable of degrading single-stranded RNA, single-stranded DNA and double-stranded DNA. The team used a high-resolution imaging technique called cryo-EM and discovered that when this protein Cas12a2, a CRISPR-associated nuclease, binds to a specific sequence of genetic material from a potentially dangerous virus, called a target RNA, a side portion of Cas12a2 swings out to reveal an active site. Then, as reported in the journal *Nature* on January 4, 2023, the active site starts to indiscriminately cut any genetic material it comes into contact with. This is the first CRISPR protein that has been found to degrade such a wide range of genetic material. This discovery holds potential for the development of new inexpensive and highly sensitive at-home diagnostic tests for a wide range of infectious diseases, including COVID-19, influenza, Ebola and Zika. The University of Texas at Austin recruited Dr. Taylor from the University of California, Berkeley, with the support of a$2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160088) in September 2016.

75. Injections are a part of everyday life for patients with conditions such as rheumatoid arthritis. Fear of needles and injection-associated infection and pain cause reduced patient compliance. Seeking to improve the lifestyle of patients with autoimmune disorders, researchers at Baylor College of Medicine and collaborating institutions used the probiotic bacteria *Lactobacillus reuteri* as a novel oral drug delivery platform to treat rheumatoid arthritis in an animal model. They chose *L. reuteri* because these bacteria are indigenous to human and other animal guts, has long been used as a cell factory in the food industry, and is recognized as safe by the U.S. Food and Drug Administration. The study was published on January 3, 2023, in the *Proceedings of the National Academy of Sciences*. "Daily delivery of these peptide-secreting

bacteria, called LrS235, dramatically reduced clinical signs of disease, including joint inflammation, cartilage destruction and bone damage in an animal model of rheumatoid arthritis," said co-corresponding author Christine Beeton, Ph.D., professor of integrative physiology at Baylor. Dr. Beeton noted that these bacteria could be stored in capsules without the need for refrigeration or needles. Baylor College of Medicine received a $5.17 million CPRIT Core Facility Support Awards grant (RP180672) in August 2018. The Texas A&M University System Health Science Center received two CPRIT Core Facility Support Awards grants (RP150578, RP170719), totaling $11.8 million in 2015 and 2017.

76. Scientists have discovered that many activities that happen inside the cell's nucleus occur within small, organized regions called biomolecular condensates. These areas serve as hubs where specific tasks are carried out efficiently. CPRIT Scholar Benjamin Sabari, Ph.D., assistant professor, Department of Molecular Biology at The University of Texas Southwestern Medical Center, and colleagues discovered a previously unrecognized mechanism that cells use to turn genes on and off to regulate the timing, location, and amount of a given gene product (usually a protein) present in a cell. Surprisingly, this level of control involves "disordered" regions of proteins whose function has long been a mystery. In this study, published in *Cell* on January 19, 2023, the researchers showed that condensates composed of the intrinsically disordered region (IDR) of MED1 selectively partition RNA polymerase II together with its positive allosteric regulators while excluding negative regulators. These findings could lead to new ways of controlling gene regulation and may one day lead to new treatments for a broad array of diseases. This study is the Sabari laboratory's first independent published research. The University of Texas Southwestern Medical Center recruited Dr. Sabari in 2019 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR190090).

77. In a Phase I clinical trial led by researchers at The University of Texas MD Anderson Cancer Center, Afamitresgene autoleucel (afami-cel), an adoptive T cell receptor (TCR) therapy targeting the MAGE-A4 cancer antigen, achieved clinically significant results for patients with multiple solid tumor types. The goal of TCR therapies is to more accurately target solid tumor cells without the toxicities to normal cells often associated with chimeric antigen receptor (CAR)-based cell therapies. The outcomes, published on January 9, 2023, in *Nature Medicine*, were noteworthy in the subgroup of patients with synovial sarcoma, where afami-cel achieved an objective response rate of 44% compared to the overall response rate of 24% across all cancer types. According to principal investigator David S. Hong, M.D., professor, Department of Investigational Cancer Therapeutics, these early results demonstrate a proof-of-concept for this novel cell therapy approach in solid tumors. "The overall toxicity from afami-cel was manageable, and we saw evidence of early activity in other cancer types. These results suggest this is an approach with the potential to work in solid tumors where there are currently no approved cellular therapies," said Dr. Hong. The University of Texas MD Anderson Cancer Center received a $6 million CPRIT Core Facility Support Awards grant (RP150535) in May 2015.

78. Maintenance of healthy bone mass depends upon constant homeostasis. Imbalance between osteoblast-mediated bone formation and hematopoietic osteoclast-mediated bone resorption results in osteoporosis, and in aging patients with osteoporosis, the decrease in bone formation often coincides with the increase in marrow adiposity. However, it was unclear how these two processes are coupled in the bone marrow. In this study, Ralf Krahe, Ph.D., professor, Department of Genetics, and fellow researchers from The University of Texas MD Anderson Cancer Center studied the *in vivo* role of the chromatin modifier NO66 in osteoblastogenesis, the process of bone formation. As reported in the *Journal of Osteoporosis* on January 10, 2023, the team used Col1a1-NO66 transgenic mice, which constitute a new epigenetic animal model to study the chromatin alterations in the context of age-related osteoporosis. The data revealed that osteoblast-specific overexpression of NO66 shows minimal alteration in the formation of developmental bone; however, it affects the homeostasis of mature bones. The University of Texas MD Anderson Cancer Center received a $1.45 million CPRIT Individual Investigator grant (RP130054) in 2012.

79. All living cells retain the ability to adapt to molecular stressors, such as those posed by changes in external environment or failures of intrinsic quality control processes. This adaptability stems from a network of interrelated stress response

signaling pathways. Researchers from The University of Texas MD Anderson Cancer Center and colleagues previously used CRISPR screening data from cancer cell lines to identify factors that play roles in multiple stress response signaling pathways. This analysis led them to identify HAPSTR1, which had no known biochemical function, and validated that HAPSTR1 broadly regulates stress signaling, in turn controlling cellular and organismal resilience. In the current study, CPRIT Scholar Nidhi Sahni, Ph.D., assistant professor, Departments of Epigenetics and Molecular Carcinogenesis and Bioinformatics and Computational Biology, and team discovered a paralog for HAPSTR1—HAPSTR2—which emerged through a retroposition event early in mammalian evolution. Published in *Nature* on January 11, 2023, the results identified a novel protein-coding retrogene that buffers a conserved stress response pathway in mammals and augmented their understanding of an ancient stress resilience pathway. The University of Texas MD Anderson Cancer Center recruited Dr. Sahni from the Dana-Farber Cancer Institute in 2015 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160021).

80. Since sequencing the human genome over twenty years ago, geneticists have conducted large, genome-wide association studies to identify genomic regions linked to human disease. In addition to DNA sequence, another stable level of molecular information that may also affect one's risk of disease is the epigenome – a system of molecular modifications to DNA that tells different cells in the body the genes to turn on or off in that cell type. A team led by Robert Waterland, Ph.D., professor, Department of Pediatrics and Nutrition at Baylor College of Medicine and the Dan L. Duncan Comprehensive Cancer Center, reported a surprising finding: the commercial high-throughput platform that has been the workhorse for hundreds of population studies of DNA methylation is not appropriate for studies of epigenetic-based variants. Thus, Dr. Waterland and his colleagues have taken a "mirror-image approach," in which they focus on a different set of CpG sites: those at which DNA methylation differs substantially among people but is consistent across the different tissues of each person. These sites are "CoRSIVs" - correlated regions of systemic interindividual variation - and have been associated with diverse health outcomes including thyroid function, cognition, cleft palate, schizophrenia, childhood obesity, and autism spectrum disorder. The research team reasoned that CoRSIVs are most useful for population studies because scientists can use DNA from a blood sample to investigate epigenetic causes of disease in internal organs like the brain or heart. The team presented the first large-scale assessment of mQTL (methylation quantitative trait loci) at human genomic regions. This study, published in *Genome Biology* on January 12, 2023, also reported that CoRSIVs exhibit much stronger mQTL than previously observed. "We hope that the new tool we've developed will accelerate progress in understanding epigenetic causality of disease," said Dr. Waterland. Baylor College of Medicine received a $1.05 million CPRIT Individual Investigator Research Awards grant (RP170295) in November 2016.

81. Patients with EGFR-mutant advanced non-small cell lung cancer (NSCLC) typically develop resistance to treatment with tyrosine kinase inhibitors (TKIs) targeting EGFR and subsequent therapy with immune checkpoint inhibitors is ineffective. Researchers at The University of Texas MD Anderson Cancer Center found that targeting IL-6, an anti-inflammatory cytokine associated with poor outcomes in NSCLC, could improve immunotherapy response in treatment-resistant lung cancer with EGFR mutations. In this study, researchers led by Sonia Patel, Ph.D., and John Heymach, M.D., Ph.D., chair, Department of Thoracic/Head and Neck Medical Oncology, investigated the role of IL-6 in the tumor microenvironment by using an IL-6 inhibitor in lab models of EGFR-mutant NSCLC. As reported on January 3, 2023, in *Clinical Cancer Research*, the team discovered that tumors with resistance to EGFR TKIs upregulate IL-6, creating a microenvironment that suppresses the activity of natural killer (NK) cells and T cells. Inhibiting IL-6 improved the efficacy of immunotherapy, providing a potential target pathway to overcome TKI resistance in this subset of patients. The University of Texas MD Anderson Cancer Center received a $4 million CPRIT Research Training grant (RP210028) in May 2021 to instruct postdoctoral fellows for careers in translational cancer research.

82. Glioblastoma multiforme (GBM) is the most common primary brain tumor and has one of the worst morbidity and mortality rates. Glutaminase isoenzyme GLS is an enzyme that plays a role in pathways promoting cancer growth in GBM. Using the clinically approved GLS inhibitor CB-839 (Telaglenastat), Ralph J. DeBerardinis, M.D., Ph.D., chair, Department of

Pediatrics at The University of Texas Southwestern Medical Center, and fellow researchers studied the metabolic effects of inhibiting GLS activity by using CB-839 in several human glioma cell lines. As reported in *Cancers* in January 2023, one of them, the T98G glioblastoma cell line, showed significant changes in the levels of certain molecules related to the creation of new genetic material (nucleotides). Additionally, these cells had more molecules that had undergone modifications through methylation and acetylation processes. These alterations can contribute to the aggressive nature of GBM. These findings pave the way for further CB-839 or other GA-targeted studies and point to the future development of combination targeted therapies that are designed based on a specific tumor molecular signature. The University of Texas Southwestern Medical Center received two CPRIT High Impact/High Risk grants (RP100437, RP140021-P3) in 2010 and 2014 totaling $625,000 to study metobolic imaging of hyperpolarized 13C substrates.

83. Wearable sensor usage has increased significantly recently, particularly in monitoring both psychological states and human activity. Human Activity Recognition (HAR) is one of the efficient ways to support the challenges in this field. Research on HAR enables one person to either remotely monitor or recognize another person's activity and vital statistics, such as body temperature, heart rate, brain activity, and muscle movement, via a mobile device or by using sensor-based Internet of Things (IoT). Principal investigator Zhongming Zhao, Ph.D., chair, Center for Precision Health, The University of Texas Health Science Center at Houston, and colleagues set out to focus on the accurate classification of daily human activities from both accelerometer and gyroscope sensor data after converting into spectrogram images. As reported in *Scientific Reports* on January 18, 2023, the primary contribution of this work is the proposed two-fold architecture model, which outperforms the prior state-of-the-art HAR models proposed in the literature. It offers a strong basis for combining a transfer learning deep feature extraction model with a wrapper-based feature selection approach that has already been trained for HAR. The University of Texas Health Science Center at Houston received a $4.42 million CPRIT Core Facility Support Awards grant (RP180734) in August 2018 to support the UTHealth Cancer Genomics Core research.

84. DNA undergoes persistent damage and repair, and if this damage goes unrepaired, it can result in genomic instability and mutations that predispose towards the development of cancer. Although genomic DNA is predominantly duplex under physiological conditions, particular sequence motifs can favor the formation of alternative secondary structures, including the G-quadruplex. The primary DNA repair pathway for repairing damage is the base excision repair (BER) pathway. Although the repair of endogenous DNA damage by the BER pathway has been extensively studied in duplex DNA, substantially less is known about repair in non-duplex DNA structures. Therefore, researchers at The University of Texas Medical Branch at Galveston, including corresponding author Lawrence Sowers, Ph.D., chair, Department Pharmacology and Toxicology, sought to better understand the effect of DNA damage and repair on the quadruplex structure. The team proposed that while duplex is the preferred configuration, there is kinetic conversion between duplex and quadruplex. This is supported by their studies using a quadruplex stabilizing molecule, pyridostatin, that is able to promote quadruplex formation starting from duplex DNA. Their results reported in *Molecules* on January 18, 2023, suggest how DNA damage and repair intermediates can alter duplex-quadruplex equilibrium. The University of Texas Medical Branch at Galveston was awarded a $4 million CPRIT Research Training grant (RP170593) in 2016 to bring together principles of computational and physical science with basic and clinical cancer biology to develop an emerging generation of computational cancer biologists.

85. It remains an important clinical challenge to identify which patients with estrogen receptor–positive (ER1), node-positive breast cancer will have very low risk of disease recurrence after adjuvant endocrine therapy alone, and therefore do not benefit from chemotherapy. The 21-gene breast recurrence score (RS) is used to decide whether chemotherapy would provide additional benefit to hormone therapy alone for patients with lymph node-positive breast cancer. A different test, sensitivity to endocrine therapy (SET2,3), developed by William Fraser Symmans, MBChB, professor, Department of Pathology at The University of Texas MD Anderson Cancer Center, predicts the cancer's sensitivity to endocrine therapy relative to baseline prognostic characteristics. Researchers from the National Clinical Trials Network's Southwest Oncolo-

gy Group (SWOG) conducted a blinded retrospective clinical validation of SET2,3 in two randomized treatment arms from the SWOG S8814 trial comparing adjuvant anthracycline-based chemotherapy followed by tamoxifen endocrine therapy for five years, versus tamoxifen alone. The combined results provided clinically meaningful assessment of prognosis during the first five years of follow-up. The data published in *Journal of Clinical Oncology* on January 17, 2023, demonstrate that SET2,3 added complementary prognostic information to RS results in the S8814 trial for postmenopausal patients with node-positive disease treated with tamoxifen. The University of Texas MD Anderson Cancer Center received a $6 million CPRIT Multi-Investigator Research Awards grant (RP180712) in August 2018 to study rational combination treatment options to reverse resistance in hormone receptor-positive breast cancer refractory to standard therapy.

86. Aundrietta Duncan, Ph.D., director of Non-Clinical Development at Salarius Pharmaceuticals, Inc., presented SP-3164 preclinical data and program progress at the inaugural Molecular Glue Drug Development Summit in January in Boston. Dr. Duncan presented *in vivo* data demonstrating the activity of SP-3164 therapeutic activity in cancer models and *in vitro* data demonstrating SP-3164's mechanism of action. SP-3164 is an oral, next-generation molecular glue that uses Salarius' deuterium-enabled chiral switching platform to stabilize the preferred (S)-enantiomer of avadomide, an extensively studied clinical compound that has demonstrated encouraging clinical efficacy in non-Hodgkin's lymphomas (NHL) and other hematologic malignancies. SP-3164 is a new chemical entity and has been issued a composition of matter patent. Data presented in December 2022 at the American Society for Hematology Annual Meeting showed compelling SP-3164 activity in lymphoma models and supports SP-3164's potential in NHL for the clinical trial planned to initiate in 2023. Salarius received a $16 million CPRIT Product Development Award grant (DP160014) in 2016 to support the development of novel drugs for rare pediatric cancers and other cancers by focusing on treatments that interrupt the final steps of the signaling cascade.

87. Ischemia-reperfusion injury, tissue damage that occurs after oxygen deprivation, can be observed after a variety of insults. A key protein that plays a role in this damage is calcium calmodulin-dependent protein kinase IIδ (CaMKIIδ). A new study conducted by The University of Texas Southwestern Medical Center scientists showed that editing the gene that prompts damage after a heart attack appeared to reverse this inevitable course in mice, leaving their hearts mostly unharmed. The team used CRISPR-Cas9 to edit CaMKIIδ in human heart cells growing in a petri dish. Tests showed that when unedited heart cells were placed into a low-oxygen chamber, they developed numerous markers of damage and subsequently died. However, the edited cells were protected from damage and survived. "Rather than targeting a genetic mutation, we essentially modified a normal gene to make sure it wouldn't become harmfully overactive. It's a new way of using CRISPR-Cas9 gene editing," Rhonda Bassel-Duby, Ph.D., professor, Department of Molecular Biology said. Next the team used a similar experiment on mice. The findings, published in *Science* on January 12, 2023, found that targeting CaMKIIδ using CRISPR-Cas9 gene editing was a viable intervention to protect the heart tissue from ischemia-reperfusion damage in mouse models. Injecting gene editing reagents soon after ischemia exposure was sufficient for the mice to recover from severe heart damage, suggesting that it may not be too late to intervene after a heart attack happens. The University of Texas Southwestern Medical Center was awarded a $4 million CPRIT Core Facility Support Awards grant (RP210099) in August 2021 in support of this world-class pre-clinical multimodal imaging core facility.

88. Literature on the mathematical modeling of tumor initiation, expansion, angiogenesis, and invasion seek to provide new strategies for understanding the underlying biology to make predictions of the spatiotemporal evolution of the disease as well as its response to therapy. A fundamental barrier limiting progress in the field is the paucity of studies linking mechanism-based mathematical models with the appropriate experimental data. Researchers from The University of Texas at Austin including CPRIT Scholar Thomas Yankeelov, Ph.D., professor, director of Center for Computational Oncology, used several forms of quantitative experimental data to inform a complex mathematical model to predict tumor angiogenesis, the proliferation of blood vessels penetrating the tumor for the supply of nutrients and oxygen for continued tumor growth and metastasis. The team calibrated and determined the ability of an agent-based model to make accurate predictions of tumor angiogenesis by systematically incorporating data of different scales to inform model

parameters. The results, published in *PLOS Computational Biology* on January 18, 2023, represent the first effort to calibrate a mechanism-based mathematical model to spatially and temporally-resolved experimental data of angiogenesis, thereby enabling predictions of future vessel development that could then be directly tested against observation. The University of Texas at Austin recruited Dr. Yankeelov from Vanderbilt University in 2015 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR160005).

89. Posoleucel is an off-the-shelf virus-specific T-cell product designed to treat or prevent multiple viral infections that are frequently observed in the allogeneic hematopoietic stem cell transplant (allo-HSCT) setting. Results from AlloVir's Phase 2 CHARMS trial show that posoleucel appears safe and effective for treating refractory viral infections occurring after allo-HSCT. The trial included 58 adult (69%) and pediatric (31%) patients, who had received allo-HSCT and had an unresponsive viral infection or were intolerant to standard antiviral therapies. The primary efficacy outcome was antiviral response at 6 weeks after the first dose. At that time, the overall response rate (ORR) was 95%. The ORR was 98% for patients with a single infection and 83% for patients with multiple infections. Researchers found that posoleucel elicited a complete response or partial response in nearly all treated patients. These results were published in *Clinical Cancer Research* on January 17, 2023. AlloVir, Inc. was awarded a $6 million CPRIT Product Development Research grant (DP170043) in August 2017 to help establish the safety and effectiveness of their lead product that treats severe viral infections in cancer patients after stem cell transplants.

90. Researchers from The University of Texas Southwestern Medical Center (UTSW) and colleagues have discovered that artificial intelligence can be combined with traditional pathology to develop treatment plans for patients suffering from non-small cell lung cancers. Tyrosine kinase inhibitors (TKIs) are effective drugs for many patients with tumors that contain the epidermal growth factor receptor (EGFR) mutations, but some tumors are unresponsive. The goal of this study was to find a way to determine tumor characteristics that predict responsiveness to this treatment. Corresponding authors from UTSW, Yang Xie, Ph.D., professor, Department of Bioinformatics, and Guanghua "Andy" Xiao, Ph.D., professor of Data Sciences, and team developed a tissue image–based model to predict the survival benefit of EGFR TKI therapy in patients with EGFR-mutant metastatic lung adenocarcinoma. The team focused on metastatic non-small cell lung cancers from 272 patients with EGFR gene mutation who were enrolled in studies conducted by the Lung Cancer Mutation Consortium. The findings, published in *The Journal of Clinical Investigation* on January 17, 2023, report that their prediction model harnessed the power of artificial intelligence for sophisticated pathology image analysis culminating in the development of an algorithm to predict response to EGFR TKIs. The University of Texas Southwestern Medical Center received an $885,185 CPRIT Academic Research grant (RP190107) in February 2019 and a $5.4 million Core Facility Support Awards grant (RP180805) in August 2018.

91. Glioblastoma (GBM) is a highly devastating brain tumor. However, efficient DNA repair in response to standard chemo and radiation therapies often contributes to GBM therapy resistance which leads to low long-term survival rates, with only 7.2% of patients surviving beyond five years. Researchers in the Department of Population Health Sciences at The University of Texas Health Science Center at San Antonio, including Yidong Chen, Ph.D., have made significant progress in studying a promising new molecule that inhibits GBM tumors' ability to repair themselves. The molecule, known as NCD38, targets a specific subset of GBM cells called glioma stem cells. By disrupting their highly efficient DNA repair activity, NCD38 offers new possibilities for treatment. Published in *Neuro-Oncology* on January 18, 2023, the study demonstrated that mice receiving this novel therapy in combination with chemotherapy showed extended survival compared to those receiving a single drug alone. These results provide a steppingstone for developing new strategies to combat GBM treatment resistance and pave the way for enhanced patient care. The University of Texas Health Science Center at San Antonio received a $3.68 million CPRIT Core Facility Support Awards grant (RP160732) in May 2016 to update and expand the existing infrastructure and establish the UTHSCSA Cancer Genome Sequencing and Computation Core.

92. The University of Texas Southwestern Medical Center researchers have discovered a method that cells use to turn genes

on and off that involves portions of proteins whose function has not been well understood. CPRIT Scholar Benjamin Sabari, Ph.D., assistant professor in the Departments of Molecular Biology and Obstetrics and Gynecology, and his colleagues focused their study on MED1, a protein that forms part of a complex involved in transcription, a critical step in the process through which genes produce proteins. MED1, which has a large intrinsically disordered region (IDR), has also been linked to estrogen receptor positive breast cancer. The results, reported in *Cell* on January 19, 2023, showed that the proteins in these MED1 condensates were enriched for positive regulators of transcription, while negative regulators were left out and could lead to new ways of controlling gene regulation. "We think this is likely just the tip of the iceberg. Interactions among these disordered regions of proteins have largely been ignored because it was unclear how they worked. Now, they're opening a new world of regulatory interactions that we previously didn't know existed," said Dr. Sabari. The researchers hope that understanding how interactions among different IDRs within condensates are dysregulated in these diseases and finding ways to alter their interactions might one day lead to a new class of treatments for these conditions. The University of Texas Southwestern Medical Center recruited Dr. Sabari in 2019 with a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR190090).

93. Ribosomopathies are a group of human diseases caused by mutations in genes that are required for ribosome biogenesis (RiBi), the process by which ribosomes, the molecular machines that synthesize all of the proteins in our bodies, are made. The importance of a correctly functioning RiBi machinery for maintaining tissue homeostasis is illustrated by the observation that ribosomopathy patients have an increased risk for developing cancer later in life. In this study, Yidong Chen, Ph.D., professor, Department of Population Health Sciences, The University of Texas Health Science Center at San Antonio, and colleagues used a conditional approach to delete the *Rps6* gene in hepatoblasts of the embryonic liver or mature hepatocytes of the adult liver and showed that Rps6 is required for establishing and maintaining hepatic homeostasis. This study, published in *PLOS Genetics* on January 19, 2023, not only reveals a previously unappreciated dependence of the developing liver on adequate levels of Rps6 and exquisitely controlled p53 signaling but suggests that the increased cancer risk in ribosomopathy patients may stem from an inability to preserve normal tissue homeostasis in the face of chronic injury and regeneration. The University of Texas Health Science Center at San Antonio was awarded two CPRIT Core Facility Support Awards (RP160732, RP220662) in 2016 and 2022 for a total of $7.6 million for the support of the UTHSA Cancer Genome Sequencing and Computation Core (UTHSA-CGSCC).

94. Scientists at Rice University's Center for Theoretical Biological Physics are conducting a novel approach to studying DNA. Instead of focusing on chromosomes as linear sequences of genetic code, scientists including CPRIT Scholar José Onuchic, Ph.D., chair, Department of Physics, and professor, Department of Chemistry and Biosciences at Rice, are looking for clues on how their folded 3D shapes might determine gene expression and regulation. Within the nucleus, the genome of eukaryotes folds into partially organized three-dimensional structures specific to the cell type and phase of life. It is increasingly evident that these architectural features are related to the process of transcriptional regulation; the disruption has been observed to lead to disease. The team used data-driven physical simulations to study the three-dimensional architecture of the *Aedes aegypti* (mosquito) genome. The analysis, published in *Nature Communications* on January 19, 2023, showed the *Aedes aegypti's* chromosomes organize as fluid-yet-oriented "liquid crystals," different from all other species. Further analysis of the mechanical properties of the genome revealed that the chromosomes of *Aedes aegypti* are highly sensitive to the deformation of the nuclei which provides a possible physical mechanism linking mechanical cues to gene regulation. "Understanding DNA is a key to understanding how life works," said Rice theoretical physicist Peter Wolynes, Ph.D., a co-author on the study. "We are only just beginning to learn how the 3D architecture of chromosomes influences the functioning of genomes." Dr. Onuchic was recruited by Rice University in 2011 from the University of California, San Diego with the support of a $6 million CPRIT Recruitment of Established Investigators grant (R1110).

95. Certain tumors become dependent on the oxidative phosphorylation (OXPHOS) metabolic pathway for cellular energy production, making it an attractive target for new cancer therapies. However, clinical benefit with OXPHOS inhibitors has

yet to be achieved. Seeking to find the benefit of OXPHOS inhibitors, Marina Konopleva, M.D., Ph.D., and fellow researchers at The University of Texas MD Anderson Cancer Center, advanced IACS-010759, a highly potent and selective small-molecule complex I inhibitor, into two dose-escalation phase I trials in patients with relapsed/refractory acute myeloid leukemia and advanced solid tumors. The primary endpoints were safety, tolerability, maximum tolerated dose and recommended phase 2 dose (RP2D) of IACS-010759. The results, published in *Nature Medicine* on January 19, 2023, reported that IACS-010759 had a narrow therapeutic index with emergent dose-limiting toxicities, including elevated blood lactate and neurotoxicity, which obstructed efforts to maintain target exposure. Consequently, no RP2D was established, only modest target inhibition and limited antitumor activity were observed at tolerated doses, and both trials were discontinued. The results reveal important insights for the field, providing guidance and caution for future development of OXPHOS inhibitors. The University of Texas MD Anderson Cancer Center was awarded a $900,000 CPRIT Individual Investigator grant (RP180309) in February 2018 and two Core Facility Support Awards (RP120348, RP170002) in 2011 and 2016 totaling $11 million to enable high-impact research projects that will lead to cancer research breakthroughs in the next-generation sequencing facility.

96. Scientists have discovered that many activities that happen inside the cell's nucleus occur within small, organized regions called biomolecular condensates. These areas serve as hubs where specific tasks are carried out efficiently. CPRIT Scholar Benjamin Sabari, Ph.D., assistant professor, Department of Molecular Biology at The University of Texas Southwestern Medical Center, and colleagues discovered a previously unrecognized mechanism that cells use to turn genes on and off to regulate the timing, location, and amount of a given gene product (usually a protein) present in a cell. Surprisingly, this level of control involves "disordered" regions of proteins whose function has long been a mystery. In this study, published in *Cell* on January 19, 2023, the researchers showed that condensates composed of the intrinsically disordered region (IDR) of MED1 selectively partition RNA polymerase II together with its positive allosteric regulators while excluding negative regulators. These findings could lead to new ways of controlling gene regulation and may one day lead to new treatments for a broad array of diseases. This study is the Sabari laboratory's first independent published research. The University of Texas Southwestern Medical Center recruited Dr. Sabari in 2019 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR190090).

97. Breast cancer-related lymphedema (BCRL) occurs in ~ 40% of patients after axillary lymph node dissection (ALND), radiation therapy (RT), or chemotherapy. First-line palliative treatment uses compression garments, and second-line treatment consists of specialized massage and reparative microsurgeries. However, both therapies are most effective at early stages of lymphedema development. Melissa B. Aldrich, Ph.D., associate professor, Center for Molecular Imaging at The University of Texas Health Science Center at Houston, and researchers hypothesized that elevated plasma cytokine and chemokine levels precede BCRL development, and thus, could identify those at highest risk much earlier than current strategies. The data, published in *Cancers* on January 21, 2023, identify plasma cytokines/chemokines that predict BCRL development over a year before clinically recognized symptoms appear. These results establish BCRL as a perpetual inflammatory disorder and suggest the use of plasma cytokine/chemokine levels to predict those at highest risk. The University of Texas Health Science Center at Houston received a $900,000 CPRIT Individual Investigator grant (RP200181) in 2020 to help design the most effective procedures for eliminating cancer-related lymphedema.

98. Small cell lung cancer (SCLC) is a highly malignant cancer for which there are no currently approved targeted therapies, thus the disease remains commonly treated with conventional chemotherapy, inevitably leading to acquired resistance and relapse. Transcription factors, which play a crucial role in controlling when and how genes are turned on or off, are difficult proteins to target with small molecule inhibitors because of their lack of enzymatic activity for chemical intervention. However, transcription factors can be modified by enzymes to regulate their activity, and they can recruit proteins with enzymatic activity to function as transcriptional coregulators. These enzymes could serve as therapeutic targets as a workaround for this issue. In this study, researchers led by CPRIT Scholar Pawel Mazur, Ph.D., Department of Experimental Radiation Oncology at The University of Texas MD Anderson Cancer Center, identified nuclear factor I

B (NFIB) as a coactivator associated arginine methyltransferase (CARM1) substrate and showed that this transcription factor utilizes CARM1 as a coactivator. Using an SCLC mouse model, the team showed that both CARM1 and the CARM1 methylation site on NFIB are critical for the rapid onset of SCLC. Furthermore, CARM1 and methylated NFIB are responsible for maintaining similar open chromatin states in tumors. This data, published in *Nature Communications* on January 23, 2023, suggests that CARM1 might be a therapeutic target for SCLC. The University of Texas Medical Branch at Galveston received a $3.5 million CPRIT Core Facility Support Awards grant (RP190682) in 2019 to support state-of-the-art mass spectrometry technologies, expertise, and support for Texas cancer investigators. The University of Texas MD Anderson Cancer Center recruited Dr. Mazur in 2016 from Stanford University with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members (RR160078) and received a $998,000 Individual Investigator grant (RP220391) in February 2022.

99. Endometriosis, a chronic disease in which endometrial glands and stroma implant outside the uterus, afflicts 1 in 10 reproductive-age women. Evidence suggests that the microbiome, a community of microorganisms living inside the body, is altered in women with endometriosis. Currently there is no reliable non-invasive method to detect the presence of endometriosis and many women find hormonal therapy and surgery as ineffective in avoiding the recurrences. To understand the causal role of gut microbiota and endometriosis, scientists at Baylor College of Medicine and colleagues implemented a novel model using antibiotic-induced microbiota-depleted (MD) mice to investigate the endometriosis disease progression. The team discovered that an altered gut microbiome plays a pivotal role in endometriosis disease progression in an animal model. The findings, published *in Cell Death Discovery* on January 25, 2023, suggest that certain microbiome communities and/or their metabolites can contribute to endometriosis progression and that modifying the composition of these communities could help control the condition in human patients. Baylor College of Medicine was awarded a $4 million CPRIT Core Facility Support Award (RP210227) in August 2021 to access cutting-edge proteomics and metabolomics technologies and computational expertise.

100. Targeted therapies, such as endocrine therapies (ET), can exert selective pressure on cancer cells and promote adaptations that confer treatment resistance. Typically, ER+ breast cancers are treated first with systemic therapy to shrink tumors, surgery to remove remaining tumors, and then radiation with or without additional systemic therapy. However, 20%-35% of ER+ breast cancers show some degree of resistance to hormone therapy. To develop a new approach to predict radiation therapy resistance, Ram S. Mani, Ph.D., assistant professor of Pathology | Urology, study leader Prasanna Alluri, M.D., Ph.D., assistant professor of Radiation Oncology, and fellow researchers from The University of Texas Southwestern Medical Center studied the link between the response to hormone and radiation therapies. The scientists used OTX015, an experimental drug known as bromodomains and extraterminal domains (BET) which regulate gene transcription. The team was able to reverse radiation therapy resistance of hormone therapy-resistant cells grown in a petri dish, as well as hormone therapy-resistant tumors grown in mice. The results, published in *NPJ Precision Oncology* on January 24, 2023, provide a therapeutic rationale for personalization of radiation treatments in breast cancer patients based on their response to ET. The University of Texas Southwestern Medical Center received a $900,000 CPRIT Individual Investigator grant (RP190454) in February 2019 to help develop epigenetic therapies for cancer and personalized epigenomics.

101. Cancer metastasis to the lung occurs in 20% to 54% of patients and represents one of the leading causes of morbidity and mortality among cancer patients with metastatic disease. Corresponding author Harlan Jones, Ph.D., associate professor, Department of Microbiology, Immunology & Genetics at The University of North Texas Health Science Center at Fort Worth, and colleagues sought to understand how distant primary tumors metastasize to the lung and other metastatic sites. In this study, published in *Pharmaceutics* on January 29, 2023, the team showed that intranasal delivery of their engineered nasal nano-vaccine significantly reduced lung colonization by intravenous challenge of an extra-pulmonary tumor. Compared to mice that received the vaccine in its native form, nasal nano-vaccinated mice had superior protection against breast tumor lung-colonization. These findings demonstrate that the team's engineered nasal nano-vaccine has the potential to be used as a prophylactic approach prior to the seeding of tumors in the lungs, and

thereby prevent overt lung metastases from existing extra pulmonary tumors. The University of North Texas Health Science Center at Fort Worth was awarded a $3.8 million CPRIT Research Training grant (RP210046) in May 2021 to support the development of creative and innovative research education programs.

102. KRAS is a gene that creates a protein that is involved in cell growth, cell maturation, and cell death. NRAS, HRAS, and KRAS, are small GTPases that cycle between inactive GDP-bound and active GTP-bound states to regulate cell growth. Point mutations that lock KRAS into the GTP-bound state occur with high frequency in pancreatic, colon, and non-small lung cancers. This prominence of KRAS as an important oncogenic driver creates an urgency to decode its biological and biophysical vulnerabilities, noted corresponding author John F. Hancock, Ph.D., BChir, chair, Department of Integrative Biology and Pharmacology at The University of Texas Health Science Center at Houston. Oncogenic KRAS expression generates a metabolic dependency on aerobic glycolysis, known as the Warburg effect, which is a phenomenon where cancer cells produce energy (ATP) through a less efficient process. The researchers report an effect of increased glycolytic flux and is directly linked to KRAS oncogenic function. The findings, published in *Nature Communications* on January 28, 2023, reveal that this metabolic shift not only influences energy production and cell growth but also has a significant impact on the regulation of KRAS function. Targeting this aspect of KRAS regulation is a potential weakness that could be exploited for therapeutic purposes in cancer treatment. The University of Texas Health Science Center at Houston received a $900,000 CPRIT Individual Investigator grant (RP200047) in February 2020 to support the identification of how these drugs work, design new drugs, and determine whether they have clinical utility as new anti-KRAS cancer agents.

103. The human papillomavirus (HPV) genome is integrated into host DNA in most HPV-positive cancers, but the consequences for chromosomal integrity are unknown. A new study, led by CPRIT Scholar Maura Gillison, M.D., Ph.D., Keiko Akagi, Ph.D., and David Symer, M.D., Ph.D., from The University of Texas MD Anderson Cancer Center, using long-read DNA sequencing unravels a long-standing mystery in how the human papillomavirus (HPV) affects, or is affected by, host DNA and how that process drives cancer development. In this study published in *Cancer Discovery* on January 30, 2023, the researchers described heterocateny, a previously unreported form of genomic structural variation. Heterocateny is characterized by diverse, interrelated and repetitive patterns of virus and host DNA segments within a cancer. It is the result of genetic instability caused by HPV insertion into and excision from host chromosomes, a process by which the virus hijacks, amplifies and recombines host DNA. With this new heterocateny model, the authors demonstrated for the first time how HPV contributes to intratumoral heterogeneity and clonal evolution, driving the creation and development of tumors. These findings may have broader implications for cancers caused by other DNA tumor viruses that integrate into host DNA, including the hepatitis B virus. The University of Texas MD Anderson Cancer Center recruited Dr. Gillison in 2016 from the Ohio State University with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR170005).

104. Despite recent improvements in targeted and immune therapy, pancreatic ductal adenocarcinoma (PDAC) is still considered to be incurable. One of the major obstacles to treating PDAC is due to a tumor microenvironment that is highly resistant to immunotherapy. Researchers including CPRIT Scholar Leng Han, Ph.D., Department of Biochemistry and Molecular Biology at The University of Texas Health Science Center at Houston, and CPRIT Scholar Zhi Tan, M.D., Ph.D., Department of Pathology at Baylor College of Medicine, set out to further understand the role of these cells by characterizing the gene signature of tumor-associated nonmyelinating Schwann cells (TASc). The researchers found that the abundance of TASc was correlated with poor patient outcomes. Specifically, TASc express a long noncoding RNA (lncRNA) named PVT1, which triggers a signal pathway that promotes tumor growth. The findings, published in *Science Advances* on February 1, 2023, report that treatment response to immune checkpoint inhibitors improved using a TASc inhibitor *in vivo*, highlighting TASc and lncRNAs as potential therapeutic targets for pancreatic cancer. Texas A&M University System Health Science Center received a CPRIT Academic Research grant (RP190570) in 2019. Baylor College of Medicine recruited Dr. Tan in 2022 with the support of a CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR220039). The University of Texas MD Anderson Cancer Center received two CPRIT Academic Research grants (RP180259, RP200423).

The University of Texas Health Science Center at Houston recruited Dr. Han in 2015 with the support of a CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR150085).

105. Neuroendocrine prostate cancer (NEPC) is a lethal disease with median survival of less than one year from the time of detection which accounts for approximately 25% of all therapy- and castration-resistant prostate cancer (tCRPC). Clinical diagnosis of NEPC relies on pathological examination of tissue biopsies, but the accuracy is subject to the heterogeneity of the collected tissue. Based on their previously reported design of theranostic small-molecule prodrug conjugates (T-SMPDCs), researchers at The University of Texas Southwestern Medical Center reported a T-SMPDC tailored for targeted positron emission tomography (PET) imaging and chemotherapy of NEPC. As reported in *Pharmaceutics* on February 1, 2023, the proof-of-concept results validate the design concept of the T-SMPDC, which may hold a great potential for targeted diagnosis and therapy of NEPC. In addition, the modular assembly feature of this accomplished synthesis allows a rapid adaption of the T-SMPDC platform to target other intracellular oncotargets or to deliver other potent chemotherapy molecules as necessary. The University of Texas Southwestern Medical Center was awarded a CPRIT Shared Instrumentation Awards grant (RP110771) and CPRIT Core Facility grant (RP170638) totaling $9.8 million to support the acceleration of new basic research discoveries to positive clinical outcomes for cancer patients in North Texas.

106. IQGAP1 is a scaffold protein with a multidomain architecture that allows for interactions with numerous diverse proteins. Researchers from the National Institutes of Health evaluated whether tyrosine phosphorylation of IQGAP1 modulates the binding of selected proteins. This study provides molecular insight into the regulation of signaling pathways and expands the mechanisms by which IQGAP1 scaffolds proteins to modulate intracellular signaling cascades. Published in *Cells* on February 2, 2023, the results showed that IQGAP1 binds directly to MET receptor tyrosine kinase, and that this interaction impairs MET signaling. Additionally, the results demonstrated that MET-catalyzed phosphorylation of IQGAP1 creates a docking site for several SH2 domains, including those of Abl1 and Abl2. This work identifies for the first time that IQGAP1 is a phosphotyrosine-regulated scaffold for SH2-containing proteins, which reveals a novel mechanism through which IQGAP1 participates in intracellular signaling, providing insight into its role in cellular communication and regulation. The University of Texas MD Anderson Cancer Center received a $2.6 million CPRIT Core Facility Support Awards grant (RP180804) to provide the instrumentation and expertise to determine the strength of protein-protein interactions and to identify relevant binding partners.

107. The lymphatic system plays a crucial role in the maintenance of body fluid homeostasis and immune surveillance. Natural aging or stress-induced premature aging influences the lymphatic vessel structure and function, which significantly affect the role of lymphatics in tumor dissemination and metastasis. Cellular senescence, a stress-responsive stable cell cycle arrest, is one of the key factors of aging. The role of cellular senescence on cardiovascular diseases, cancer, vascular endothelial cells, and immune cells has been broadly discussed, but the effects of senescence on the lymphatic system and its impact on age-related diseases are not well understood. In this review, published in *International Journal of Molecular Sciences* on February 2, 2023, scientists reported that senescent cells (cells that have stopped dividing) secrete a cocktail of proinflammatory cytokines, chemokines, growth factors, proangiogenic factors (factors that promote the formation of new blood vessels), reactive oxygen species (ROS), and proteases that represent the senescence-associated secretory phenotype (SASP). The SASP is known for its role in promoting inflammation and influencing the surrounding cellular environment, potentially contributing to age-related diseases and conditions. In future studies, understanding the dichotomy of prosenescent benefits and consequences on the overall lymphatic augmentation of metastasis can aid in improving the treatment plans for cancer patients. Texas A&M University System Health Science Center received a $250,000 CPRIT High Impact/High Risk grant (RP210213) in August 2021 to examine the role of cellular senescence on diseases.

108. During translation of the genomic RNA of SARS-CoV-2, the causative virus in the COVID-19 pandemic, contains a complicated hairpin turn that triggers frameshifting which is essential for coronavirus replication. The host factors that regulate

this process have not yet been identified. To better understand this frameshifting event, senior author CPRIT Scholar Joshua Mendell, M.D., Ph.D., professor of Molecular Biology and chair in Medical Science, and his colleagues isolated the hairpin section and added RNA that coded for red and green fluorescent proteins. They then introduced this modified RNA into human cells and used CRISPR gene editing to knock out every gene in the human genome, one at a time. The data was published in *Cell Reports* on January 29, 2023. "Frameshifting must happen to translate the virus's entire genome," said Frederick Rehfeld, Ph.D., assistant instructor of Molecular Biology. "It thus provides a vulnerability that could be exploited with therapeutics that target this process." The University of Texas Southwestern Medical Center received a $1.05 million CPRIT Academic research grant (RP220309) in February 2022 to investigate the mechanism by which chemical modification of ribosomal RNA controls cellular senescence and the role of this process in lung cancer pathogenesis. UT Southwestern recruited Dr. Mendell from Johns Hopkins University in June 2010 with the support of a CPRIT Recruitment of Rising Stars grant (R1008).

109. Iron is an essential micronutrient with differing intake patterns and metabolism between men and women. Epidemiologic evidence on the association of dietary iron and its heme and non-heme components with colorectal cancer (CRC) development is inconclusive. Veronika Fedirko, Ph.D., MPH, associate professor, Department of Epidemiology at The University of Texas MD Anderson Cancer Center, and international colleagues examined baseline dietary questionnaire-assessed intakes of total, heme, and non-heme iron and CRC risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. The team modelled substitution of a 1 mg/day of heme iron intake with non-heme iron using the leave one-out method. The results, published in the *British Journal of Cancer* on February 9, 2023, reported that of 450,105 participants (318,680 women) followed for 14.2 ± 4.0 years, 6162 (3511 women) developed CRC. In men, total iron intake was not associated with CRC risk. In women, CRC risk was not associated with intakes of total, heme or non-heme iron. Substitution of heme with non-heme iron demonstrated lower CRC risk in men. These findings suggest potential sex-specific CRC risk associations for higher iron consumption that may differ by dietary sources. The University of Texas MD Anderson Cancer Center recruited Dr. Fedirko in May 2020 with a $4 million CPRIT Recruitment of Rising Stars grant (RR200056).

110. Long-term prognosis remains poor for colorectal cancer (CRC) patients with advanced disease who are treatment resistant. Researchers at The University of Texas Health Science Center at Houston, including Qingyun J. Liu, Ph.D., professor and director, Center for Translational Cancer Research, described the generation and preclinical evaluation of a novel antibody-drug conjugate (ADC) consisting of an anti-GPR56 antibody conjugated with the DNA-damaging payload duocarmycin. GPR56, an adhesion G protein-coupled receptor (GPCR), is highly expressed in CRC tumors and correlates with poor survival. The results of this study, published in the *British Journal of Cancer* on February 9, 2023, reported that high GPR56 was shown to be associated with the microsatellite stable (MSS) subtype that accounts for 80–85% of CRC. GPR56 ADC selectively induced cytotoxicity in CRC cells and tumor organoids at low nanomolar potency in a GPR56-dependent manner and showed significant antitumor efficacy against GPR56-expressing xenograft models. This study provides the rationale for the future development of a GPR56-targeted ADC approach to potentially treat a large fraction of MSS CRC patients. The University of Texas Health Science Center at Houston was awarded a $2 million CPRIT Academic Research grant (RP190542) in August 2019 to create a novel class of therapeutics that targets a group of receptors with increased levels in cancers of the digestive system.

111. Approximately 10-15% of patients with non-small cell lung cancer (NSCLC) have epidermal growth factor receptor (EGFR) mutations. Treatment with EGFR tyrosine kinase inhibitors (TKIs) is effective at killing most cancer cells. However, a small number of drug-tolerant cells persist and can remain dormant for long periods of time, but they eventually grow and metastasize. Corresponding author John Heymach, M.D., Ph.D., chair of the Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, and colleagues discovered that CD70, a cell surface protein normally found on immune cells, is highly overexpressed in resistant cells as well as in the residual cancer cells

immediately following TKI treatment. The team demonstrated that CD70 can be effectively used to target these cells with antibody-drug conjugates (ADCs) or cell therapies in laboratory models. "Residual cancer cells left over from TKI treatment are essentially a reservoir from which future resistant cells eventually grow," Dr. Heymach said. "These findings set the stage for a really promising approach in which we may give initial effective therapies and immediately follow them with these CD70-targeting drugs to eliminate the remaining residual cells." The study, published in *Cancer Cell* on February 13, 2023, looked at CD70 in the context of lung cancer, although its overexpression is also found in a number of different cancer types such as breast, pancreatic, ovarian, kidney and melanoma. The University of Texas MD Anderson Cancer Center received two CPRIT Core Facility Support Awards (RP120348 and RP170002) for a total of $11 million to enable high-impact research projects that lead to cancer research breakthroughs.

112. Gliomas are the most common type of primary brain tumors originating from brain tissue. Seizures are a frequent feature of malignant glioma, known as glioma-related epilepsy. A team led by researchers at Baylor College of Medicine reported in the journal *Neuron* on February 13, 2023, that the tumors from seizure patients can interfere with the ability of surrounding neurons to handle potassium, an important ion in neuronal communication. The disruption of this neural function drives seizures, which causes disease progression. The researchers applied single-cell RNA sequencing to determine tumor gene expression in both human patients and animal models and analyzed intraoperative recordings of brain activity of human glioma. They found that patients who have seizures have increased expression of genes involved in formation of neuronal connections or synapses. The team also searched for the location where the seizures started in the brain and discovered that in animal models that have seizures, tumor cells are much closer and more embedded into the neurons than in the models that do not have seizures. "Analysis of the brain recordings of patients that had seizures showed that they started where tumor cells were close to and interacted with neurons, confirming the findings in the animal models," said Benjamin Deneen, Ph.D., professor and chair at the Center for Stem Cells and Regenerative Medicine at Baylor. "The findings support further studies into novel strategies to control the seizures and tumor growth." Baylor College of Medicine received two CPRIT Academic Research, Core Facility Awards (RP210227, RP200504) in 2020 and 2021 totaling $8 million to facilitate comprehensive multiomic studies in preclinical models and clinical tumor specimens.

113. Craniofacial birth defects are among the most common human congenital malformations. These craniofacial anomalies, including cleft lip and palate, occur because of defects in neural crest cells, whose role is to give rise to the complex craniofacial region. In early vertebrate development, cranial neural crest cells acquire the ability to differentiate into many different cell types to generate the craniofacial structure and peripheral nervous system. CPRIT Scholar Ronald J. Parchem, Ph.D., assistant professor, Department of Molecular and Cellular Biology at Baylor College of Medicine, and team discovered that changes in chromatin accessibility in neural crest cells are regulated by the miR-302 microRNA family. Loss of miR-302 leads to reduced chromatin accessibility and a reduction in peripheral neuron differentiation. "The transient state in which chromatin is much more accessible enables neural crest cells to activate many genetic programs, which leads to the generation of multiple cell types required to develop the craniofacial region," said Dr. Parchem. The findings, published in *Proceedings of the National Academy of Sciences* on February 1, 2023, provide insight into ways that stem cells can increase their ability to differentiate into multiple cell types, which may improve the ability to generate tissues for regenerative medicine. Baylor College of Medicine recruited Dr. Parchem in 2015 from the University of California, San Francisco with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR150106) and received a $5.17 million Core Facility Support Awards grant (RP180672) in August 2018.

114. Researchers at Baylor College of Medicine report that social isolation causes memory and learning deficits and other behavioral changes. Many brain studies have focused on the effects of social deprivation on neurons, but little is known about the consequences for the astrocyte, the most abundant brain cell. The astrocyte supports the functions of neurons, participate in synapse formation and function, release neurotransmitters and make the blood-brain barrier. Researchers at Baylor College of Medicine wanted to investigate the effects of social isolation in the brain, specifically in astrocytes. Working with animal models, the team reported in the journal *Neuron* on February 13, 2023, that during

social isolation, astrocytes become hyperactive, which then suppresses brain circuit function and memory formation. The researchers evaluated the effect of social deprivation on astrocyte Ca2+ activity and discovered that social isolation greatly increased it, specifically the activity involving Ca2+ channel TRPA1. This in turn was followed by the release of the inhibitory neurotransmitter GABA that stopped neural circuits involved in memory and learning. Inhibiting astrocyte hyperactivity reversed the cognitive deficits associated with social deprivation. "Under normal group housing conditions, astrocytes facilitate and promote circuit function and memory," said corresponding author Benjamin Deneen, Ph.D., professor and chair at the Center for Stem Cells and Regenerative Medicine at Baylor. "However, we found that during social deprivation, astrocytes in the brain region known as the hippocampus actually suppress circuit function and memory formation. The broad conclusion is that astrocyte function is tuned to social experiences." Baylor College of Medicine received a $5.17 million CPRIT Core Facility Support Awards grant (RP180672) in August 2018 to purchase high-end equipment that will help identify new therapeutic targets and the generation of novel drugs.

115. Aberrant glycosylation patterns refer to irregular or abnormal modifications of sugar molecules on proteins and lipids in cells. In cancer cells, the normal glycosylation patterns are often disrupted, leading to distinct sugar modifications on cell surface proteins. Post-translational O-glycosylation of proteins with the addition of N-acetylglucosamine serves as (O-GlcNAc) a cellular regulator that has been linked to cancer and this sugar's variability is emerging as a metabolic biomarker in cancer. Corresponding author Jennifer S. Brodbelt, Ph.D., chair and professor, Department of Chemistry at The University of Texas at Austin, and colleagues investigated the use of mass spectrometry imaging to visualize the location of this sugar in primary tumor sections. The team developed a two-step procedure which revealed that O-GlcNAc was localized to both viable tumor and tumor margin regions validated by histopathology of an H&E-stained liver tumor section. These imaging results, published in *Cancers* on February 15, 2023, suggest that elevated levels of O-GlcNAc are associated with areas of increased cellular proliferation and malignancy. The correlation between higher O-GlcNAc levels and these characteristics was observed in a malignant VX2 tumor model, indicating a potential link between altered glycosylation patterns and the aggressive behavior of cancer cells. The University of Texas at Austin was awarded a $3.8 million CPRIT Core Facility Support Awards grant (RP190617) in August 2019 to establish a state-of-the art mass spectrometry imaging center that will serve and support cancer researchers throughout Texas.

116. EphA2 tyrosine kinase, a key regulator of tumorigenesis and cancer progression, is upregulated in many cancers and correlated with poor survival of patients, including those with endometrial cancer. EphA2-targeted drugs have shown modest clinical benefit. To improve the therapeutic response to such drugs, researchers from Texas A&M University System Health Science Center and The University of Texas MD Anderson Cancer Center hypothesized that Wee1 inhibition sensitizes cells to EphA2-targeted therapy and examined the anti-tumor effects of both agents in endometrial cancer mouse models and evaluated potential mechanisms of synergy. The findings, published in the *International Journal of Molecular Sciences* on February 15, 2023, report that EphA2- and Wee1-targeted therapies show synergistic interaction in endometrial cancer in both *in vitro* and *in vivo* experiments. The combination of cell cycle checkpoint inhibitors and EphA2-targeted therapy may have utility in the treatment of endometrial cancer and warrants further investigation. Texas A&M University System Health Science Center received two CPRIT Core Facility Support Awards grant (RP200668, RP150578) in 2015 and 2020 totaling $9.9 million to provide key resources to support cancer-related drug repurposing and combinatorial drug discovery research.

117. As of August of 2022, 596 million SARS-CoV-2 cases have been reported worldwide, with over six million corresponding COVID-19 attributable deaths. Multiple counter measures have been implemented to mitigate resilient viral spread, with vaccination coverage (at least one COVID-19 vaccination) corresponding to 66.5% of the world population (5.3 billion people). However, a gap in knowledge exists regarding appropriate thresholds for escalation and de-escalation of workplace COVID-19 preventative measures. CPRIT Scholar Christopher Amos, Ph.D., associate director of Quantitative Science at Baylor College of Medicine, and colleagues conducted 133,056 simulation experiments, evaluating the spread of SARS-CoV-2 virus in order to establish a quantitative reference estimating community and workplace viral spread that

would be readily digestible for business organizational use. As reported in *Scientific Reports* on February 16, 2023, the team used a COVID-19 Outbreak Simulator that was specifically designed for risk assessment and continuity planning for COVID-19 outbreaks. Researchers estimated relevant SARS-CoV-2 parameters from the clinical literature for viral transmission dynamics and used the simulator to observe parameter specific viral outbreak outcomes in feed-forward time simulations (simulations in which the system's response is computed based on inputs that occurred in the past). The results introduce generalizable reference heatmaps which can be used to rapidly identify and implement suitable mitigation strategies for an organization, given site-specific details. The team hopes that these simulation findings will allow for quantifiable and transparent policy decision-making that can respond to shifting viral, organizational, and community specified parameters. Baylor College of Medicine recruited Dr. Amos from Dartmouth - Geisel School of Medicine in 2017 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR170048).

118. High-grade gliomas, such as glioblastoma, are extremely aggressive and have a high recurrence rate despite treatment combinations of surgery, radiotherapy, and chemotherapy. Tumors exhibit high molecular, phenotypic, and physiological heterogeneity. In this study, David Hormuth, Ph.D., and CPRIT Scholar Thomas Yankeelov, Ph.D., both from the University of Texas at Austin, and colleagues used quantitative magnetic resonance imaging (MRI) data to capture this heterogeneity through imaging-based subregions or "habitats" in a mouse model of glioma. The team demonstrated the ability to model and predict the growth of the habitats using coupled ordinary differential equations (ODEs) in the presence and absence of radiotherapy. As reported in *Scientific Reports* on February 20, 2023, the researchers presented the first application of an ODE-based model to describe the dynamics of image-informed tumor habitats. This method provides a global description of heterogeneous tumor growth and provides an avenue for predicting changes in heterogeneity and tumor progression. The University of Texas at Austin received a $1.2 million CPRIT Academic Research grant (RP220225) in February 2022. The University of Texas at Austin recruited Dr. Yankeelov from Vanderbilt University in 2015 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR160005).

119. Efforts to identify lesions of head and neck cancers with high malignant potential are important to improve patient outcomes, as 5-year survival rates remain low due to late detection. Depth-resolved label-free optical imaging by the method of multiphoton autofluorescence microscopy (MPAM) may offer new ways to examine cellular and extracellular atypia associated with epithelial squamous cell carcinoma (SCC). The goal of this study was to perform a histo-optical MPAM assessment of resected head and neck tumors in order to provide an indication of agreement with the gold standard of histology. Principal investigator Gracie Vargas, Ph.D., professor and chair, Department of Neuroscience at The University of Texas Medical Branch at Galveston, and colleagues evaluated the method of MPAM for its ability to identify cellular and microstructural atypia in head and neck tissues from resected discarded tumor tissue, without the need for exogenous dyes or tissue sectioning. Published in *Cancers* on February 18, 2023, the results indicate that MPAM provides a valuable histo-optical assessment for the detection of atypia in dysplasia and SCC, which indicates that this method may be promising for potential clinical translation. The University of Texas Medical Branch at Galveston received an $852,748 CPRIT Academic research grant (RP150449) in 2015 to develop a novel optical imaging approach for identifying early cancer and treatable precancers having a high chance for malignancy in the oral cavity and oropharynx.

120. Neoadjuvant chemotherapy (NACT) used for triple negative breast cancer (TNBC) eradicates tumors in ~45% of patients. Unfortunately, TNBC patients with substantial residual cancer burden have poor overall survival rates. CPRIT Scholar Gloria Echeverria, Ph.D., Departments of Medicine and Molecular and Cellular Biology at Baylor College of Medicine, and colleagues previously demonstrated mitochondrial oxidative phosphorylation (OXPHOS) was elevated and was a unique therapeutic dependency of residual TNBC cells surviving NACT. In this study, the team investigated the mechanism underlying this enhanced reliance on mitochondrial metabolism. Upon comparing mitochondrial effects of conventional chemotherapies, they found that DNA-damaging agents increased mitochondrial elongation, mitochondrial content, flux of glucose through the TCA cycle, and OXPHOS, whereas taxanes instead decreased mitochondrial elongation and OXPHOS. Using TNBC cell lines and an *in vivo* PDX model of residual TNBC, the team found that sequential treatment with

DNA-damaging chemotherapy was able to suppress mitochondrial fusion and OXPHOS and significantly inhibit regrowth of residual tumor cells. The data, published in *Oncogene* on February 22, 2023, suggest that these findings may provide an opportunity to overcome mitochondrial adaptations of chemoresistant TNBC. CPRIT Scholar Gloria Echeverria, Ph.D., Baylor College of Medicine recruited Dr. Echeverria in November 2019 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR200009).

121. Although immune checkpoint therapy (ICT) has demonstrated durable response in a subset of patients with melanoma, the majority of patients do not respond. This is because the tumor microenvironment suppresses the immune response. Myeloid-derived suppressor cells (MDSCs), representing pathologically activated immature myeloid cells, are critical drivers of this tumor microenvironment, negatively correlating with ICT efficacy and contributing to ICT resistance. While there are several mechanisms that contribute to MDSC immunosuppression, an important mechanism of suppression by murine MDSCs is the increased production of reactive oxygen species (ROS). In this study, David Piwnica-Worms, M.D., Ph.D., Department of Cancer Systems Imaging at The University of Texas MD Anderson Cancer Center, and colleagues focused on evaluating the contribution of myeloperoxidase (MPO) in the tumor microenvironment in established tumors in adult murine models of ICT. In a preclinical study, use of verdiperstat – a myeloperoxidase-specific inhibitor – enhanced responses to immune checkpoint inhibition in two models. Long-term survival was 100% in the primary model when checkpoint inhibitors were used in combination with verdiperstat, highlighting its therapeutic potential according to the report published in the *Journal for ImmunoTherapy of Cancer* on February 17, 2023. The team's work in adult mice with genetic knockouts, tool compounds, and two different clinically translatable MPO inhibitors demonstrated that MPO is a promising therapeutic target for enhancing ICT efficacy with potentially minimal side effects. Baylor College of Medicine received a $5 million CPRIT Core Facility Awards grant (RP170005) in September 2016 to support cancer researchers with state-of-the-art proteomics and metabolomics technologies.

122. Researchers from The University of Texas Southwestern Medical Center revealed a mechanism that bacteria use to increase cGAS activity to overcome phage counterattacks. cGAS is an evolutionarily conserved enzyme that plays a pivotal role in immune defense against infection. Recently, Zhijian "James" Chen, Ph.D., professor, Department of Molecular Biology, identified the cGAS enzyme pathway that alerts the human immune system to disease-causing invaders like viruses. In this study, published in *Nature* on February 27, 2023, the team identified a novel protein modification that enhances the bacterial defense against bacteriophages (a type of virus that infects bacteria) and works through cGAS, mirroring the enzyme's role in humans. Next, a genetic screen revealed a phage-encoded protein that fights back against the bacteria's anti-phage response pathway. These results show that the antiviral function of the human cGAS pathway is highly conserved in bacteria and "reveals a new mechanism in the arms race between bacteria and the viruses that infect them, called bacteriophages or 'phages' for short," said Dr. Chen. "The study of anti-phage immune defense in bacteria led to the discovery of the CRISPR system that scientists now use for gene editing. We think ongoing studies of other pathways of anti-phage immunity – such as the cGAS regulatory pathway we uncovered in this study – may also lead to new developments in biotechnology and medicine." The University of Texas Southwestern Medical Center received a $6 million CPRIT Multi-Investigator Research Awards grant (RP180725) in August 2018 to develop innovative therapeutic strategies that challenge current standard clinical practice.

123. One of the indications of cancer is uncontrolled growth. This growth depends on proteins which are responsible for the structural and functional elements of cells. But to make more proteins, cells require more protein factories, or ribosomes. During Ribosomal RNA (rRNA) maturation, the primary transcript of rRNA undergoes various modifications to form the mature and functional rRNA molecule that becomes a structural component of the ribosome. This includes the extensive post-transcriptional modification of nucleotides that cluster in functionally important regions of the ribosome. CPRIT Scholar Jan Erzberger, Ph.D., assistant professor, Department of Biophysics, and colleagues from The University of Texas Southwestern Medical Center, proposed a model in which G2922 methylation levels regulate Nog2 recruitment to the pre-60S near the nucleolar/nucleoplasmic phase boundary, forming a kinetic checkpoint to regulate 60S production. The

team revealed cryo-EM reconstructions showing that failure to methylate G2922 causes the premature activation of Nog2 GTPase activity. This approach, published in *Nature Communications* on March 2, 2023, provides a template to study the GTPase cycles and regulatory factor interactions of the other K-loop GTPases involved in ribosome assembly. The University of Texas Southwestern Medical Center recruited Dr. Erzberger in 2015 from ETH Zurich with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR150074) and UT SOUTHWESTERN was awarded a $5.5 million CPRIT Core Facility Support Award (RP170644) to establish a new cryo-electron microscopy core facility in August 2017.

124. Human noroviruses (HuNoVs) are the leading cause of acute gastroenteritis worldwide, posing a significant risk to global health, for which there are no specific treatments or vaccines. A team led by researchers at Baylor College of Medicine used human intestinal enteroids, a laboratory model of the human gastrointestinal tract that recapitulates its cellular complexity, diversity and physiology, to uncover the process by which HuNoVs invade cells. Corresponding author Mary K. Estes, Ph.D., professor, Department of Molecular Virology and Microbiology at Baylor College of Medicine, and fellow researchers focused their study on the human norovirus pandemic strain GII.4, the virus responsible for causing the most cases of gastroenteritis around the world. The results, reported in the journal *Nature Communications* on February 28, 2023, showed that the dominance of GII.4 among human norovirus strains is attributed to its efficient exploitation of cellular pathways and its capability to evade or overcome the host's immediate defense responses. "Other viruses use some components of the pathways mentioned in our paper, but this is the first time a virus has been shown to use all of them together. We now are interested in figuring out the role each of these molecules plays in this novel, interesting process, and whether it relates to the pandemic nature of GII.4," said Dr. Estes. The findings provide insight into the viral infection process, highlighting unique pathways and strategies to combat norovirus infections. Texas A&M University System Health Science Center received two CPRIT Core Facility Support Awards grant (RP150578, RP170719) in 2015 and 2017 totaling $11.8 million to promote highly collaborative and productive partnerships between experts in advanced imaging research and outstanding cancer researchers.

125. Emerging evidence suggests that cryptic translation within long noncoding RNAs (lncRNAs) may produce novel proteins with important developmental/physiological functions. Like protein-coding genes, lncRNAs can exert tumor-promoting/suppressing functions and may serve as independent diagnostic or prognostic biomarkers. To investigate the role of this cryptic translation in complex diseases such as cancer, researchers led by Yiwen Chen, Ph.D., assistant professor, Department of Bioinformatics and Computational Biology at The University of Texas MD Anderson Cancer Center, used an integrative genomic strategy combining CRISPR/Cas9 knockout screens with data from the Cancer Genome Atlas. The researchers uncovered lncRNA-encoded proteins that might be involved in estrogen receptor α-positive luminal breast cancer, the most common breast cancer subtype. The results, published in *The Journal of Clinical Investigation* on March 1, 2023, indicate that the cryptic proteome encoded by lncRNAs represents an understudied proteome, part of which is hijacked by cancer cells to promote their fitness, and suggest that the hidden lncRNA-encoded proteins should be further studied for potential therapeutic targets. Baylor College of Medicine received two CPRIT Core Facility Awards (RP170005, RP210227) in 2016 and 2021 totaling $9 million to provide cancer researchers with access to cutting-edge proteomics and metabolomics technologies and computational expertise.

126. Colorectal cancer (CRC) screening is effective in reducing CRC incidence and death, but it is underutilized. Federally qualified health centers (FQHCs) serve populations at high risk for being unscreened, including uninsured and rural populations. However, these efforts are challenging, particularly in states like Texas where 40% of patients seen in FQHCs are uninsured; the proportion of patients up to date with CRC screening in the 72 FQHCs in Texas was only 34.2% in 2020 and 36.2% in 2021. Michael Pignone, M.D., MPH, chair, Department of Internal Medicine, The University of Texas at Austin, and colleagues obtained data from multiple sources (the CDC, the Texas Department of State Health Services, etc.), conducted geospatial analysis, and identified and mapped a list of priority FQHCs in Texas where the number of FQHC patients without up-to-date CRC screening is high and participation of the FQHCs in CPRIT-funded CRC screening

projects is absent. The results and map were published in Preventing Chronic Disease on March 2, 2023. The geospatial analysis produced a list of 11 FQHCs where improvements in CRC screening among age-eligible patients could have the largest impact. In the next phase of the research, the team will use the mapped information to contact and consult with the FQHCs to enhance CRC screening in their systems. The University of Texas at Austin received a $300,000 CPRIT Prevention grant (PP210045) in August 2021 to develop an evidence-informed blueprint, implementation guide, and consultation service for expanding mailed FIT programs to underserved areas of Texas.

127. Squamous cell cancer of the anal canal is caused by prior infection with human papillomavirus (HPV) in more than 90% of cases. Although the availability of a preventative HPV vaccine is expected to reduce the incidence of HPV-associated cancers such as anal cancer in the United States, the annual incidence of anal cancer continues to increase. Most patients present with localized disease, where concurrent chemoradiation is the standard treatment, and experience excellent clinical outcomes with this multimodality approach. However, patients who have persistent disease may undergo abdominoperineal resection with permanent end colostomy. Anti-PD1 antibodies have no proven benefit for those with localized disease treated with chemoradiation. Primary Investigator Van Morris, M.D., Department of Gastrointestinal Medical Oncology at The University of Texas MD Anderson Cancer Center, and colleagues utilized a novel digital spatial profiling technology on pretreatment anal cancer specimens to identify biomarkers associated with recurrence after chemoradiation. The results, published in *Cancers* on March 10, 2023, reported that recurrent tumors had higher baseline expression of immune checkpoint biomarkers, higher MAPK signaling activation, and higher PI3K/Akt signaling activation. These findings provide a rationale that supports future clinical trials with immunotherapy that seek to improve survival beyond chemoradiation for patients with localized squamous cell cancer of the anus. The University of Texas MD Anderson Cancer Center received a $1.05 million CPRIT Academic Research grant (RP220416) in February 2022 to understand better the biology that uniquely defines these microscopic tumor deposits of colorectal cancer, as detected by ctDNA in the blood, to design more effective treatments.

128. Genetic defects in BRCA2 and RAD51C predispose to familial inherited breast and ovarian cancer. Biallelic inactivation of BRCA2 (FANCD1) or RAD51C (FANCO) also causes Fanconi anemia (FA), an autosomal recessive disorder caused by inactivation of one of 23 identified FANC genes. CPRIT Scholar Katharina Schlacher, Ph.D., associate professor, Department of Cancer Biology at The University of Texas MD Anderson Cancer Center, and colleagues showed that polygenic, double-homozygous $Brca2^{\Delta 27/\Delta 27}$ + $Rad51c^{dah/dah}$ gene mutations in mice closely recapitulate the FA disease manifestations found in patients, providing a comprehensive preclinical cancer mouse model of FA. The data, published in *Nature Communications* on March 11, 2023, report that breast cancer-genome analysis confirms that polygenic FANC tumor-mutations correlate with lower survival, which expands the researchers' understanding of FANC genes beyond an epistatic FA-pathway. Collectively, the data proposes that the interaction between mutations in different genes creates a scenario where replication stress is significantly increased, potentially contributing to the development and progression of disease. The data collectively support this polygenic replication stress concept, providing a testable principle for further research and investigation. The University of Texas MD Anderson Cancer Center recruited Dr. Schlacher in 2014 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (R1312). MD Anderson received two CPRIT Academic Research grants (RP180463, RP180813) in 2018 totaling $6.5 million.

129. Synthesis of a smooth conductive film over an elastomer is vital to the development of flexible optics and wearable electronics, but applications are hindered by wrinkles and cracks in the film. To date, a large-scale wrinkle-free film in an elastomer has yet to be achieved. Jian Sheng, Ph.D., School of Engineering & Computing Sciences at Texas A&M University - Corpus Christi, and colleagues presented a robust method to fabricate wrinkle-free, stress-free, and optically smooth thin film in elastomer in *Nanomaterials* on March 14, 2023. The researchers applied nanoparticles between the film and elastomer to jam the interface and subsequently suppress interfacial instabilities to prevent the formation of wrinkles. Using polydimethylsiloxane (PDMS) and parylene-C as a model system, the team synthesized large-scale (>10 cm) wrinkle-free Al film over/in PDMS and demonstrated the principle of interface jamming by nanoparticles. They varied

the jammer layer thickness to show that, as the layer exceeds a critical thickness (e.g., 150 nm), wrinkles are successfully suppressed. In addition, Nano-indentation experiments revealed that the interface becomes more elastic and less viscoelastic with respect to the jammer thickness. The proposed method is simple, reproducible, low-cost, and scalable with potential in nanoscale sensor and actuator applications. Texas A&M University - Corpus Christi received a $247,703 CPRIT Academic Research grant (RP200593) in 2020 to support a nanotechnology to identify CTCs in whole blood.

130. Increasing evidence suggests that the gut microbiome may modulate the efficacy of cancer immunotherapy. CPRIT Scholar Robert Jenq, M.D., chair, Department of Genomic Medicine at The University of Texas MD Anderson Cancer Center, and colleagues demonstrated that wide-spectrum antibiotics treatment ('high-risk antibiotics') prior to CD19-targeted chimeric antigen receptor (CAR)-T cell therapy is associated with adverse outcomes in a B cell lymphoma patient cohort from five centers in Germany and the United States (Germany, n = 66; United States, n = 106; total, n = 172). This effect is likely to be confounded by an increased pretreatment tumor burden and systemic inflammation in patients pretreated with high-risk antibiotics. To resolve this issue and gain insights into antibiotics-masked microbiome signals impacting CAR-T efficacy, the team focused on the high-risk antibiotics non-exposed patient population. As reported in *Nature Medicine* on March 13, 2023, significant correlations were noted in these patients. Furthermore, predictive pre-CAR-T treatment microbiome-based machine learning algorithms trained on the high-risk antibiotics non-exposed German cohort and validated by the respective U.S. cohort, robustly segregated long-term responders from non-responders. The conserved microbiome features identified could serve as a basis for making predictions about how individuals may respond to CAR-T cell immunotherapy, regardless of differences in their clinical backgrounds or geographical locations. This has potential implications for advancing personalized medicine and improving the effectiveness of CAR-T cell therapies. The University of Texas MD Anderson Cancer Center recruited Dr. Jenq from the Memorial Sloan-Kettering Cancer Center in 2016 with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR160089).

131. Bone cancer, or malignant bone disease (MBD), frequently causes catastrophic bone damage in the form of tumor-filled osteolytic bone lesions (OLs). MBD tumors secrete proteins called Wnt inhibitors (WI) that inhibit the repair of OLs. Of the known WIs, Dickkopf-1 (Dkk-1) is most commonly involved with MBD. Blockade of WI activity (especially Dkk-1) is a potentially promising OL repair therapy. Carl Gregory, Ph.D., associate professor, Cell Biology and Genetics, and colleagues at the Texas A&M University System Health Science Center, made an additional discovery that further increases the significance of targeting WIs in MBD: Tumor-derived Dkk-1 also accelerates proliferation and enhances survival of tumors. The specific effects of Dkk-1 activity on tumor physiology are therefore unpredictable with examples of Dkk-1 serving as either a driver or suppressor of malignancy. The researchers questioned whether it is possible to predict the role of Dkk-1 on tumor progression based on the tissue origin of the tumor. Published in *Frontiers in Oncology* on March 15, 2023, the data reported states that Dkk-1 is significantly more likely to serve as a tumor suppressor in tumors arising from ectoderm and endoderm while the converse is true for mesodermal tumors. Patient survival data indicated high Dkk-1 expression is generally a poor prognostic indicator. These findings provide further support for the importance of Dkk-1 as a therapeutic cancer target in some cases. Texas A&M University System Health Science Center received a $864,971 CPRIT Academic Research grant (RP170496) in November 2016 to establish how Dkk-1 upregulates ALDH1A1 in human bone tumor cells and to examine how this knowledge can be employed to develop novel bone-preserving and anti-tumor strategies for MBD.

132. Some viruses restructure host chromatin, influencing gene expression, with implications for disease outcome. Whether this occurs for SARS-CoV-2, the virus causing COVID-19, is largely unknown. CPRIT Scholar Wenbo Li, Ph.D., associate professor, Department of Biochemistry and Molecular Biology, and fellow researchers from The University of Texas Health Science Center at Houston sought to understand the impacts of the pandemic-causing SARS-CoV-2 on host chromatin by comprehensively mapping the chromatin architectures of human cells after infection using high-throughput chromosome conformation capture (Hi-C) 3.0 and chromatin immunoprecipitation (ChIP-seq) methods. This widespread host chromatin restructuring was not found following common-cold-virus HCoV-OC43 infection. These findings, published in

Nature Microbiology on March 23, 2023, show that SARS-CoV-2 acutely rewires host chromatin, facilitating future studies of the long-term epigenomic impacts of its infection. Given the increasingly realized high incidence of post-acute SARS-CoV-2 sequelae (long COVID), understanding the viral impacts on host chromatin and epigenome will not only provide new strategies to fight SARS-CoV-2 in the acute phase, but also pave the way for unravelling the molecular basis of long COVID for its intervention. The University of Texas Health Science Center at Houston recruited Dr. Li from the University of California, San Diego in September 2016 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160083), received a $4.43 million Core Facility Support Awards grant (RP180734) in August 2018 to establish the UTHealth Cancer Genomics Core, and received a $4 million Research Training grant (RP210042) in May 2021.

133. The glucocorticoid receptor (GR) is an important anti-cancer target in lymphoid cancers but has been understudied in solid tumors like lung cancer. Liver Kinase B1 (LKB1) protein is the second most commonly mutated tumor suppressor in non-small cell lung cancer (NSCLC) after TP53. CPRIT Scholar Esra Akbay, Ph.D., assistant professor, Department of Pathology at The University of Texas Southwestern Medical Center, and colleagues set out to identify some of the most common oncogenic driver and tumor suppressor mutations. In this study, the team identified a dexamethasone-GR mediated anti-cancer response in a subset of aggressive NSCLCs that harbor Serine/Threonine Kinase 11 (STK11/LKB1) mutations. Using the potent GR agonist, dexamethasone (DEX), the team discovered that growth inhibition occurred in lung adenocarcinoma and squamous tumor lines with and without other oncogenic mutations such as KRAS. As reported in *Frontiers in Oncology* on March 23, 2023, GR agonists are potential anti-cancer agents against a subtype of NSCLC identified by loss of LKB1 function and high expression of CPS1. The expression of CPS1 and the LKB1/STK11 mutations provide a stable, readily identifiable biomarker for vulnerability identification in precision medicine protocols. As commercial panels continue to develop, identification of STK11 alterations will become more common leading to the identification of thousands of lung and cervical cancer patients who could potentially benefit from STK11 targeted therapy. The University of Texas Southwestern Medical Center recruited Dr. Akbay from the Dana-Farber Cancer Institute/Harvard Medical School in September 2016 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160080), and CPRIT grant (RP120732).

134. For patients with certain forms of blood cancers, such as acute lymphoblastic leukemia or B-cell non-Hodgkin Lymphoma, chimeric antigen receptor or CAR T-cell therapy can be a "miracle cure." Despite the extraordinary efficacy, some patients receiving CAR-T cell therapy, a form of immunotherapy, will experience serious, life-threatening side effects due to the lack of precise control over the dose, location, and timing of activity of the engineered T cells - "on-target, off-tumor" cytotoxicity. Researchers designed FDA-approved CAR T-cell therapies primarily to recognize the CD19 protein, which is abundantly expressed on the surface of cancer cells. However, the CD 19 protein is also present on normal B lymphocyte. CAR T-cell therapies lack the ability to discriminate between normal CD19-positive cells and CD19-positive tumor cells, which could lead to a common side effect known as B-cell aplasia, depletion of B-cells in the blood and a poor immune response to infections. Patients urgently need intelligent CAR T-cell-based therapies with precise spatial and temporal control over therapeutic activities. To address this issue, CPRIT Scholar Yun "Nancy" Huang, Ph.D., associate professor at the Center for Epigenetics and Disease Prevention, and Yubin Zhou, M.D., Ph.D., professor and Presidential Impact Fellow, both at Texas A&M University School of Medicine's Institute of Biosciences and Technology, engineered light-switchable, anti-CD19 CAR T-cells (LiCAR-T) that precisely mount anti-tumor immune responses in the dual presence of tumor antigen and light. As reported in the March 23, 2023, edition of *Nature Reviews Bioengineering*, the researchers built the LiCAR-T system upon engineered CAR T-cells that remain inactive without photo stimulation, but quickly restore their tumor-killing function when illuminated with blue light. To move this technology one step closer to real-world applications, the investigators overcame the limited depth of tissue penetration (less than 1 mm) of visible light by reengineering "upconversion" nanoparticles capable of capturing near infrared light that is invisible to human eyes and converting it into blue light. Clinicians can introduce the nanoparticles surgically or by injection. This near infrared light-tunable nano-optogenetic platform enables spatiotemporal control of CAR T-cell mediated cytotoxicity against both hematological

malignancies and solid tumors with tailored doses and duration, thereby greatly mitigating side effects associated with the current immunotherapy. Moreover, this research exemplifies the power of integrating multi-disciplinary approaches in biomedical research. The Texas A&M University System Health Science Center recruited Dr. Huang in 2014 with the support of a $1.8 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR140053). Texas A&M also received a $1.2 million Academic Research grant (RP180131) in 2018 and a $3.13 million Cancer Therapeutics Training Program grant (RP210043) in 2021.

135. Deoxyribonucleic acid (DNA) has been studied for decades yet researchers still lack a sufficient understanding of DNA and nucleosome mechanics to ascertain how these features combine with other factors to determine the structural and mechanical properties of higher-order structures. The objective of this study was to reproduce the mechanical properties of DNA and nucleosomes with a simple and computationally efficient mathematical model, with the compromise of relinquishing any attempt at reproducing the details of the chemical complexity of the system. CPRIT Scholar José Onuchic, Ph.D., professor, Department of Physics and Astronomy, Chemistry and Biosciences at Rice University, and colleagues developed a computationally efficient, easy-to-use, and widely editable chromatin model designed to address this challenge. The Widely Editable Chromatin Model (WEChroM) reproduces the complex mechanics of the double helix and is used to investigate the behavior of circular DNA in the presence of positive and negative supercoiling. The data, reported in *PLOS Computational Biology* on March 27, 2023, open the path to studying the structural and mechanical ensembles of genetic systems as large as tens of kilobases of chromatin, i.e., the size of mammalian genes. Dr. Onuchic was recruited by Rice University in 2011 from the University of California, San Diego with the support of a $6 million CPRIT Recruitment of Established Investigators grant (R1110).

136. Squamous cell carcinoma of the anus (SCCA) is a rare gastrointestinal cancer. Factors associated with progression of HPV infection to anal dysplasia and cancer are unclear and screening guidelines and approaches for anal dysplasia are less clear than for cervical dysplasia. In this study, CPRIT Scholar Andy Futreal, Ph.D., professor, Department of Genomic Medicine at The University of Texas MD Anderson Cancer Center, and colleagues aimed to identify differences in anal microbiome composition in the settings of HPV infection, anal dysplasia, and anal cancer. The team combined anal microbiome samples collected from two prospectively enrolled cohorts. The data, reported in *Frontiers in Immunology* on March 29, 2023, suggest an association between the anorectal microbiome among anal cancer development. This work highlights potential roles in an understudied disease that needs to be further explored. Implications of this work could include improved diagnostic tools for this rare and difficult to detect disease, especially among high-risk patients which could allow doctors to intervene early and prevent anal dysplasia and the progression to cancer. The University of Texas MD Anderson Cancer Center recruited Dr. Futreal in November 2011 with the support of a $7 million CPRIT Recruitment of Established Investigators grant (R1205).

137. All intracellular pathogens, such as bacteria or viruses, must accomplish entry into a new host cell. Apicomplexan parasites use an invasion machinery composed of specialized cytoskeletal complex and secretory organelles, known as the apical complex. The apical complex is essential for parasite motility, and for invasion into and egress from host cells, and includes the pathogens that cause malaria and toxoplasmosis. Its structure and mechanism of motion are poorly understood, which makes therapeutic intervention difficult. Cellular cryo-electron tomography (cryo-ET) is a powerful imaging technique, but the suitable thickness of biological samples is limited to a few hundred nanometers. Most intact eukaryotic cells are thicker than this. Therefore, previous cryo-ET studies of whole eukaryotic cells have imaged either naturally thin cell regions or cells that were compressed due to embedding in a thin layer of ice. Daniela Nicastro, Ph.D., professor, Department of Cell Biology, and colleagues at The University of Texas Southwestern Medical Center used cryo-FIB-milling and cryo-electron tomography to visualize the 3D-structure of the apical complex in its protruded and retracted states, overcoming the compression artifacts that occur when preparing intact cells in a thin layer of ice. These significant advances allowed them to interrogate the native structure of the conoid complex and its movements during retraction and protrusion. The data, published in *Nature Communications* on March 30, 2023, show that both the ultrastructure and

molecular organization of the protruded and retracted states of the conoid are indistinguishable, indicating the conoid fibers do not deform like a spring during conoid movements, and therefore do not provide energy to assist in either conoid motion or in secretion. Because this complex is essential for apicomplexan parasite infection, understanding the molecular basis of its function could reveal important new targets for therapeutic intervention for some of the world's most devastating diseases. The University of Texas Southwestern Medical Center received a $5.5 million CPRIT Core Facility Support Awards grant (RP170644) to support additional infrastructure to advance the Cryo-EM Core Facility (CEMF) and establish a Service for Single-Particle structure determination (SSP).

138. Non-enveloped viruses require cell lysis to release new virions from infected cells, suggesting that these viruses require mechanisms to induce cell death. Noroviruses are one such group of viruses, but there is no known mechanism that causes norovirus infection-triggered cell death and lysis. In this study, CPRIT Scholar Dustin Hancks, Ph.D., assistant professor, Department of Immunology; Tiffany A. Reese, Ph.D., assistant professor, Departments of Immunology and Microbiology; and colleagues at The University of Texas Southwestern Medical Center, identified a molecular mechanism of norovirus-induced cell death. The team found that the norovirus-encoded NTPase NS3 contains an N-terminal four-helix bundle domain homologous to the membrane-disruption domain of the pseudokinase mixed lineage kinase domain-like (MLKL). The data, published in *Nature* on March 29, 2023, suggest that noroviruses have acquired a host MLKL-like pore-forming domain to facilitate viral egress by inducing mitochondrial dysfunction. The University of Texas Southwestern Medical Center recruited Dr. Hancks in 2017 with the support of a $2 million Recruitment of First-Time, Tenure-Track Faculty Members grant (RR170047) and received a $900,000 CPRIT Individual Investigator grant (RP200118) in February 2020.

139. Endotype discovery based on gene expression profiles has revolutionized the understanding of cancer and individualized patient therapy. Researchers at Baylor College of Medicine and Texas Children's Hospital, in collaboration with the German Center for Infection Research, hypothesized that a similar approach could identify distinct and clinically relevant tuberculosis (TB) endotypes. The team applied unbiased clustering to identify separate tuberculosis endotypes with classifiable gene expression patterns and clinical outcomes and identified two main endotypes of the disease. They found that one endotype had a higher risk of treatment failure and death than the other. Using computer models, they then predicted what types of drugs could be used to treat each tuberculosis endotype. Their findings, published in the *European Respiratory Journal* in March 2023, could improve personalized treatment options for the disease in the future. "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 Andrew DiNardo, M.D., Ph.D., assistant professor, Department of Medicine-Infectious Diseases at Baylor and Texas Children's Hospital. Baylor College of Medicine received three CPRIT Academic Research, Core Facility Awards (RP170005, RP200504, RP210227) in 2016, 2020 and 2021 totaling $13 million to facilitate comprehensive multiomic studies in preclinical models and clinical tumor specimens and access to cutting-edge proteomics and metabolomics technologies and computational expertise.

140. Etoposide (ETO) is an anticancer drug that targets topoisomerase II (TOP2), an enzyme that plays a crucial role in the regulation of DNA topology. ETO stabilizes a normally transient TOP2–DNA covalent complex (TOP2cc), thus leading to DNA double-strand breaks (DSBs). Recent studies suggest that additional factors are required for TOP2cc repair, which include the protein associated with TDP2 and TOP2, named ZATT. In this study, Junjie Chen, Ph.D., professor and chair, Department of Experimental Radiation Oncology, and colleagues from The University of Texas MD Anderson Cancer Center, explored whether ZATT may alter the conformation of TOP2cc in a way that renders the accessibility of TDP2 for TOP2cc removal. The team reported genome-wide CRISPR screens revealed that ZATT also has a TDP2-independent role in promoting cell survival following ETO treatment. Several genes whose loss led to increased ETO sensitivity with ZATT loss are related to cell-cycle regulation and cell-cycle checkpoint control and further emphasized that the protein level of TOP2 is a key determinant of the cellular response to ETO treatment. These results, published in *International Journal of Molecular Sciences* on March 29, 2023, uncover a TDP2-independent function of ZATT, which may help in the devel-

opment of therapeutic strategies that improve ETO efficacy, and suggest that a tight and important regulation of TOP2 is important for cell proliferation. ZATT is a promising strategy to increase ETO efficacy for cancer therapy. The University of Texas MD Anderson Cancer Center received a $5.1 million CPRIT Academic Research grant (RP160667) in August 2016 to support investigation into ZATT as a synthetic lethal target of TOP-2 poison etoposide.

141. Some gastrointestinal health benefits from caffeine include decreased odds of ulcerative colitis and acute colitis development with *in vitro* and *in vivo* studies, reduced hepatic fibrosis in patients with mild to advanced hepatic fibrosis, and lower risk of developing colorectal cancer. Caffeine is known to enhance secretion of dopamine, serotonin, and acetylcholine in the central nervous system. While these effects could explain caffeine's neuropsychiatric effects, they do not readily explain caffeine's effects on cancer, cardiovascular disease, liver disease, and diabetes. In this cross-sectional study, Li Jiao, M.D., Ph.D., Department of Medicine at Baylor College of Medicine, and colleagues hypothesized that individuals with higher caffeine intake could have different microbial community composition and structure compared to those with lower caffeine intake. The team compared the community composition and structure of the colonic adherent microbiota based on caffeine intake using 16S rRNA gene sequencing among 34 individuals with endoscopically normal colons who donated 97 colonic biopsies. As reported in *Nutrients* on April 3, 2023, this cross-sectional study showed that the colonic mucosa-associated bacteria differed significantly in the community composition and structure based on daily caffeine and coffee intake in adults. Better knowledge of the association between caffeine and coffee intake and the gut microbiota may help refine dietary guidance. Baylor College of Medicine received an $899,131 CPRIT Individual Investigator Academic Research grant (RP140767) in 2014 to provide novel and crucially needed data on the combined role that diet, gut microbiota, and the TLR protein family play in colorectal adenoma risk.

142. In 2019, an estimated 1.3 million deaths were attributed to antibiotic resistant bacterial infections worldwide. Researchers at Baylor College of Medicine and colleagues have been studying the process that drives antibiotic resistance at the molecular level seeking to contribute a solution to this growing problem. The team reported in the journal *Molecular Cell* on March 24, 2023, crucial and surprising first steps that promote resistance to ciprofloxacin (cipro), one of the most commonly prescribed antibiotics. The findings point to potential strategies that could prevent bacteria from developing resistance, extending the effectiveness of new and old antibiotics. "We discovered that cipro triggers cellular stress responses that promote mutations. This phenomenon, known as stress-induced mutagenesis, generates mutant bacteria, some of which are resistant to cipro. Cipro-resistant mutants keep on growing, sustaining an infection that can no longer be eliminated with cipro," said co-corresponding author Susan M. Rosenberg, Ph.D., chair in the Department of Cancer Research and professor of Molecular and Human Genetics at Baylor College of Medicine. "Also, cipro breaks bacterial DNA in the same way that the anti-cancer drug etoposide breaks human DNA in tumors. We hope this may additionally lead to new tools to combat cancer chemotherapy resistance." The data demonstrate a critical node in ciprofloxacin-induced mutagenesis, imply RNAP-regulation of DNA-break repair, and identify promising targets for resistance-resisting drugs. Baylor College of Medicine received a $5.17 million CPRIT Core Facility Support Award (RP180672) in August 2018 with the goal to assist cancer researchers who study the interactions between cancer cells and their environment.

143. Rice University bioengineers are working to make sure that patient care is no longer hindered by missing crucial doses of medicines and vaccines. It is estimated that 50% of patients fail to take prescription medicine or take it incorrectly. The annual toll in the United States alone has been estimated at more than 100,000 deaths, up to 25% of hospitalizations and more than $100 billion in healthcare costs. CPRIT Scholar Kevin McHugh, Ph.D., assistant professor, Department of Bioengineering, and colleagues from Rice University have developed a next-level technology time-released capsule for the treatment of chronic disease. The novel technology, dubbed PULSED (Particles Uniformly Liquified and Sealed to Encapsulate Drugs), employs high-resolution 3-D printing and soft lithography to produce arrays of more than 300 nontoxic, biodegradable cylinders that are small enough to be injected with standard hypodermic needles. The team demonstrated four methods of loading the microcylinders with drugs and reported that they could adjust the PLGA recipe to vary how quickly the particles dissolved and released the drugs — from as little as 10 days to almost five weeks, as reported

in *Advanced Materials* on March 2, 2023. The PULSED system is a low-cost, promising platform for creating long-acting drug formulations which offers compatibility with crystalline and amorphous polymers, easily injectable particle sizes, and compatibility with several newly developed drug loading methods. "Our microparticles will stay where you put them," Dr. McHugh said. "The idea is to make chemotherapy more effective and reduce its side effects by delivering a prolonged, concentrated dose of the drugs exactly where they're needed." Rice University recruited Dr. McHugh in May 2019 from the Massachusetts Institute of Technology with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR190056).

144. Approximately 94% of the diagnosed cases of human papillomavirus (HPV)-attributed cancer in the U.S. each year can be prevented by the HPV vaccine. Texas ranks 47 out of the 50 U.S. states for HPV up to date (UTD) rates, with only 51.5% of adolescents aged 13 to 17 years UTD on the vaccine. Disparities are present between rural and urban vaccination rates, with adolescents living in rural non–metropolitan statistical areas having the lowest HPV vaccine UTD rates. Jane R. Montealegre, Ph.D., assistant professor, Department of Pediatrics, Hematology/Oncology at Baylor College of Medicine, and colleagues conducted a needs assessment to understand current clinical practices regarding HPV vaccination in rural East Texas primary health-care settings, assessing health-care providers' perceived barriers to HPV vaccination, as well as current strategies in place to address those barriers. As reported in *Vaccines* on March 25, 2023, survey respondents still recognized parental vaccine hesitancy as a barrier to HPV vaccination in their clinics and that face-to-face communication between the provider and parent remains the most effective strategy. Baylor College of Medicine received a $1.28 million CPRIT Prevention grant (PP190051) in August 2019 to significantly increase the proportion of adolescent patients within a network of safety net clinics who are protected by the HPV vaccine against HPV-associated cancers.

145. Acute myeloid leukemia (AML) is an aggressive malignancy that causes uncontrolled accumulation of white blood cells with poor outcomes. Researchers at Baylor College of Medicine and collaborating institutions reported in *Cancer Research* on April 1, 2023, a new vulnerability of this cancer that can be targeted with a class of experimental drugs. These drugs target a protein complex called SWI/SNF, which many cells use to make DNA more open and accessible. "AML is typically very hard to treat. The rapid tumor regression we saw in response to SWI/SNF inhibitors has encouraged us to continue our research into similar vulnerabilities of AML and other cancers," said CPRIT Scholar H. Courtney Hodges, Ph.D., assistant professor, Department of Molecular and Cellular Biology. The robust regression of leukemic burden seen over a short 2-week treatment period suggests a considerable therapeutic window in immunocompetent settings for some patients and provides a compelling justification for continued study of SWI/SNF inhibitors in the treatment of AML. Baylor College of Medicine recruited Dr. Hodges in 2017 from the Stanford University College of Medicine with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR170036), and received a $5.17 million Core Facility Support Awards grant (RP180672) in 2018. The University of Texas MD Anderson Cancer Center received a $5.9 million Core Facility Support Awards grant (RP120348) in 2011.

146. Improved therapies for glioblastoma (GBM) are desperately needed and require preclinical evaluation in models that capture tumor heterogeneity and intrinsic resistance seen in patients. Targeted therapy for molecularly defined subsets of GBM has been tested extensively but is largely met with drug resistance and minimal improvements in survival. Lysine-specific demethylase 1 (LSD1/KDM1A) is amongst the chromatin modifiers implicated in stem cell maintenance, growth and differentiation. Joya Chandra, Ph.D., Department of Pediatrics at The University of Texas MD Anderson Cancer Center, and colleagues performed RNA-seq to identify genes and biological processes associated with inhibition. Efficacy of various LSD1 inhibitors was assessed in nine patient-derived glioblastoma stem cell (GSC) lines and an orthotopic xenograft mouse model. The results, reported in *Frontiers in Neurology* on April 4, 2023, identified five genes that correlate with resistance to LSD1 inhibition in treatment resistant GSCs, in GSK-LSD1 treated mice, and in GBM patients with low LSD1 expression. This evaluation of pharmacological LSD1 inhibition suggests the need for future investigations of brain penetrant LSD1 inhibitors alone, or in combination with other therapeutic approaches to synergize efficacy for GBM. Salarius Pharmaceuticals LLC received a $16.1 million CPRIT Product Development Research grant (DP160014) in May 2016

to support the development of novel drugs for rare pediatric cancers and other cancers by focusing on treatments that interrupt the final steps of the signaling cascade.

147. Researchers from The University of Texas Southwestern Medical Center determined the shape of a nuclear protein implicated in cancer that acts on a family of enzymes involved in regulating RNA stability. As reported in *Science Advan*ces on April 5, 2023, the team discovered that although two forms of the BCCIP protein – alpha (α) and beta (β) – are virtually identical, only one of them appears to affect the FAM46 enzymes, and that's due to a folding mechanism that researchers had never encountered. Malfunction of the FAM46 proteins is associated with a number of diseases and loss-of-function mutation of FAM46C occurs frequently in multiple myeloma. The team used cryo-electron microscopy (cryo-EM), as well as the more traditional X-ray crystallography which revealed the details of the BCCIPα-FAM46 interaction. "Determining the structure of a protein is of fundamental importance to understanding how proteins interact, their role in diseases and disorders, drug design, and more," said CPRIT Scholar Xiaochen Bai, Ph.D., associate professor, Department of Biophysics and Cell Biology. The University of Texas Southwestern Medical Center recruited Dr. Bai in 2016 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members (RR160082). The University of Texas Southwestern Medical Center received a $5.49 million CPRIT Core Facility Support Awards grant (RP170644) in 2017.

148. Despite evidence demonstrating an overall survival benefit, the addition of metastasis-directed therapy (MDT) to hormone therapy for oligometastatic prostate cancer, to date, has not been evaluated in a randomized clinical trial. In this Phase II randomized basket trial, EXTEND, principal investigator Chad Tang, M.D., associate professor, Department of Radiation Oncology at The University of Texas MD Anderson Cancer Center, and colleagues set out to determine whether the addition of MDT to intermittent hormone therapy improves oncologic outcomes and preserves time with eugonadal testosterone compared with intermittent hormone therapy alone in men with oligometastatic prostate cancer. The data, published in *JAMA Oncology* on April 6, 2023, included 87 men and median follow-up was 22.0 months. Progression-free survival was improved in the combined therapy arm compared with the hormone therapy only arm. Combination of MDT with intermittent hormone therapy was well-tolerated and lengthened the period men could maintain a break from hormone therapy without progression, suggesting this approach could improve the quality of life for men with advanced prostate cancer. The University of Texas MD Anderson Cancer Center received a $2.4 million CPRIT Individual Investigator Research Awards for Clinical Translation grant (RP180140) in February 2018 to gain insight into the basic biology of oligometastatic disease and the effects of aggressive therapy on the entire body.

149. Multiple myeloma (MM) is the second most common hematological malignancy. In 2022, the National Cancer Institute indicated about 34,470 new cases were diagnosed with MM, and about 12,640 deaths are estimated in the United States, with a 57.9% 5-year survival rate. Understanding molecular mechanisms of the cell-signaling pathway in MM cells and the interaction of MM cells with their bone marrow microenvironment has led to the development of novel therapies. Bortezomib (BTZ) is a gold-standard treatment for MM; however, its efficacy is limited by off-target dose-limiting side effects. Researchers, including CPRIT Scholar Abdel Kareem Azab, Ph.D., Department of Biomedical Engineering at The University of Texas Southwestern Medical Center, recently developed tumor-associated endothelial cells (TAECs)-targeted nanoparticles, which improve efficacy and reduce the side effects of BTZ in MM. In an article published in *Blood Cancer Journal* on April 7, 2023, the researchers reported that nanoparticle delivery systems were shown to be capable of targeting large doses of therapy into the target area while sparing healthy tissues. The team developed E-selecting/TAECs/TME-targeting lipid nanoparticles (Lipo E-X), which improved therapeutic efficacy and reduced the off-target side effects of BTZ and enhanced its therapeutic index, as a potential solution to the dose-limiting side effects observed clinically and experimentally when using BTZ as a free drug. The University of Texas Southwestern Medical Center recruited Dr. Azab in May 2022 with the support of a $2 million CPRIT Recruitment of Rising Stars grant (RR220088).

150. The blood-brain barrier (BBB) is a protective barrier that controls the entry of endogenous and foreign substances in the central nervous system from the bloodstream. Anesthetics like isoflurane alter the structure of cell membranes in the

brain, making it easier for certain substances to pass through the BBB and potentially cause harm. Clinical implications may arise when potentially neurotoxic drugs gain enhanced access to the central nervous system under inhalational anesthetics. Ulrich Bickel, M.D., professor and associate dean, Department of Pharmaceutical Sciences, and colleagues at the Texas Tech University Health Sciences Center, studied the effects of isoflurane and sevoflurane, two commonly used anesthetics, on the fluidity of lipid membranes and the permeability of the BBB. The data, published in *The Journal of Pharmacology and Experimental Therapeutics* on May 1, 2023, found that these anesthetics caused an increase in the permeability of the BBB in mice, which suggests that they may make it easier for harmful substances to enter the brain. Texas Tech University Health Sciences Center received a $2.83 million Core Facility Support Awards grant (RP200572) in August 2020 to enhance the quality of obtainable data in ongoing and future cancer research projects with the addition of three cutting edge instruments.

151. CPRIT Scholar Thomas Yankeelov, Ph.D., professor, Department of Biomedical Engineering, Diagnostic Medicine, and Oncology, and David Hormuth, Ph.D., Center for Computational Oncology, both from The University of Texas at Austin, and colleagues are developing a web-based tool called MIRACCL (molecular and imaging response analysis of co-clinical trials) to help manage and analyze data generated from patient-derived xenograft (PDX) models of cancer. PDX models have shown promise in replicating much of the biology and treatment responses of the matched tumors-of-origin. However, a major challenge in co-clinical trials is how to manage, integrate, and analyze the abundance of data generated across both spatial and temporal scales, as well as across species. MIRACCL leverages the wealth of PDX-related and clinical data, the robust informatics capabilities of LinkedOmics, and the high-quality displays enabled in ePAD to provide an intuitive, easy-to-use, and analytically robust tool, thus removing the need to involve multiple specialists. As reported in *MDPI Tomography* on April 10, 2023, the researchers simulated data for a co-clinical trial in triple-negative breast cancer (TNBC) for prototyping and cross-referenced image features derived from datasets to "omic" data to evaluate MIRACCL's functionality. Once completed, the MIRACCL platform will provide users with integrative analyses of pre-clinical PDX-based trials, clinical trials, and co-clinical trials, in which imaging features can be integrated with molecular "omic" data to address treatment response assessment and prediction, as well as possible mechanisms of treatment resistance. The University of Texas at Austin recruited Dr. Yankeelov in 2015 from Vanderbilt University with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR160005). The University of Texas at Austin was awarded a $1.2 million Academic Research grant (RP220225) in 2022. Baylor College of Medicine received two CPRIT Core Facility Support Awards grants (RP170691, RP220646) in 2017 and 2022 totaling $8.76 million.

152. As we age, genetic mutations can accumulate in our non-cancerous tissues. Some of these mutations, called somatic mutations, can potentially increase the risk of developing cancer or other diseases. In this study, CPRIT Scholar Yujin Hoshida, M.D., Ph.D., director of the Liver Tumor Translational Research Program and Hao Zhu, M.D., professor, Pediatric Research, Internal Medicine - Hematology/Oncology at The University of Texas Southwestern Medical Center, and colleagues developed an *in vivo* lineage tracing platform to identify whether somatic mutations play a role in adaptive cellular or organismal responses in chronic liver disease. The researchers developed a tool called MOSAICS that can identify somatically mutated clones that are positively selected in chronic liver disease. They used this tool to identify genes that modify hepatocyte fitness in the context of fatty liver disease in a high-throughput manner. The study, published in *Cell* on April 10, 2023, found that MOSAICS selected for mutations that ameliorate lipotoxicity (which triggers cellular distress and dysfunction), including mutant genes identified in human nonalcoholic steatohepatitis (NASH). The study concluded that positive selection of mutant clones in MOSAICS mice and in human tissues is an effective way of identifying metabolic disease regulators and therapeutic targets. The University of Texas Southwestern Medical Center recruited Dr. Hoshida from the Icahn School of Medicine at Mount Sinai in 2018 with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR180016). The University of Texas Southwestern Medical Center was awarded a $237,501 CPRIT High Impact/High Risk grant (RP220614) in September 2022 to establish the mechanistic basis for exploiting immunotherapy in cancer prevention.

153. Researchers, including CPRIT Scholar Andre Catic, M.D., Ph.D., assistant professor, Huffington Center on Aging at Baylor College of Medicine, have discovered that a mutation in a protein called SKD3, which is important for maintaining protein quality control in animal cells, can cause a genetic disease known as 3-methylglutaconic aciduria (MGCA7). The protein SKD3 belongs to a family of proteins called unfoldases, which are found in many organisms, including humans. SKD3 performs a vital function by removing damaged proteins in structures inside cells thus maintaining the integrity of these organelles. As reported in the journal *Nature Communications* on April 11, 2023, the team focused on the unfoldase present in humans, which can cause MGCA7 when mutated. This work provides evidence that SKD3 is a central player in maintaining protein quality control in mitochondria. Failure of the protein quality control machinery to clear misfolded proteins results in toxic forms of defective proteins, which are characteristics of many human diseases. Baylor College of Medicine recruited Dr. Catic in 2014 from Harvard University with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR140038).

154. Lung adenocarcinomas (LUADs) are a type of lung cancer that can display different structures and characteristics. Scientists do not fully understand how these differences reflect tumor evolution and disease progression. To better understand this morphology, CPRIT Scholar Peter Van Loo, Ph.D., professor, Departments of Genetics and Genomic Medicine at The University of Texas MD Anderson Cancer Center, and colleagues from the UK integrated whole-exome sequencing data generated from 805 primary tumor regions and 121 paired metastatic samples across 248 LUADs from the TRACERx 421 cohort, together with RNA-sequencing data from 463 primary tumor regions, with detailed whole-tumor and regional histopathological analysis. The data, published in *Nature Medicine* on April 12, 2023, provide insights into the relationship between LUAD morphology, the underlying evolutionary genomic landscape, and clinical and anatomical relapse risk. The study also revealed that certain types of LUADs are associated with a higher risk of relapse and metastasis, which could have important implications for treatment decisions and patient outcomes. The University of Texas MD Anderson Cancer Center recruited Dr. Van Loo in 2020 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR210006).

155. Esophageal adenocarcinoma (EAC) is a highly lethal cancer that can develop from a pre-cancerous condition called Barrett's esophagus. Extrachromosomal DNA (ecDNA), a type of DNA found outside the chromosomes in the cell, drives the growth of tumors and their resistance to treatment. It is not clear whether ecDNA is a later result of genetic instability or whether it is an early event in the transition from pre-cancerous conditions to cancer. To better understand the development of ecDNA, CPRIT Scholar Sihan Wu, Ph.D., assistant professor, Children's Medical Center Research Institute at The University of Texas Southwestern Medical Center, and fellow researchers analyzed whole-genome sequencing (WGS) data from patients with EAC or Barrett's esophagus, which included 206 biopsies in Barrett's esophagus surveillance and EAC cohorts from Cambridge University. The research, published in *Nature* on April 12, 2023, found that the prevalence of ecDNA increased from 24% to 43% in early- versus late-stage esophageal cancer, indicating the continual formation of the DNA circles during cancer progression. They also found that 33% of people with Barrett's esophagus who developed esophageal cancer had ecDNA in their precancerous cells. The University of Texas Southwestern Medical Center recruited Dr. Wu in 2021 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR210034).

156. The evolution of new traits enables expansion into new ecological and behavioral niches. However, demonstrated connections between divergence in protein structure, function and lineage-specific behaviors remain rare. In this study, Ryan Hibbs, Ph.D., Departments of Neuroscience and Biophysics at The University of Texas Southwestern Medical Center, and colleagues showed that both octopus and squid use cephalopod-specific chemotactile receptors (CRs) which allow them to sense and respond to specific chemical cues in their surroundings. Although the receptors serve a common purpose in environmental perception, the structural differences reflect the adaptations of octopus and squid to their distinct marine environments and behavioral requirements. The researchers identified the founding member of squid CRs that detect soluble bitter molecules, which play an important role in the context of ambush predation, where the

squid relies on sensing specific molecules to advance its predatory behavior. The team compared the structure of squid CRs with those found in octopuses and nicotinic receptors. The results provide insights into the evolutionary adaptations and functional variations of these receptors in different marine environments and predatory strategies. This analyses, published in *Nature* on April 12, 2023, shows how changes in protein structure can drive the diversification of traits and behavior. The University of Texas Southwestern Medical Center was awarded a $5.5 million CPRIT Core Facility Support Awards grant (RP170644) in August 2017 to advance the Cryo-EM Core Facility and establish a Service for Single-Particle structure determination.

157. Chemotactile receptors (CRs) are a cephalopod-specific innovation that allow octopuses to explore the seafloor via 'taste by touch.' In this study, Ryan Hibbs, Ph.D., Departments of Neuroscience and Biophysics at The University of Texas Southwestern Medical Center, and colleagues presented the cryo-electron microscopy structure of an octopus CR and compared it with nicotinic receptors to determine features that enable environmental sensation versus neurotransmission (communication between cells). They found that while the basic structure for passing ions and transmitting signals is similar, the part of the receptor that detects specific molecules is subject to change and evolution, allowing the octopus to adapt to new environments and discover new things. This research, published in *Nature* on April 12, 2023, provides insights into how evolutionary changes at the atomic level can lead to new behaviors in organisms. The University of Texas Southwestern Medical Center was awarded a $5.5 million CPRIT Core Facility Support Awards grant (RP170644) in August 2017 to advance the Cryo-EM Core Facility and establish a Service for Single-Particle structure determination.

158. The insulin receptor (IR) family controls metabolic homeostasis and cell growth. Distinct from IR, whose activation requires ligand binding, insulin receptor-related receptor (IRR) is activated by alkaline pH. However, how this activation works remains unclear. Here, Xiao-chen Bai, Ph.D., Departments of Biophysics and Cell Biology at The University of Texas Southwestern Medical Center, and fellow researchers presented cryo-EM structures of human IRR in both neutral pH inactive and alkaline pH active states. Combined with mutagenesis (genetic modification) and cellular assays, the team showed that the protein IRR undergoes a structural change in response to changes in pH. When the pH increases, specific motifs within IRR that are sensitive to pH experience electrostatic repulsion, causing the protein to transition from an autoinhibited state to an active state. This activation involves a scissor-like rotation between protein subunits, ultimately leading to the adoption of a T-shaped conformation that is associated with the active, functional form of the protein. As reported in *Nature Structural & Molecular Biology* on April 13, 2023, this study reveals an unprecedented alkaline pH-dependent activation mechanism of IRR, opening up opportunities to understand the structure–function relationship of this important receptor. Understanding how IRR works could help scientists develop new ways to treat diseases related to metabolism and growth. The University of Texas Southwestern Medical Center received a $5.5 million CPRIT Core Facility Support Awards grant (RP170644) in August 2017 to advance the Cryo-EM Core Facility and establish a Service for Single-Particle structure determination.

159. As reported in the journal *JAMA Oncology* on April 6, 2023, the phase II EXTEND (External Beam Radiation to Eliminate Nominal Metastatic Disease) trial has shown that the addition of metastasis-directed therapy to intermittent hormone therapy improved progression-free survival in patients with oligometastatic prostate cancer. In the trial, 87 patients with no more than five metastases who had received hormone therapy for at least 2 months were randomly assigned to receive metastasis-directed therapy consisting of definitive radiation therapy to all sites of disease and intermittent hormone therapy or hormone therapy alone. Corresponding author Chad Tang, M.D., Department of Radiation Oncology at The University of Texas MD Anderson Cancer Center, and colleagues found that progression-free survival was significantly improved with combination treatment compared with hormone treatment only in men with oligometastatic prostate cancer. They concluded that the combination of metastasis-directed therapy with intermittent hormone therapy may allow for excellent disease control. The findings could also pave the way for future clinical trials testing various combination therapies to improve outcomes in this patient population. The University of Texas MD Anderson Cancer Center received a $1.5 million CPRIT Early Clinical Investigator grant (RP200669) in August 2020 and a $2.4 million CPRIT Academic

Research grant (RP180140) in February 2018 to build upon this trial and conduct a larger randomized clinical trial and to gain insight into the basic biology of oligometastatic disease and the effects of aggressive therapy on the entire body.

160. Studies have shown that the available HPV vaccines reduced cervical cancer incidence by 90% in fully vaccinated girls and young adults. However, approximately 80% of eligible individuals (male and female) are not up to date on this vaccination series. Abbey Berenson, M.D., Ph.D., professor, Departments of Obstetrics & Gynecology and Pediatrics and fellow researchers from The University of Texas Medical Branch at Galveston set out to determine predictors of incomplete HPV vaccination among individuals aged 27–45 in the U.S. This retrospective cohort study used multilevel multivariable logistic regression models for data on 7,662 individuals identified as being fully or partially vaccinated against HPV, nested within 3,839 neighborhoods across the U.S. The results, published in *Vaccines* on April 10, 2023, revealed that the odds of not completing the HPV vaccine series included participants older than 30 years of age and participants living in South-region neighborhoods of the U.S. compared with those residing in Northeast-region neighborhoods. This study revealed that interventions to improve HPV vaccination series completion rates for this age group should take into consideration both individual and contextual factors. The University of Texas Medical Branch at Galveston received a $2 million CPRIT Prevention grant (PP200005) in February 2020 to provide up-to-date, accurate, and credible data to inform the design of programs and interventions to address the high rate of incomplete HPV vaccine series.

161. Renal cell carcinoma (RCC) is the most common type of kidney cancer. Most patients are treated with immunotherapy, but nearly 30% will eventually develop brain metastases. In this study, researchers from The University of Texas MD Anderson Cancer Center, including co-author Nicolas Navin, Ph.D., created the largest single-cell atlas of brain metastases from RCC enabling the discovery of key biological mechanisms driving an immunosuppressive tumor microenvironment in the brain distinct from that of the kidney or other metastatic sites. Findings were presented on April 18, 2023, at the American Association for Cancer Research (AACR) Annual Meeting. The study, led by Elshad Hasanov, M.D., Ph.D., medical oncology fellow at MD Anderson, reported that RCC is more difficult to treat when it metastasizes to the brain compared to other sites. "We've seen systemic therapies work in treating primary tumors and other metastatic sites, but they are not as effective for brain metastases," Dr. Hasanov said. "We now see it's not just because of the blood-brain barrier, but it also is due to interactions between the tumor and other immune and stromal cell populations, creating an immunosuppressive microenvironment in the brain that allows tumors to somehow escape immunotherapy." This data helps to identify potential therapeutic targets and to work toward designing therapies that can improve patient outcomes. The University of Texas MD Anderson Cancer Center received a $4.9 million CPRIT Core Facility Support Awards grant (RP180684) in August 2018 to establish an Integrated Single Cell Genomics (SCG) Core Facility.

162. Carbon-nitrogen bonds (C–N bonds) are one of the most abundant bonds in organic chemistry and biochemistry; however, the direct use of common raw materials used in the mass production of chemical products to form C-N bonds remains challenging. CPRIT Scholar Julian West, Ph.D., assistant professor of chemistry, and colleagues at Rice University uncovered a visible-light-induced, iron-catalyzed method to prepare carbon-nitrogen bonds, which are useful precursors to pharmaceuticals and other chemical products. Building on prior research, Dr. West and his team use "a super-cheap, abundant and nontoxic iron catalyst, iron nitrate, we pull off the acid, and then we stick nitrogen on, which works for a bunch of really different molecules. The thing that's really cool about it is that a lot of drug molecules — or things that can affect health — have carboxylic acids, which means this approach is a useful tool to tweak and optimize bioactive molecules." The results were published in *Chem Catalysis* on April 12, 2023. 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).

163. Epoxide ring-opening reactions are a common chemical process used to produce alcohol products that are valuable in many subfields of chemistry. However, the hydrogenative opening of epoxides (a chemical reaction in which an epoxide molecule reacts with hydrogen gas in the presence of a metal catalyst) via ionic means remains challenging because

of harsh conditions and reactive hydride nucleophiles. CPRIT Scholar Julian West, Ph.D., assistant professor of chemistry, and colleagues at Rice University developed a method to prepare alcohol products from epoxides by using vitamin B12 and thiol-enabled hydrogen atom transfer. As reported in *Cell Reports Physical Science* on April 19, 2023, the new reaction pathway can produce the desired alcohol compounds under extremely mild conditions, using only visible light and ethanol or methanol and water solution as solvents. The development of this reaction marks the first demonstration of synergistic VB12 photocatalysis and thiol HAT catalysis, and the team is actively investigating new applications of this powerful system. 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).

164. A major goal in structural biology is to understand protein assemblies in their natural, biologically relevant states. By doing this, scientists can learn more about how proteins function in our bodies and how they can be targeted with drugs to treat diseases. CPRIT Scholar David Taylor, Ph.D., Department of Molecular Biosciences, and colleagues from The University of Texas at Austin used AlphaFold2 (AF2) (an artificial intelligence system that can predict three-dimensional structures of proteins from amino acid sequences with atomic-level accuracy) structure predictions to determine whether they match native protein conformations. The team compared intramolecular distance restraints, an important tool for modeling and simulating the behavior of molecules in biological systems, to the AF2-predicted structures of the 100 most cross-linked proteins identified by mass spectrometry. The team hoped that by doing this, they would have the power to detect biologically active structural conformations, which can then be used to design drugs that target specific structural features of proteins involved in disease processes. The findings, published in *Communications Biology* on April 15, 2023, suggest that while there is a high concordance between their cross-links and AF2 structure predictions, they observed violations between domains of multidomain proteins (proteins with multiple distinct structural regions) and those undergoing substantial conformational changes. These situations may introduce complexities or discrepancies that need to be considered when interpreting the structural data. Overall, this combination of AF2 and cross-linking data can add confidence to the models, guide their interpretation, and may also serve as a valuable complement to other approaches, such as cryo-electron tomography, for illustrating proteins' endogenous structures. The University of Texas at Austin recruited Dr. Taylor from the University of California, Berkeley, in 2016 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160088).

165. Polyploidy, the duplication of the entire genome within a single cell, is a significant characteristic of cells in many tissues, including the liver. The quantification of hepatic ploidy typically relies on flow cytometry and immunofluorescence (IF) imaging, which are not widely available in clinical settings due to high financial and time costs. To improve accessibility for clinical samples, CPRIT Scholar Yujin Hoshida, M.D., Ph.D., director, of the Liver Tumor Translational Research Program, and colleagues at The University of Texas Southwestern Medical Center developed a computational algorithm to quantify hepatic ploidy using hematoxylin-eosin (H&E) histopathology images, which are commonly obtained during routine clinical practice. The algorithm, as reported in *MDPI Genes* on April 16, 2023, uses a deep learning model to first segment and classify different types of cell nuclei in H&E images, which then determines cellular ploidy and nuclear ploidy. The researchers have developed a publicly accessible website which implements hepatic ploidy analysis on human H&E images. This is the first successful attempt to automate ploidy analysis on H&E images and is expected to serve as an important tool for studying the role of polyploidy in human liver disease. The University of Texas Southwestern Medical Center received 5 CPRIT Academic Research grants (RP190107, RP180805, RP230330, RP220614, RP230363) totaling $9 million. The University of Texas Southwestern Medical Center recruited Dr. Hoshida from the Icahn School of Medicine at Mount Sinai in 2018 with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR180016).

166. Proximal tubules, which help to filter and remove waste products from the body, are constantly challenged by foreign substances during the lifespan. Cells in the proximal tubules of the kidney, however, do not divide to create new cells. In mild injury or disease, kidney cells have limited repair capabilities, and stem cells in the kidney can form new kidney cells, but only up to a point. Researchers from The University of Texas at Dallas, including Jie Zheng, Ph.D., professor,

Departments of Chemistry and Biochemistry in the School of Natural Sciences and Mathematics, discovered a previously unknown "housekeeping" process in kidney cells that ejects unwanted content, which results in cells that rejuvenate themselves. The study, published in *Nature Nanotechnology* on April 17, 2023, explains how this self-renewal process helps kidneys remain healthy for a lifetime. "In the field of nanomedicine, we want to minimize accumulation of nanoparticles in the body as much as possible. We don't want them to get stuck in the kidneys, so it's very important to understand how nanoparticles are eliminated from the proximal tubules," Zheng said. "Also, if we could learn how to regulate or monitor this self-renewal process, we might find a way to keep kidneys healthy in patients with high blood pressure or diabetes." The University of Texas at Dallas received a $900,000 CPRIT Academic Research grant (RP200233) in February 2020 to advance CT and fluorescence imaging of kidney cancers with glutathione-mediated contrast enhancements.

167. Protein turnover plays a key role in maintaining protein homeostasis. It is important to healthy biological functioning and is often dysregulated in diseases. In this study, William K. Russell, Ph.D., Department of Biochemistry and Molecular Biology at The University of Texas Medical Branch at Galveston, and fellow researchers sought to develop an approach to compute protein turnover from partial isotope profiles. The team provided theoretical formulas for the time courses of six mass isotopomers. The formulas are utilized to determine label enrichment, followed by protein turnover rate estimations. The approach with slow and fast turnover proteins. The results, published in *Communications Chemistry* on April 17, 2023, indicate that the approach taken in this work improved the goodness-of-fit (GOF) characteristics of the protein turnover model in various tissue types with slow (heart, muscle) and fast (liver, kidney) protein turnover tissues. The implemented tool, d2ome + , is publicly available. It increases the proteome coverage in protein turnover studies using heavy water metabolic labeling and LC-MS. The team expects that it will be useful to a broader community as a data processing tool and promote the applications of the heavy water labeling platform for protein turnover studies. The University of Texas Medical Branch at Galveston received a $3.55 million CPRIT Core Facility Support Awards grant (RP190682) in August 2019 for a targeted proteomics and metabolomics mass spectrometry core facility.

168. Metabolism reprogramming is recognized as one of the hallmarks of human cancers. In general, tumor cell metabolism features activate biosynthetic pathways to support oncogenic growth. Tumor cells also strengthen defense mechanisms against various environmental or internal insults, which can be a consequence of activated metabolism. However, cellular metabolism is highly plastic and adaptive, making tumor metabolism challenging to target therapeutically. Researchers from The University of Texas MD Anderson Cancer Center, including Ziheng Chen, Ph.D., Department of Genomic Medicine, identified unique differential dependency on mitochondrial complex I activity among human pancreatic ductal adenocarcinoma (PDAC) cells and found that upregulation of peroxisome-derived ether phospholipids enabled PDAC cells to adapt to and survive mitochondrial complex I inhibition. As reported in *Nature Communications* on April 17, 2023, the researchers further demonstrated a direct relationship between the regulation of mitochondrial ROS (reactive oxygen species) and lipid peroxidation that affects tumor cell viability. This information could be used to develop new strategies to effectively kill PDAC cells by targeting multiple aspects of mitochondrial metabolism. The University of Texas MD Anderson Cancer Center received a $4 million CPRIT Research Training grant (RP210028) in May 2021 to instruct postdoctoral fellows for careers in translational cancer research.

169. Neoadjuvant chemotherapy (NAC), also known as preoperative chemotherapy, was initially administered in inflammatory or locally advanced breast cancers to reduce the size of inoperable tumors and make them operable or make breast conservation possible in cases that would otherwise require a mastectomy. Circulating tumor cells (CTCs) and cancer-associated macrophage-like cells (CAMLs) in the blood can be used as potential biomarkers for predicting pathological complete response (pCR) before resection. To study these rare cancer-associated cells, co-corresponding author Siva Vanapalli, Ph.D., professor and chair, Department of Chemical Engineering, and colleagues at the Texas Tech University conducted a preliminary study where blood from patients was collected before, during, and after NAC, and Labyrinth microfluidic technology was used to isolate CTCs and CAMLs. The data, published in *Bioengineering* on April 18, 2023, showed that increased CAMLs in circulation after treatment combined with lowered CTCs was associated with pCR. The

CTC–CAML interaction is likely to become increasingly relevant as newer immunotherapies arise. The Labyrinth microfluidic technology offers a promising venue for comprehensive profiling of cancer-associated cells that can be leveraged to answer several relevant clinical questions. Texas Tech University received a $657,000 CPRIT Academic Research grant (RP190658) in August 2019 to engineer A label-free isolation and staining-free detection technology.

170. The human endometrium, the mucous membrane that lines the uterus, has a unique ability to regenerate its lining, which is of paramount importance for a woman's reproductive health. However, the vital factors that control this early endometrial programming are not well understood. Researchers from Baylor College of Medicine and collaborating institutions investigated factors directing uterine remodeling to provide new insights into fertility-associated gynecological conditions. "In this study, we looked to understand the role Beclin-1 plays in endometrial reprogramming for the successful establishment of pregnancy," said corresponding author Ramakrishna Kommagani, Ph.D., associate professor, Department of Pathology at Baylor College of Medicine. As reported in *Developmental Cell* on April 10, 2023, the researchers found that when the team removed Beclin-1 specifically from uterine cells, the uteri did not develop properly, and this led to infertility caused by reduced uterine receptivity and failed embryo implantation. However, when Beclin-1 was restored, the uterus developed normally, suggesting that Beclin-1 is a key factor in the early programming of the uterus which helps to maintain its regenerative ability. Baylor College of Medicine received a $5.17 million CPRIT Core Facility Support Award CPRIT (RP180672) in August 2018 to purchase high-end equipment that will help identify new therapeutic targets and the generation of novel drugs.

171. A team of researchers at Baylor College of Medicine, including CPRIT Scholar Eric Van Nostrand, Ph.D., assistant professor, Department of Biochemistry at Baylor College of Medicine, has developed a new powerful resource to study extracellular RNA (exRNA), a novel form of cell-to-cell communication. In this study, published in *Cell Genomics* on April 20, 2023, researchers applied computational analyses to identify extracellular RNA binding proteins (exRBPs) in plasma, serum, saliva, urine and cerebrospinal fluid. The computational predictions were validated experimentally at about 80% in both plasma and cell cultures in the lab and shed light on the role of RBPs as exRNA carriers across human biofluids. Using this information, the team developed a map of candidate exRBPs and their exRNA cargo in bodily fluids that can be used to track normal and disease processes which is available at no cost to the scientific community. The extended exRNA Atlas resource and results of their analyses lay a foundation for the development of a new class of biomarkers. Baylor College of Medicine recruited Dr. Van Nostrand in May 2020 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR200040).

172. Anaplastic thyroid cancer (ATC) is a lethal cancer which often results from a transformation of pre-existing differentiated thyroid cancer. Researchers led by Jennifer Rui Wang, M.D., Ph.D., and Stephen Y. Lai, M.D., Ph.D., The University of Texas MD Anderson Cancer Center, investigated this transformation using single-cell transcriptomes and genetic alteration data from patients with different thyroid cancer subtypes to create a model that tracks the evolution of ATC progression. The data, published on April 23, 2023, in the *Journal of Clinical Investigation*, showed that during the terminal stages of ATC progression, mATC tumor cells excessively over-produce collagen family members and are highly active in promoting cellular interactions. These discoveries provide further insights into cell-cell signaling in the tumor microenvironment during ATC transformation and shed light on the development of new therapeutic strategies to improve patient survival and quality of life. The University of Texas MD Anderson Cancer Center received a $4.9 million CPRIT Core Facility Support Awards grant (RP180684) in August 2018 to establish an Integrated Single Cell Genomics (SCG) Core Facility at The MD Anderson Cancer Center to provide cutting-edge technologies for single cell sequencing and bioinformatics support; and a $900,000 Academic Research grant (RP170366) in November 2016 to assess tumor metabolism.

173. Conventional mono- and combination chemotherapy are often ineffective due to high cytotoxicity, poor solubility, rapid blood clearance, and undesired side effects to healthy cells or tissues. To address these limitations, researchers are using tiny particles called nanomedicines to deliver the drugs. But there is still a need for a better way to deliver multiple

drugs at once. Focusing on this issue, co-corresponding author Subhash Chauhan, Ph.D., professor, Department of Immunology and Microbiology at The University of Texas Rio Grande Valley, and colleagues proposed to synthesize a fluorescence resonance-energy transfer (FRET) pair-based, stimuli-responsive drug-drug conjugate. The efficient FRET-based donor-acceptor system is used to study interactions among various biomolecules and to visualize drug release from the delivery system in a non-invasive and real-time manner. The data, published in the journal *Pharmaceutics* on April 24, 2023, reported that the researchers developed tiny structures called nano-assemblies which were able to enter cancer cells successfully and had a greater effect on stopping cancer cell growth than when the drugs were used alone. The researchers believe that these results are promising for future cancer treatment, as the nano-assemblies could be used to deliver drugs directly to cancer cells and monitor how the drugs are released in a non-invasive way. The University of Texas Rio Grande Valley received a $6 million CPRIT Texas Regional Excellence in Cancer Award (RP230419) in 2023 and a $2.52 million Core Facility Support Awards grant (RP210180) in 2021.

174. Communication between neurons and glia has an important role in establishing and maintaining higher-order brain function. Researchers at Baylor College of Medicine, including Benjamin Deneen, Ph.D., professor, Department of Neurosurgery and director of the Center for Cancer Neuroscience, reported on April 26, 2023, in the journal *Nature* that neuronal activity is necessary and sufficient for astrocytes (which make up the majority of cells in the human central nervous system) to develop their complex shape, and interrupting this developmental process results in disrupted brain function. The team found that in the adult brain, the bushy shape of astrocytes is fundamentally linked to effective brain function. The ends of the branched-out astrocyte structure interact with neurons and regulate synaptic activity. "Figuring out how astrocytes acquire their complex, bushy structure is essential to understanding how the brain develops and functions and may bring new insight into how neurodevelopmental conditions emerge. In this study, we investigated the cells and processes that direct the development of astrocyte structure," said corresponding author Dr. Deneen. The findings suggest that neuronal activity is both necessary and sufficient to drive full astrocyte maturation into a bushy-shaped cell. Baylor College of Medicine received a $5.17 million CPRIT Core Facility Support Award CPRIT (RP180672) in August 2018 to purchase high-end equipment that will help identify new therapeutic targets and the generation of novel drugs.

175. The current treatment for patients with high-risk IDH1-mutated acute myeloid leukemia (AML) is effective, but relapses remain common. AML in the relapsed setting has few effective treatment approaches, with an average life expectancy at relapse of < 6 months. In a first-of-its-kind study, researchers led by Courtney DiNardo, M.D., associate professor, Department of Leukemia at The University of Texas MD Anderson Cancer Center, evaluated the safety and efficacy of the IDH1 inhibitor ivosidenib (IVO) and the BCL2 inhibitor venetoclax (VEN) as an oral doublet regimen and ivosidenib, venetoclax and azacytidine as a triplet combination. The results, published on April 27, 2023, in *Blood Cancer Discovery*, showed that the overall composite remission rate across all cohorts on the study was 87%. The minimal residual disease negativity rate by flow cytometry was 75%, and IDH1 clearance occurred in 86% of patients who received the triplet combination. Patients with signaling gene mutations appeared to particularly benefit from the triplet regimen. The treatment was safe and well tolerated by patients and the researchers are currently enrolling patients in the Phase II portion of the trial. The University of Texas MD Anderson Cancer Center received a $1.9 million CPRIT Individual Investigator Research Awards for Clinical Translation grant (RP220299) in February 2022 to eradicate residual leukemia through leukemia-directed therapy.

176. Genomically-targeted therapies and immunotherapies have led to improved patient survival in diverse cancer types. However, it is challenging to implement precision therapies involving immunotherapies due to the complex nature of the molecular landscape of tumor-immune interfaces. To address this challenge, researchers, including Anil Korkut, Ph.D., assistant professor, Department of Bioinformatics and Computational Biology at The University of Texas MD Anderson Cancer Center, introduced the Immuno-oncology gene interaction Maps (ImogiMap), a bioinformatics method, tool, and web application to automate searches for interactions between tumor-associated and immune checkpoint processes. The ImogiMap method is a simple, versatile, and yet informative method for quantitative characterization and statistical validation. The findings, published in *Communications Biology* on April 27, 2023, suggest that ImogiMap generates

hypotheses on relations between tumor-associated processes and immune regulation at a scale not accessible easily by experimental methods. ImogiMap may help researchers to identify patient cohorts that may respond to combination therapies based on their molecular signatures. The University of Texas MD Anderson Cancer Center received a $200,000 CPRIT High-Impact/High-Risk Award (RP170640) in August 2017 to develop rational approaches to identify effective combination therapies.

177. The cellular immune response is a vital part of our defense mechanism against various diseases, including viral infection and cancer. As part of this immune response, cytotoxic T-cells are a type of immune cell that can kill cancer cells by pinpointing and eliminating infected cells. However, T-cell cross-reactivity can cause devastating side effects in T-cell-based cancer immunotherapy. In this study, researchers, including Lydia Kavraki, Ph.D., professor, Departments of Bioengineering and Computer Science at Rice University, proposed a scoring method to determine the similarity between peptide-HLA complexes to predict T-cell cross-reactivity. The data, published in *Frontiers in Immunology* on April 28, 2023, report that PepSim, a novel computational method for calculating the similarity between pHLAs to predict T-cell cross-reactivity, helps to fill a gap in the existing methods for predicting T-cell cross-reactivity. This method can accurately separate cross-reactive from non-crossreactive pHLAs in a diverse set of datasets including cancer, viral, and self-peptides. PepSim is available as a web server at pepsim.kavrakilab.org. The University of Texas Medical Branch at Galveston received a $4 million CPRIT Research Training grant (RP170593) in November 2016.

178. The oral route is considered the most convenient route of drug administration for both systemic and local delivery and possesses the advantages of patient compliance, convenience, and cost effectiveness. Despite tremendous demand and efforts, only ~50% of the therapeutic modalities are available in oral dosage forms. Researchers from The University of Texas at El Paso recognized the need to design and develop formulations that can protect the macromolecules in the destructive GI environment and, thereby, increase the absorption and permeation in the stomach or intestine. They hypothesized that an oral vehicle that can adhere and maintain retention within the stomach for a longer duration can be more effective to treat stomach-related diseases. The results, published in *Biomolecules* on April 28, 2023, reported that the team developed a carrier that is highly specific to the stomach and maintains its retention for a longer duration. This vehicle is composed of β-Glucan And Docosahexaenoic Acid (GADA) to observe its affinity and specificity to the stomach. The University of Texas at El Paso received a $5.88 million CPRIT Texas Regional Excellence in Cancer Award grant (RP210153) in August 2021 to define underlying mechanisms that support emerging evidence that links socioeconomic and biological factors to the development of cancer disparities among Hispanics.

179. Normal and cancer cells have devised well-coordinated adaptive mechanisms to withstand environmental or oncogenic stresses. These processes include the unfolded protein response, autophagy, endoplasmic reticulum-associated degradation (ERAD) of unfolded proteins and altered mitochondrial functions. Researchers from The University of Texas Health Science Center at San Antonio have found that a molecule called ALKBH5 regulates the crosstalk among these processes to maintain normal endoplasmic reticulum (ER) function. Using functional studies and electron microscopy, the team reported in the journal *Cells* on April 29, 2023, that RNA demethylase ALKBH5 regulates ER homeostasis and adaptive survival mechanism -- a cellular strategy that enables an organism to endure and thrive in adverse conditions -- by controlling the unfolded protein response (UPR), autophagy, and mitochondrial function in normal and cancer cells. These results suggest that normal cells and cancer cells may have different mechanisms and thresholds to negotiate ER stress and that ALKBH5 serves an important role in maintaining ER homeostasis and cellular fitness. The University of Texas Health Science Center at San Antonio received a $3.7 million CPRIT Core Facility Support Awards grant (RP160732) in May 2016 to establish the UTHSCSA Cancer Genome Sequencing and Computation Core.

180. The available risk stratification indices, used to assess the likelihood of cancer recurrence or progression, for hepatocellular cancer (HCC) have limited applicability. Hashem El-Serag, M.D., MPH, Section of Gastroenterology and Hepatology at Baylor College of Medicine, and colleagues developed and externally validated an HCC risk stratification index in U.S.

cohorts of patients with cirrhosis. Patients with cirrhosis were enrolled from eight centers and followed until development of HCC, death, or December 31, 2021. The team identified an optimal set of predictors with the highest discriminatory ability (C-index) for HCC. External validation was performed in a cohort of 21,550 patients with cirrhosis seen in the U.S Veterans Affairs system between 2018 and 2019 with follow-up through 2021. The data, published in *Clinical Gastroenterology and Hepatology* on April 29, 2023, reveal that the risk index, including objective and routinely available risk factors, can differentiate patients with cirrhosis who will develop HCC and help guide discussions regarding HCC surveillance and prevention. Baylor College of Medicine was awarded a $9.77 million CPRIT Multi-Investigator Research Awards grant (RP150587) in May 2015.

181. In this study, Raffaella Righetti, Ph.D., associate professor, Department of Electrical & Computer Engineering at Texas A&M University, and colleagues developed and tested new theoretical models and imaging techniques to assess fluid transport parameters in cancers using non-invasive ultrasound methods. Currently, there are no non-invasive methods to directly image extracellular volume fraction (EVF), interstitial fluid volume fraction (IFVF), and interstitial hydraulic conductivity (IHC) in tumors. EVF, IFVF, and IHC are clinically significant parameters, which carry important information for cancer diagnosis and drug delivery. As reported in *Scientific Reports* on May 2, 2023, the researchers analyzed novel non-invasive ultrasound poroelastography techniques for imaging the EVF, IFVF, and IHC in cancers *in vivo*. The controlled experiments were performed on tissue mimicking polyacrylamide samples and validated using scanning electron microscopy (SEM). *In vivo* applicability of the proposed methods was demonstrated using a breast cancer model implanted in mice. Based on the controlled experimental validation, the proposed methods can estimate interstitial fluid transport parameters with an error below 10% with respect to benchmark SEM data. *In vivo* results demonstrate that EVF, IFVF and IHC increase in untreated tumors whereas these parameters are observed to decrease over time in treated tumors. Based on the importance of these parameters in cancer treatment and widespread availability of ultrasound imaging systems, the developed methods may become a useful alternative option to current methods. Texas A&M Engineering Experiment Station received a $900,000 CPRIT Individual Investigator grant (RP200452) in February 2020 to develop new, safe, and accurate methods for imaging properties of cancers.

182. The gut microbiota is a crucial regulator of anti-tumor immunity during immune checkpoint inhibitor therapy. Several bacteria that promote an anti-tumor response to immune checkpoint inhibitors have been identified in mice. Transplantation of fecal specimens from responders can improve the effectiveness of anti-PD-1 therapy in patients with melanoma, but the increased efficacy from fecal transplants varies and it is unclear how gut bacteria promote anti-tumor immunity. In this study, Jennifer A. Wargo, Ph.D., Department of Genomic Medicine at The University of Texas MD Anderson Cancer Center, and colleagues showed how gut microbes enhance the body's response to PD-1 checkpoint blockade, a common type of immunotherapy currently used for the treatment of 25 forms of cancer. According to the data published in *Nature* on May 3, 2023, the researchers found that blocking a specific pathway called PD-L2-RGMb helped to overcome resistance to PD-1 inhibitors. This research suggests that the gut microbiota can promote better responses to PD-1 inhibitors and illustrates a potentially effective treatment strategy for patients who do not respond to PD-1 inhibitors. The University of Texas MD Anderson Cancer Center received a $4 million CPRIT Research Training grant (RP210028) in May 2021 to instruct postdoctoral fellows for careers in translational cancer research.

183. CPRIT Scholar Jun Wu, Ph.D., assistant professor, Department of Molecular Biology at The University of Texas Southwestern Medical Center, and fellow researchers have developed a method to produce bovine blastoids, a crucial step in replicating embryo formation in the lab. Current efforts for cattle breeding are hindered by a limited supply of embryos, so understanding the mechanisms for creating successful bovine blastocyst-like structures in the lab could prove valuable for improving reproduction in cattle. As reported in *Cell Stem Cell* on May 4, 2023, the researchers used immunofluorescence and single-cell RNA sequencing analyses, to show that the lab-generated blastoids resembled natural bovine blastocysts in morphology, size, cell number, and lineage composition, and could produce maternal recognition signaling upon transfer to recipient cows. This technology could potentially lead to faster genetic gains in beef or dairy production

or lead to reducing disease incidence in the animals. The University of Texas Southwestern Medical Center recruited Dr. Wu in August 2017 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR170076).

184. Breast cancer can have a profound impact on the body even before it spreads to other organs. Researchers at Baylor College of Medicine and collaborating institutions have discovered that breast tumors can disrupt the bone marrow, where the body produces immune cells, in a way that promotes tumor growth instead of fighting it. Published in the journal *Cell Stem Cell* on May 4, 2023, the study shows that breast cancer tumors send molecular signals to the bone marrow that alter the natural environment of the bone marrow, which then suppresses the response to defend against the tumor. However, these changes persist long after tumor removal. Corresponding author Xiang Zhang, Ph.D., professor, Department of Molecular and Cellular Biology at Baylor College of Medicine said, "To understand how this happens, we characterized the organization of the bone marrow in breast cancer animal models before the tumor had metastasized." The findings suggest that additional therapies targeting tumor-induced systemic effects on the immune response may be necessary for optimal treatment outcomes. The team also outlined how to speed up the recovery of the immune system to accelerate the restoration of the normal conditions in the bone marrow after tumor removal. The findings warrant further research that could potentially lead to improved treatments for patients. Baylor College of Medicine received 2 CPRIT Core Facility Support Awards (RP200504, RP180672) in 2018 and 2020 for a total of $9.1 million to support the Comprehensive Cancer Epigenomics Core (CCEC) facility, which focuses on epigenomics.

185. According to the Centers for Disease Control and Prevention, approximately half of all new cases of sexually transmitted infections, including HPV, occurred in adolescents and young adults 15–24 years old in the U.S. in 2018. All for Them (AFT) is a CPRIT-funded, comprehensive, multilevel, multicomponent program to increase initiation and completion of the HPV vaccine series among middle-school-aged adolescents attending public schools in medically underserved areas in Texas. Led by Paula Cuccaro, Ph.D., assistant professor, Health Promotion & Behavioral Science at The University of Texas Health Science Center at Houston, AFT comprised a social marketing campaign, school-based vaccination clinics, and school nurse continuing education. As published in *Vaccines* on May 5, 2023, the team found that securing partnership with district leaders is pivotal to ensuring buy-in from principals for program implementation; school nurses are more successful at supporting school-based vaccination with school-level support and their engagement may also dispel HPV vaccine hesitancy among parents; and social marketing strategies are integral to program implementation, which also can be achieved through increased community presence of the project team. The University of Texas Health Science Center at Houston received a $1.5 million CPRIT Prevention grant (PP170046) to increase access to immunization services for youth in MUAs and establish an ongoing program of SBVCs in public middle schools.

186. Germ cell tumors (GCTs) are neoplasms of the testis, ovary, and extragonadal sites that occur in infants, children, and adults. Data suggest that pediatric and adult GCTs may arise by distinct mechanisms or from different stages of primordial germ cells (PGC) development. WNT signaling regulates cell migration, proliferation, differentiation, apoptosis and pluripotency. Aberrant WNT signaling is associated with many types of human cancers. Here James F. Amatruda, M.D., Ph.D., The University of Texas Southwestern Medical Center, and colleagues report the genomic analysis of 145 primary GCTs of childhood and adolescence. They describe several convergent mechanisms predicted to drive WNT signaling activity in both type I and type II GCTs. Integrated analysis of these data, reported in *Nature Communications* on May 6, 2023, revealed a pattern of somatic mutations, copy-number alterations, differential methylation and gene expression that together mediate increased activity of the WNT signaling pathway in GCTs. These results suggest that inhibition of aberrantly active WNT pathway may be a promising therapeutic strategy to improve survival of GCT patients. The University of Texas Southwestern Medical Center received a $930,500 CPRIT Academic Research grant (RP110394) in October 2010.

187. Patients with advanced castration-resistant prostate cancer do not respond well to androgen deprivation therapy or im-

munotherapy, especially if they have mutations or defects in tumor suppressors PTEN and p53. The immune checkpoint protein B7-H3 is overexpressed in advanced prostate cancer, but its role is not well understood. Researchers led by Wei Shi, Ph.D., and CPRIT Scholar Di Zhao, Ph.D., used multi-omics analyses to identify B7-H3 as one of the most abundant immune checkpoints in prostate tumors containing PTEN and TP53 genetic inactivation. The results, published in *Science Translational Medicine* on May 10, 2023, showed that inhibiting B7-H3 using a monoclonal antibody in combination with PD-L1 or CTLA-4 blockade demonstrated significant tumor-suppressing activity in preclinical models, illustrating the potential of biomarker-driven combinatorial immunotherapy. The University of Texas MD Anderson Cancer Center recruited Dr. Zhao in February 2019 with the support of a $2 million Recruitment of First-Time, Tenure-Track Faculty Members grant (RR190021), and received a $1.2 million Shared Instrumentation Awards grant (RP121010) in March 2012.

188. Prostate cancer is the leading diagnosed malignancy and the second leading cause of cancer death among men in the United States. This malignancy can continue to grow even with very low amounts of testosterone in the body, called castrate-resistant prostate cancer (CRPC). Androgen-deprivation therapy, a treatment that reduces the levels of male hormones, is the first-line treatment for locally advanced or metastatic prostate cancer. Although patients initially respond to the therapy, almost all patients develop CRPC within a few years. Researchers led by Ping Yi, Ph.D., assistant professor, Departments of Biology and Biochemistry at the University of Houston, found a specific chemical modification that occurs on the AR protein that involves another protein called TRAF4. "We demonstrated that overexpression of TRAF4 leads to the conversion of androgen-sensitive prostate cancer cells into castration-resistant cells, both in lab experiments and in live samples," said Dr. Yi. The findings, published in *Cell Biology* on May 8, 2023, also suggest that TRAF4 is associated with promoting the spread of cancer to other parts of the body. The researchers believe that their findings provide a possible treatment option for CRPC patients. Baylor College of Medicine received a $5 million CPRIT Core Facility Awards grant (RP170005) in September 2016 to support cancer researchers with state-of-the-art proteomics and metabolomics technologies.

189. Analyzing chromosomal profiles and identifying changes in genes and proteins are crucial for diagnosing and predicting the prognosis of many types of cancer. As reported in *Nature* on May 10, 2023, new findings by CPRIT Scholar Peter Ly, Ph.D., assistant professor, Departments of Pathology and Cell Biology at The University of Texas Southwestern Medical Center, shed light on how errors occur during cell division, resulting in chromosomal abnormalities found in cancer. Understanding these processes can have important implications for diagnosing, predicting outcomes, and developing new therapies for various types of cancer. During the process of cell division, called mitosis, chromosomes sometimes fail to separate correctly, leading to the loss or gain of entire chromosomes. Additionally, complex rearrangements in the genome can occur when mis-segregated chromosomes shatter and form structures known as micronuclei. Dr. Ly and his research team used live-cell imaging to observe these micronucleated chromosomes and found that the fragments of chromatin cluster closely together throughout mitosis. As a result, a single daughter cell inherits the clustered fragments asymmetrically, and later, DNA repair processes incorrectly reassemble the pieces, forming rearranged chromosomes. A protein complex called CIP2A-TOPBP1 plays a role in this process by prematurely associating with the broken DNA ends in ruptured micronuclei. Disruption of this protein complex caused fragments to disperse during cell division, leading to cell death. This crucial process of clustering chromatin fragments during mitosis allows the reassembly of acentric fragments into rearranged chromosomes. These rearranged chromosomes contain most or all the original chromosomes but in a different order. Interestingly, Dr. Ly and his research team discovered that this process is common in cancers. Analysis of cancer genomes from various types of cancer revealed clusters of rearranged DNA sequences, termed balanced chromothripsis, which result in the acquisition of oncogenic driver events. This suggests that targeting the CIP2A-TOPBP1 protein complex is a potential cancer treatment approach, especially for tumors with chromosomal instability and DNA repair deficiencies. The University of Texas Southwestern Medical Center recruited Dr. Ly to Texas from the Ludwig Institute for Cancer Research and University of California, San Diego, School of Medicine with a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR180050) in 2018.

190. Phospholipids are major membrane lipids which act as a barrier to protect the cell against various environmental insults and more importantly, enable multiple cellular processes to occur in subcellular compartments. Phosphatidylcholine (PC) is the most abundant phospholipid in eukaryotic cell membranes. Inhibition of PC synthesis leads to arrested cell growth and cell death. In eukaryotes, two highly homologous enzymes catalyze the final step of de novo PC synthesis. CHPT1/CEPT1 joins two substrates, cytidine diphosphate-choline (CDP-choline) and diacylglycerol (DAG), to produce PC, and Mg2+ is required for the reaction. However, mechanisms of substrate recognition and catalysis remain unresolved. Lie Wang, Ph.D., and Ming Zhu, Ph.D., both from the Department of Biochemistry and Molecular Biology at Baylor College of Medicine, pursued the structure of eukaryotic CDP-Aps and examined their functions to gain a better understanding of the mechanisms. As reported in *Nature Geoscience* on May 15, 2023, the structural and functional analysis of xlCHPT1 enhanced understanding of substrate recognition and catalysis in eukaryotic CDP-Aps and establishes a framework for further investigations. Baylor College of Medicine received a $5.38 million CPRIT Core Facility Award (RP190602) in 2019 to add new technologies to the two CryoEM Cores which will provide 3-D cellular structure at molecular resolution.

191. Cardiolipin (CL) is a hallmark phospholipid of mitochondrial membranes. Despite established significance of CL in supporting respiratory supercomplex (SC) organization (the arrangement of individual respiratory complexes within the inner mitochondrial membrane into larger, higher-order structures), a mechanistic understanding of this lipid-protein interaction is still lacking. Researchers, including corresponding author, Eugenia Mileykovskaya, Ph.D., Department of Biochemistry and Molecular Biology, McGovern Medical School at The University of Texas Health Science Center, sought to understand the role of lipids in the organization of respiratory SCs. Using cryo-EM maps and molecular models, the team reported that reduced CL levels resulted in a broad range of pathological alterations in mitochondrial function including lower levels of SCs with an increase in free CIII and CIV as observed in neurodegenerative diseases, ischemia followed by reperfusion, induction of apoptosis, heart failure, cancer, Barth Syndrome, hypothyroidism, obesity, and aging. The data, reported in *Nature Communications* on May 15, 2023, showed that anionic phospholipids interact with positive amino acids and appear to nucleate a phospholipid domain at the interface between the individual complexes, which dampen charge repulsion and further stabilize interaction, respectively, between individual complexes. Baylor College of Medicine received a $5.38 million CPRIT Core Facility Award (RP190602) in 2019 to add new technologies to the two CryoEM Cores which will provide 3-D cellular structure at molecular resolution, allowing researchers to visualize how cancer impacts the molecular interactions within the living cell.

192. Rhabdomyosarcoma (RMS) is a devastating pediatric sarcoma and patients with relapsed disease have very poor survival outcomes. However, there has not been any significant change in therapy options for the last three or four decades, and the mechanisms underlying treatment failures remain poorly understood. In this study, corresponding author Lin Xu, Ph.D., assistant professor at the School of Public Health at The University of Texas Southwestern Medical Center, and colleagues examined the underlying biology of therapy-resistant RMS stem cells in response to the standard chemotherapy drug vincristine. To study the stem cells, which are sparse in RMS tissue, the team developed RMS spheres grown in the lab and utilized a zebrafish model. The researchers used CRISPR/Cas9 genome editing to target two genes, MYC and YBX1, which resulted in a reduction in viability of the vincristine-resistant cells. The data, reported in the journal *Cancers* on May 17, 2023, showed that the MYC protein regulated the YBX1 gene and that inhibiting MYC, in combination with vincristine, reduced tumor growth and stem-like cells in the zebrafish model. By understanding the underlying mechanisms and identifying these potential therapeutic targets, researchers are closer to developing more effective treatments for difficult-to-treat pediatric cancers like RMS. The University of Texas Southwestern Medical Center received three CPRIT Academic Research grants (RP180319, RP200103 and RP180805) in 2018 and 2020, totaling $7.7 million.

193. The diversity in bacteriophage (viruses that infect and replicate within bacteria) propagation, physical properties, and assembly makes phages versatile tools with applications in biomedicine. Their ability to interact with bacteria in various ways and their adaptability to different environments contribute to their significance in understanding and manipulating microbial systems, as seen in the evolution of multidrug resistant bacteria for which phages are sought as therapeutics.

If membrane-containing, single-stranded RNA phages exist, finding a way to isolate them will provide a more accessible model for understanding common aspects of assembly. Philip Serwer, Ph.D., professor, Departments of Biochemistry and Structural Bbology, and colleagues at The University of Texas Health Science Center at San Antonio, screened previously isolated, uncharacterized phages for unusual properties. Investigation of these phages had stopped, in part, because of limitations of genome sequencing technology, including its cost. These limitations have subsequently been removed, and as reported in *Molecular Sciences* on May 18, 2023, the team described characterization of one of these phages, 0105phi7-2, which is found to be novel in many ways. A key objective for the future is increasing the efficiency, in time and cost, of the characterization of phages for various purposes, including phage therapy of infectious disease. The University of Texas Health Science Center at San Antonio received a $3.99 million CPRIT Core Facility Support Awards grant (RP220662) in September 2022. This is a renewal grant which enabled the Core to introduce the "third-generation sequencing" technology, matched with enhanced data storage capability, for the detection of rare genetic variations at the single-molecule level from their patient population.

194. More than 35,000 people in the U.S. are diagnosed with liver cancer each year; most of those cases involve hepatocellular carcinoma (HCC). About one-fourth of HCC patients cannot be treated with surgery or liver transplantation and are instead treated with lenvatinib to halt tumor growth. However, drug resistance in HCC patients is common. In this retrospective study, David Hsieh, M.D., assistant professor, Department of Internal Medicine at The University of Texas Southwestern Medical Center, and colleagues analyzed the genetic profiles of circulating tumor DNA (ctDNA), shed from cancer cells and disseminated into the bloodstream, for 46 patients who underwent treatment for HCC. The data, published in the journal *Gastroenterology* in May 2023, report that the team discovered a genetic marker that could help physicians predict which patients with HCC are most likely to develop resistance to lenvatinib. The results suggest that drugs targeting EGFR and ERBB2 combined with lenvatinib may be a very effective treatment in select patients. The University of Texas Southwestern Medical Center received a $1.5 million CPRIT Early Clinical Investigator Award (RP200549) in August 2020 to investigate a novel strategy to enhance the activity of immune checkpoint inhibitors.

195. Genetic mutations play key roles in the evolution of genes by providing resources for novel functions. Mutations can cause genetic polymorphism (a variation among chromosomes, alleles, or other DNA sequences) in the population and contribute to the genetic diversity of the individuals. Single-Nucleotide Variant (SNV) is the most common type of variation in the population, and more than 80 million SNVs have been genotyped in large-scale genetic studies. SNVs can alter the function of the gene by changing the protein sequence and are associated with phenotype (an individual's observable traits) diversities and diseases. Yang Xie, Ph.D., and He Zhang, Ph.D., professors, Department of Bioinformatics at The University of Texas Southwestern Medical Center, set out to investigate how many potential start-gain SNVs can be found in the natural human populations, and whether they were active in translation initiation. They also wanted to know whether there were human-specific start codons - which form a unit of genetic code in a DNA - generated and fixed in the human genome after the divergence with the chimpanzee. By comparative genomic analysis, they found that 26 novel start codons have been fixed in the human genomes after the divergence with the chimpanzee and became a part of genetic mutations distinguishing between the human and other species. The study, published in *Nature* on May 19, 2023, indicates the important function of these novel coding sequences. The University of Texas Southwestern Medical Center received a $5.39 million CPRIT Core Facility Support Awards grant (RP180805) in August 2018 to provide a research platform and services to facilitate data management, harmonization, sharing and analysis for the pediatric cancer research community.

196. The incidence and prevalence of diabetes has been increasing worldwide. A key criterion for the diagnosis and management of diabetes is the rapid determination of glucose levels. When a patient's glucose level is higher than 600 mg/DL, it will cause a life-threatening condition known as diabetic hyperosmolar syndrome. Glucose oxidase-based (GOX) glucose biosensors are gaining attention due to their simplicity in production, reagent-less nature, portability, and low operational costs. However, the main limitation is that the commercially available GOX glucometers only cover the range from 20

to 600 mg/dL and cannot address all diabetes scenarios. XiuJun Li, Ph.D., professor, Department of Chemistry & Biochemistry at The University of Texas at El Paso, and fellow researchers developed a disposable paper-based glucose biosensor with direct electron transfer (DET) of GOX through simple covalent immobilization of GOX on a carbon electrode surface. As reported in *Biosensors* on May 22, 2023, this low-cost DET glucose biosensor showed remarkable selectivity, and the use of the negative operating potential avoided interference from other common electroactive compounds. It has excellent potential to monitor different stages of diabetes from hypoglycemic to hyperglycemic states, especially for self-monitoring of blood glucose. The University of Texas at El Paso received a $250,000 CPRIT High-Impact/High-Risk grant (RP210165) in August 2021 to develop a low-cost and accurate nanomaterial-mediated photothermal immunosensing biochip.

197. Scientists and clinicians who want to identify mutations and other variants in DNA face a wide selection of variant caller algorithms (algorithms used to identify genetic variations or mutations) that employ various approaches. However, discordance and inconsistency exist between bench-marking publications that compare the performances of variants callers. Caller performances are inconsistent and wide ranging, and dependent upon input data, application, parameter settings, and evaluation metric. With no single variant caller emerging as a superior standard, combinations or ensembles of variant callers have surfaced. In this study, published in *Nature* on May 25, 2023, a whole genome somatic reference standard was used to derive principles to guide strategies for combining variant calls. William Fraser Symmans, MB.ChB., professor, Department Pathology at The University of Texas MD Anderson Cancer Center, and fellow researchers then examined the ability of these principles to reduce noise (unwanted signals, errors, or inaccuracies that arise during the sequencing process) in targeted sequencing. The team reported that majority consensus remains advantageous in combinations larger than three variant callers, when applied to whole genome sequencing (WGS), whole exome sequencing (WES), and targeted amplicon sequencing data. In addition, the specific callers used is not critical. The University of Texas MD Anderson Cancer Center received a $5.99 million CPRIT Multi-Investigator Research Awards grant (RP160710) in August 2016 to study and discover reasons for the development of resistance to chemotherapy among triple negative breast cancers and test the role of mutations in p53 gene.

198. Metastatic cancer is responsible for the majority of cancer deaths. According to a new study, mitochondria that power cellular activity can fragment and change shape in breast cancer cells that migrate to the brain. This study, led by CPRIT Scholar Srinivas Malladi, Ph.D., assistant professor, Department of Pathology at The University of Texas Southwestern Medical Center, could lead to new treatment for prevention of brain metastases resulting from an initial diagnosis of breast cancer. Dr. Malladi and his colleagues discovered that cancer cells that migrate to the brain reprogram their metabolism to depend on fatty acids rather than carbohydrates as a main energy source. This switch is necessary to survive in the brain, which is a completely different environment. According to the study published in *Nature Cancer* on May 29, 2023, further experiments showed that the fragmentation was driven by an increase in a protein known to be involved in mitochondrial fission called dynamin-related protein 1 (DRP1). The team plans to test DRP1 inhibitors to determine whether they might prevent, slow, or reverse metastatic disease, an important next step toward developing a treatment. The University of Texas Southwestern Medical Center recruited Dr. Malladi with a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR170003) in November 2016. UT Southwestern received a $3.7 million Core Facility Support Award grant (RP180770) in August 2018.

199. Tumor-infiltrating T cells are a promising approach to cancer treatment. However, there is a need for more in-depth understanding of the various states of TILs within the tumor microenvironment to optimize their use in cancer immunotherapy and develop more effective treatment strategies. In this study, researchers provide important insights into the diversity and roles of immune T cells within tumors. The team developed a comprehensive T cell atlas by analyzing data from 27 single-cell RNA sequencing datasets covering 16 types of cancer. This atlas reveals previously unknown states and subpopulations of T cells within the tumor microenvironment. One significant finding is the identification of a unique group of T cells called T cell stress response (T_{STR}) cells, characterized by the expression of heat shock genes which are

detectable *in situ* in the tumor microenvironment across various cancer types. The results, reported in *Nature Medicine* on May 29, 2023, highlight the extensive heterogeneity of T cell states within the tumor microenvironment and the need to further understand how these states contribute to disease progression and immunotherapy response. "The fact that these T_{STR} cells are found in many different types of tumors opens up a whole new world of possibilities that could have high translational potential," said Lingua Wang, M.D., Ph.D., associate professor, Department of Genomic Medicine at The University of Texas MD Anderson Cancer Center. CPRIT Scholar Maura Gillison, M.D., Ph.D., professor, Department of Thoracic/Head and Neck Medical Oncology at MD Anderson, and fellow researchers developed and shared their T cell atlas with the wider research community through a user-friendly, interactive web portal, the Single-Cell Research Portal, which allows users to visualize and query the atlas without the need for bioinformatics skills. The team also developed a tool named TCellMap, which enables researchers to automatically annotate T cells from their datasets by aligning with the high-resolution T cell maps generated by this study leading to further discoveries and ultimately enhancing strategies for T cell therapy. The University of Texas MD Anderson Cancer Center recruited Dr. Gillison in November 2016 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR170005). MD Anderson Cancer Center also received three CPRIT Individual Investigator grants (RP150079, RP200385, RP220101) in 2015, 2020, and 2022, totaling $2.6 million.

200. The causes and consequences of abnormal biogenesis of extracellular vesicles (EVs), small membrane-bound structures released by cells into the extracellular environment that play a role in intercellular communication and the transport of molecules between cells, are not yet well understood in malignancies, including in breast cancers. Researchers led by George Calin, M.D., Ph.D., hypothesized that estrogen could be involved in generating these EVs and in loading specific miRNAs by downregulating signal pathways in estrogen receptor-positive (ER+) breast cancer. They examined cell lines and uncovered a dose-dependent connection between estrogen levels and released EVs, as well as an enrichment of let-7 miRNAs in these EVs. In several patient cohorts, the researchers observed increased let-7 family miRNAs in EVs derived from the blood of premenopausal ER+ breast cancer patients. This study, published in *Proceedings of the National Academy of Sciences* on May 30, 2023, uncovered novel mechanisms of hormonal influence on cell communications, highlighting their therapeutic potential for ER+ breast cancer as well as other hormone-related cancers. The University of Texas MD Anderson Cancer Center received a $4 million CPRIT Research Training grant (RP170067) in November 2016 in support of a comprehensive learning environment focused solely on cancer.

201. Inflammatory bowel disease (IBD) causes chronic and debilitating gastrointestinal morbidity and predisposes patients to colorectal cancer (CRC). The risk of IBD patients developing CRC is up to 30-fold higher than that of the general population. Several genes, including STAT3 have been demonstrated as risk factors in genome-wide association studies, although the cause of IBD has not been established. In the current study, David J. Tweardy, M.D., head, Division of Internal Medicine, and fellow researchers at The University of Texas MD Anderson Cancer Center determined that a selective, small-molecule inhibitor of STAT3, TTI-101, completely prevented DSS-induced colitis as well as the upregulation of CRC-associated genes. As reported in *Cancers* on May 30, 2023, the data indicate that small-molecule targeting of STAT3 may be beneficial in the treatment of colitis and in the prevention of colitis-associated colorectal cancer. The University of Texas MD Anderson Cancer Center received a $1.99 million CPRIT Academic Research grant (DP150069) in November 2014.

202. In 2022, there were over 18 million cancer survivors in the United States, which account for approximately 5% of the entire population. Among those cancer survivors, 67% are currently aged 65 years or older, and it is estimated to increase to 74% by 2040. Despite the benefits of digital health technology use, older adults with cancer have reported challenges to technology adoption. This study described digital health or everyday technology use in older adults with cancer from 2015 to 2021 and the associated factors with the prevalence of digital health technology use in the prepandemic period. The findings, reported in the *Journal of Medical Internet Research* on May 31, 2023, indicated that there has been a gradual increase in technology use in older adults with cancer, particularly during the COVID-19 pandemic. However, the over-

all prevalence of digital health technology usage remains relatively low (range 36%-52%) despite its significant potential for enhancing health outcomes. In addition, this data revealed that reduced digital health adoption was associated with socioeconomic inequalities, a lower number of comorbidities, and diminished physical function. As the proportion of the older population rises in cancer survivorship, future developments in digital health technology should focus on the needs of older adults with cancer for widespread and consistent use. The University of Texas Health Science Center at Houston received a $4 million CPRIT Research Training grant (RP210042) in May 2021 to support collaborative training of a new cadre of innovative cancer prevention researchers.

203. Prevalence of liver disease is continuously increasing, and nonalcoholic fatty liver disease (NAFLD) is the most common cause. In this study, Kenneth Hoyt, Ph.D., associate professor, Department of Bioengineering at The University of Texas at Dallas, and an international team, presented an approach to detect the progression of fatty liver disease based on quantitative ultrasound (QUS) imaging. This was performed on a group of 55 rats that were subjected to a control or methionine and choline deficient (MCD) diet known to induce NAFLD and ultrasound (US) measurements were performed at 2 and 6 weeks. Thereafter, animals were humanely euthanized, and livers excised for histological analysis. The results, published in *Scientific Reports* on June 1, 2023, suggest that *in vivo* QUS is a promising noninvasive imaging modality for the early assessment of NAFLD. The University of Texas at Dallas received a $3.58 million CPRIT Core Facility Support Awards grant (RP180670) in August 2018 to significantly expand the capabilities of preclinical imaging resources that are currently available for UT Dallas scientists.

204. General anesthetics and neuromuscular blockers are used together during surgery to stabilize patients in an unconscious state. Anesthetics act mainly by dampening nervous system excitability and neuromuscular blockers act by antagonizing nicotinic acetylcholine receptors. The mechanisms by which anesthetics and neuromuscular blockers inhibit nicotinic receptors are poorly understood but are the basis for safe and effective surgeries. Ryan E. Hibbs, Ph.D., Departments of Neuroscience and Biophysics at The University of Texas Southwestern Medical Center, and team took a direct structural approach to define how a commonly used anesthetic and two neuromuscular blockers act on a muscle-type nicotinic receptor. As reported in *Nature Communications* on June 1, 2023, the scientists discovered that the intravenous anesthetic etomidate binds at an intrasubunit site in the transmembrane domain and stabilizes a non-conducting, desensitized-like state of the channel. These structural studies provide a foundation for understanding the muscle relaxant effects of a representative intravenous anesthetic and how it may interact with commonly used neuromuscular blockers. The University of Texas Southwestern Medical Center received a $5.5 million CPRIT Core Facility Support Awards grant (RP170644) in August 2017 to advance the Cryo-EM Core Facility and establish a Service for Single-Particle structure determination.

205. Despite considerable efforts over the past four decades, outcomes for glioblastoma patients continue to be poor with no standard of care available for recurrent GBM (rGBM). Approved therapies have shown median overall survival (mOS)of only 6–9 months, a 1-year survival rate of 0%–10%, and 12-month progression-free survival (PFS) rate of 2%–10%. In addition, treatment of rGBM is constrained by the aggressive and infiltrative nature of the blood-brain barrier its immunosuppressive tumor microenvironment. These challenges are exacerbated in patients with primary *de novo* GBM, tumors not conducive to resection upon relapse, and contain wild-type IDH genes. This study, published in *Neuro-Oncology* in June 2023, is an open-label, single-arm phase IIb study of MDNA55 in rGBM patients with an aggressive form of GBM on their first or second recurrence. MDNA55 was administered intratumorally as a single dose treatment. The data report that single treatment with MDNA55 increased mOS by up to 50% and 12-month PFS by almost 100% when compared to approved therapies. MDNA55 demonstrated tumor control and promising survival and may benefit rGBM patients when treated at high-dose irrespective of IL4R expression level. Combining targeted treatment and advanced drug delivery techniques employed in this study provides an opportunity to explore the efficacy of MDNA55 in a pivotal trial. CPRIT awarded a $14.14 million New Company Product Development Award grant (DP150031) in 2015 to Medicenna Therapeutics, Inc. to conduct two clinical trials for glioblastoma multiforme patients to test the safety, effectiveness, and dosage of

MDNA55.

206. Camptothecin (CPT)-11 (irinotecan), a DNA topoisomerase I inhibitor, is one of the first-line therapeutic agents in the treatment of metastatic colorectal cancer, but its efficacy and safety can be compromised because of its severe side effects, such as gastrointestinal injury/inflammation and severe diarrhea. Previous studies reported that natural flavonoids such as wogonin and chrysin have anticancer and anti-diarrheal activities. Yun Zhang, Ph.D., assistant professor, Department of Pharmaceutical Sciences, and fellow researchers from Texas Southern University, investigated the efficacy and safety of irinotecan, a type of chemotherapy that interferes with the growth of cancer cells, when co-administered with flavonoids in the human colon cancer xenograft model. As reported in *The Journal of Pharmacology and Experimental Therapeutics* in June 2023, this study demonstrated that the combination therapy of CPT-11 (irinotecan) co-administered with flavonoids had no major impact on mouse body weights and the combination therapy resulted in lower tumor volume when compared with single-agent treatment. This combination therapy could be a promising approach in anti-tumor chemotherapy for better clinical outcomes. Texas Southern University received a $5.1 million CPRIT Core Facility Support Awards grant (RP180748) in August 2018 to support this core facility directly impacting the development and regulatory approval of novel treatments for cancer.

207. Newly developed COVID-19 vaccines rely on the immunogenicity (the ability of cells to provoke an immune response) of viral spike protein (S), which facilitates virus entry into healthy cells. However, emergence of novel SARS-CoV-2 Variants of Concerns (VOCs) highlight the need for new antivirals targeting the more conserved non-structural proteins (nsps) of the virus. One strategy which has been used to help find an effective therapy is drug repurposing. This strategy can be supported by computational analysis, which can lower the costs and speed up the process. In this study, CPRIT Scholar Shaun Olsen, Ph.D., and an international team of scientists utilized a collection of ebselen derivatives and analogues to evaluate their SARS-CoV-2 PLpro and Mpro inhibitory properties. The results, published in *Scientific Reports* on June 6, 2023, reveal their antiviral and cytoprotective (protecting cells from damage) activity and low cytotoxicity. The results illustrate a promising plan for novel therapeutics and the data can be used to facilitate efforts towards new anticoronaviral drugs to be used for the treatment of COVID-19. The University of Texas Health Science Center at San Antonio recruited Dr. Olsen in February 2020 with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR200030).

208. Sepsis is a leading cause of human death, yet currently there is no pathogenesis-specific therapy, and its many different underlying triggers and mechanisms are poorly understood. However, recent studies have focused on how non-coding microRNAs (miRNAs), might serve as potential biomarkers and therapeutic targets. Researchers led by George Calin, M.D., Ph.D., Department of Translational Molecular Pathology, and Sai-Ching Yeung, M.D., Ph.D., Department of Emergency Medicine, at The University of Texas MD Anderson Cancer Center, used samples from patients with sepsis as well as multiple animal models to screen for miRNA targets. The results, published in *The Journal of Clinical Investigation* on June 1, 2023, found that miR-93-5p was overexpressed across all models, was downregulated in human patients who survived sepsis, and was correlated with poor prognosis. Inhibiting miR-93-5p prolonged survival in preclinical models, especially in older organisms. Further, blocking miR-93-5p reduced inflammatory monocytes and increased circulating effector memory T cells, partially restoring the peripheral immune response. While further studies remain before starting clinical trials, this study uncovered miR-93-5p as a potential miRNA-based therapeutic target for sepsis. The University of Texas MD Anderson Cancer Center received a $4 million CPRIT Research Training grant (RP170067) in November 2016 in support of a comprehensive learning environment focused solely on cancer.

209. Appendiceal adenocarcinoma is a rare cancer that originates in the lining of the appendix. The current standard treatment is chemotherapy typically used for colorectal cancer, although the evidence to support this practice is primarily anecdotal. In a prospective trial led by Michael Overman, M.D., CPRIT Scholar John Paul Shen, M.D., and Keith Fournier, M.D., from The University of Texas MD Anderson Cancer Center, researchers evaluated if fluoropyrimidine-based (5FU) chemotherapy was effective in patients with inoperable low-grade mucinous appendiceal adenocarcinoma. The study

enrolled 24 patients, who were randomized to either 6 months observation followed by 6 months of chemotherapy, or initial chemotherapy followed by observation. As reported in *JAMA Network Open* on June 1, 2023, patients did not derive clinical benefit from 5FU-based chemotherapy, as there were no differences in tumor growth rates while receiving chemotherapy. These findings suggest that practice guidelines need to be changed to recommend against the use of 5FU-based chemotherapy for mucinous appendix cancer. The University of Texas MD Anderson Cancer Center recruited Dr. Shen in May 2018 from the University of California, San Diego, with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR180035).

210. Immunosuppressive drugs (IMD) are widely utilized to treat many autoimmune conditions and to prevent rejection in organ transplantation. Cancer has been associated with prolonged use of IMD in transplant patients. Researchers from The University of Texas Medical Branch at Galveston, including Yong-Fang Kuo, Ph.D., professor and chair, Department of Biostatistics & Data Science, analyzed Medicare data from Texas Medicare beneficiaries, regardless of their age, between 2007 and 2018, from the Texas Cancer Registry. The team analyzed the data for the risk of cancer after IMD use associated with demographic characteristics, clinical conditions, and subsequent cancer type. Of 29,196 patients who used IMD for a variety of indications, 5,684 developed cancer. This study, published in *Cancers* on June 11, 2023, showed that patients receiving IMD had a fourfold greater likelihood of developing cancer than the general population, even with short-term use. The University of Texas Medical Branch at Galveston received a $2.9 million CPRIT Core Facility Support Awards grant (RP210130) in August 2021 to continue the Data Management and Analysis Core (DMAC) of the Comparative Effectiveness Research on Cancer in Texas.

211. T-cell based immunotherapies target diseased cells, including cancer metastasis, which makes them strong candidates in the fight against cancer and infectious diseases. However, there are safety concerns regarding the possible recognition of unknown off targets displayed by healthy cells. In order to make T-cell immunotherapy safer, researchers at the University of Houston developed a tool called CrossDome. "Our CrossDome tool uses a combination of different types of information (called multi-omics) to make predictions and identify whether the treatment might accidentally harm healthy cells in addition to targeting the intended diseased cells," said Dinler Antunes, D.Sc, assistant professor of computational biology and member of the Center for Nuclear Receptors and Cell Signaling. As reported in *Frontiers in Immunology* on June 12, 2023, the team used it to predict potential mistakes in 16 well-known cases of T-cell cross-reactivity, including a melanoma-heart damage case. CrossDome successfully identified the heart protein as a potential target for the T-cells, ranking it as a high-risk candidate among thousands of other proteins. To strengthen the results further, Dr. Antunes combined information from different functional data sets to help determine how much certain genes are expressed and how likely they are to bind with a certain molecule, called HLA, to trigger an immune response. CrossDome can be easily incorporated into existing antigen discovery pipelines, therefore aiding the selection of immunotherapy applications. The University of Texas Medical Branch at Galveston received a $4 million CPRIT Research Training grant (RP170593) in November 2016 to bring together cancer biologists and clinicians with an inter-institutional program in Computational Cancer Biology (CCBTP).

212. The minichromosomal maintenance (MCM) proteins are essential DNA replication factors crucial for initiating DNA synthesis once every cell cycle. MCM8 and MCM9 are more recent evolutionary additions to the MCM family. Mutations in these genes are directly linked to ovarian insufficiency, infertility, and several cancers, yet little is known about how it works and its connection to disease. In this study, the researchers, including CPRIT scholar Yang Gao, Ph.D., assistant professor, Department of Biosciences at Rice University, first used cryo-EM to visualize and solve what the structure looks like in order to start to build a structure. Since an impure or unstable sample would prevent the cryo-EM from revealing any precise structural information on the MCM8/9 complex, they also created a stable pure protein solution. With this new information, the team created a roadmap to better understand the function of this enzyme complex and how mutations may be connected to disease. The research was published in *Nucleic Acids Research* on June 13, 2023, and provides a comprehensive and quantitative biochemical and structural characterization of the HsMCM8/9 helicase

complex. Rice University recruited Dr. Gao with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR190046) in May 2019.

213. The Oncotype DX test predicts cancer recurrence and determines the benefit of adjuvant chemotherapy based on a patient's genetic profile. However, the optimal threshold of the Oncotype DX score in predicting chemotherapy benefit and its racial variation has not been investigated. In this study, researchers from Baylor College of Medicine, including CPRIT Scholar Chao Cheng, Ph.D., associate professor, Department of Medicine, and CPRIT Scholar Christopher Amos, Ph.D., professor and chief, Department of Medicine, provide a method for more accurately calibrating multigene molecular tests, like the Oncotype DX test, in racially and ethnically diverse patients with cancer. The team conducted a population-based, retrospective cohort study using the SEER Oncotype DX database, which contains various data for breast cancer patients diagnosed between 2004 and 2015, and determined chemotherapy benefit thresholds in early-stage, estrogen-receptor-positive (ER+), and HER2-negative (HER2–) patients of different races. The results, reported in *Cancers* on June 16, 2023, highlighted racial differences in the efficacy of chemotherapy indicating that White, Black, and Asian women with early-stage breast cancer benefited from chemotherapy at different Oncotype DX scores, including some at lower threshold scores than current guidelines suggest. Baylor College of Medicine recruited Dr. Cheng in August 2018 with the support of a $4 million CPRIT Recruitment of Rising Stars grant CPRIT (RR180061) and recruited Dr. Amos in August 2017 with a $6 million Recruitment of Established Investigators grant (RR170048).

214. The brain uses two types of cells, neurons and astrocytes, which work closely together for olfactory perception. Research has shown that many of the changes occur in neurons during olfactory perception, but what the astrocyte responses are and how they contribute to the sensory experience remains unclear. Researchers at Baylor College of Medicine and collaborating institutions reported in the journal *Science* on June 16, 2023, that losing transporter Slc22a3 in astrocytes reduced serotonin levels in the cells and led to alterations in serotonin-bound DNA, which then disturbed the neural circuits of olfactory sensation. "This project has uncovered novel aspects of astrocyte function," said corresponding author Benjamin Deneen, Ph.D., professor and chair, Department of Neurosurgery and director of the Center for Cancer Neuroscience at Baylor. "We are learning that astrocytes are very plastic, just as neurons are, meaning that astrocytes can change their characteristics and functions in response to environmental stimuli. They listen to neurons and respond, and their two-way communication is at the core of sensory processing and ultimately, animal behavior." Baylor College of Medicine received a $4 million CPRIT Core Facility Support Awards grant (RP210227) in August 2018 to facilitate comprehensive multiomic studies in preclinical models.

215. Cancer cells, particularly metastasizing cancer cells, often experience high levels of oxidative stress, an imbalance between the production of reactive oxygen species (ROS) and the ability of cells to counteract or repair the damage caused by these ROS. In response to this stress, the cells have a high demand for the amino acid cysteine from the extracellular space to build up their antioxidant defense systems. The cystine transporter solute carrier family 7 member 11 (SLC7A11) has a well-established role in protecting cells from oxidative stress–induced cell death (e.g., ferroptosis), and it is overexpressed in many human cancers. Corresponding author Boyi Gan, Ph.D., professor, Department of Experimental Radiation Oncology at The University of Texas MD Anderson Cancer Center, reported that, whereas moderate overexpression of SLC7A11 is beneficial for cancer cells treated with H_2O_2, a common oxidative stress inducer, its high overexpression dramatically increases H_2O_2-induced cell death. The results published in *Nature Communications* on June 21, 2023, reveal that SLC7A11 expression level dictates cancer cells' sensitivity to oxidative stress and suggests a context-dependent role for SLC7A11 in tumor biology. The University of Texas MD Anderson Cancer Center received two CPRIT Academic Research grants (RP220258, RP230072) totaling $2.1 million in 2022 and 2023 to understand how ferroptosis is controlled at molecular levels in cancer cells and to design and test rationale therapies of combining ferroptosis inducers with other compounds in cancer treatment.

216. It is well-documented that males have higher incidence and worse prognosis with metastatic colorectal cancer (CRC)

– the second most common cause of cancer death – than females. However, the underlying mechanisms for these differences have been mainly attributed to lifestyle differences and possibly sex hormones. Corresponding author Ronald DePinho, M.D., professor, Department of Cancer Biology, and fellow researchers at The University of Texas MD Anderson Cancer Center have uncovered a gene on the Y chromosome that is upregulated in KRAS-mutated CRC, increasing tumor cell invasiveness, and reducing anti-tumor immunity in male patients. The data, published in *Nature* on June 21, 2023, showed that when the researchers removed the KDM5D gene from cancer cells in the mouse model, the cancer became less invasive, and the immune system was better able to kill the cancer cells. "We now have an actionable target meriting further investigation, providing a path to intercept that will change the natural history of the disease in men with KRAS-mutant colorectal cancer," said Dr. DePinho. The University of Texas MD Anderson Cancer Center received two CPRIT Research Training and one Individual Investigator grants (RP170067, RP210028, RP220364) in 2017, 2021, 2022 totaling $9 million.

217. Homologous recombination (HR) is a critical DNA repair process. DNA repair is a process through which cells identify and correct damage to their genetic material. Failure to repair this damage can lead to cell death or genomic instability, which may cause cells to become cancerous. Scientists at The University of Texas Health Science Center at San Antonio, including CPRIT Scholars Patrick Sung, Ph.D., Shaun Olsen, Ph.D., Alexander Mazin, Ph.D., and Elizabeth Wasmuth, Ph.D., have made an important discovery about HR by using a technique called single-molecule DNA curtain analysis. The team studied a group of proteins, BCDX2, which play a key role in HR by helping repair proteins bind to single-stranded DNA during the repair process. Using advanced imaging techniques, the scientists revealed the structures of BCDX2 both alone and when bound to single-stranded DNA. This allowed them to understand how the individual components of BCDX2 interact to form the repair complex and specifically bind to single-stranded DNA. These findings, published in *Nature* on June 21, 2023, provide important insights into how certain changes in these proteins can affect the repair process in our cells, which could have implications for understanding and treating cancer and other genetic diseases. The University of Texas Health Science Center at San Antonio recruited Dr. Sung in 2018 (RR180029), Dr. Olsen in 2020 (RR200030), Dr. Mazin in 2021 (RR210023), and Dr. Wasmuth in 2022 (RR220068). The University of Texas Health Science Center at San Antonio received a CPRIT Academic Research grant (RP220269) in 2022.

218. Myogenesis, the developmental process in embryo where the myoblast differentiates into a muscle cell, is a critical determinant of skeletal muscle development. Key transcriptional regulators work together in a complex and coordinated way to regulate the spatial and temporal expression required for myogenic commitment, regeneration and homeostasis. Dayne Mayfield, Ph.D., professor, Department of Neuroscience at The University of Texas at Austin, and colleagues have found that a specific chemical modification called methylation is necessary for activating a protein called skNAC, which plays a role in the production of myoglobin, a protein important for muscle function. They also discovered how two other proteins, SMYD1 and skNAC, work together in the process of muscle formation. As published in *Cells* on June 22, 2023, the data revealed the molecular mechanisms underlying the cooperation between SMYD1 and skNAC in myogenesis and implicates the MYND domain of the SMYD-family KMTases as an adaptor to target substrates for methylation (a mechanism that can modify the function of the genes). The University of Texas at Austin received a $200,000 CPRIT High Impact/High Risk grant (RP100612) in 2010. The University of Texas MD Anderson Cancer Center received a $5.9 million Core Facility Support Awards grant (RP120348) in 2011 to enhance the Molecular Biology Facility Core at Science Park by adding an Illumina HiSeq 1000 and its associated equipment to support next-generation sequencing.

219. Mesenchymal stromal cells (MSCs) are cells found in bone marrow that play an important role in supporting the health and functioning of hematopoietic stem cells, the cells that produce all blood cells. Several new selective murine double minute 2 inhibitors (MDM2i) have been developed and advanced into early phase clinical trials in different cancers, with promising results. However, dose-limiting hematopoietic toxicities often lead to ineffective treatment. Corresponding author Michael Andreeff, M.D., Ph.D., professor of Medicine, Department of Leukemia, director of the Flow Cytometry and Cellular Imaging Facility, and colleagues at The University of Texas MD Anderson Cancer Center, investigated the effects

of Mdm2 deficiency on MSCs and explored the role of p53 in MSCs in drug-related cytopenia (a reduction in the number of mature blood cells). These data, published in *Nature* on June 23, 2023, reported that a balance between Mdm2 and p53 is crucial in maintaining MSCs as well as to the survival of hematopoietic cells in response to DNA damage. Thus, the role of the Mdm2/p53 pathway in homeostasis of the bone marrow microenvironment could have important therapeutic implications. The University of Texas MD Anderson Cancer Center received a $6 million CPRIT Multi-Investigator Research Awards grant (RP160693) in 2016.

220. Therapy resistance to second-generation androgen receptor (AR) antagonists, such as enzalutamide, is common in patients with advanced prostate cancer (PCa). To understand this resistance, Ram S. Mani, Ph.D., assistant professor in the Departments of Pathology and Urology, The University of Texas Southwestern Medical Center, and colleagues performed analyses of enzalutamide-sensitive and -resistant PCa cells, xenografts, patient-derived organoids, patient-derived explants, and tumors. Published in *Oncogene* on June 24, 2024, the data revealed that glutamine metabolism was consistently upregulated in enzalutamide-resistant PCa cells and castration-resistant tumors. The team identified a metabolic need to maintain antioxidant programs and a potentially targetable metabolic vulnerability in enzalutamide-resistant PCa. The University of Texas Southwestern Medical Center received a $900,000 CPRIT Individual Investigator grant (RP190454) in February 2019 to help in the development of epigenetic therapies for cancer and personalized epigenomics. UT SOUTHWESTERN received a $3.99 million CPRIT Research Training grant (RP160157) in November 2015.

221. Lockdown measures enacted in 2020 to control the spread of COVID-19 led to increases in the prevalence of mental health problems. However, individuals with chronic diseases may be at increased risk and disproportionately adversely affected by the COVID-19 pandemic. CPRIT Scholar Christopher Amos, Ph.D., professor, Department of Medicine and section chief of Epidemiology and Population Sciences at Baylor College of Medicine, and colleagues examined the characteristics associated with loss of social connectedness, the strength of associations between mental health and changes in social connectedness, and whether the pandemic differentially affected those associations between mental health and social connectedness in individuals with high-risk chronic diseases. The team found that the association between the loss of close contacts since lockdowns and COVID-19-specific distress (PII-N) was stronger for those respondents living with and managing chronic illnesses that put them at higher risk for severe COVID-19. The results, published in *Environmental Research and Public Health* on June 24, 2023, reported that a loss of contacts was also associated with living situation and unemployment during the pandemic. In the event of ongoing or new public health crises, psychosocial interventions targeting individuals identified as high-risk for disease and death should be developed and rapidly implemented. Baylor College of Medicine received a $2.98 million Research Training CPRIT grant (RP160097) in November 2015.

222. Glucose plays a central role in tumor metabolism and development and is a target for novel therapeutics. CPRIT Scholar Thomas Yankeelov, Ph.D., professor, Department of Biomedical Engineering, Diagnostic Medicine, and Oncology, and David Hormuth, Ph.D., Center for Computational Oncology, and colleagues from The University of Texas at Austin, collected time-resolved microscopy data to track the growth of MDA-MB-231 breast cancer cells to characterize the response of cancer cells to blockade of glucose uptake. This study sought to extend the mathematical model the team had previously developed that predicts tumor cell growth depending on the availability of glucose. As reported in *Scientific Reports* on June 27, 2023, the team calibrated and validated the model in a triple-negative breast cancer cell line. This mechanism-based model presents predictive capability comparable to complicated machine learning models but is much easier to interpret and provides the opportunity to directly guide further experiments and analysis in a way not possible with a machine learning approach. The University of Texas at Austin recruited Dr. Yankeelov in 2015 from Vanderbilt University with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR160005). The University of Texas at Austin was awarded a $1.2 million Academic Research grant (RP220225) in 2022.

223. Lysine-specific demethylase 1 (LSD1) is an epigenetic eraser that is implicated in the regulation of tumor initiating cells.

In glioblastoma (GBM), LSD1 is overexpressed in the tumor initiating cells, glioblastoma stem cells (GSCs), and LSD1 directed therapy. However, there is no clinically viable strategy to treat GBM with LSD1 inhibition yet. Researchers from The University of Texas MD Anderson Cancer Center sought to understand the relationship between LSD1 and RTK/MAPK signaling and to evaluate the combination efficacy of LSD1 inhibition and kinase signaling inhibition in GBM. The results of this study, published in *The Journal of Pharmacology and Experimental Therapeutics* in June 2023, demonstrate that MAPK activity can be modulated via inhibition of LSD1, and perhaps support the emergence of a resistant subpopulation. This data emphasizes the importance of preemptive therapeutic strategies to improve efficacy and avoid therapeutic resistance that is common in GBM. Salarius Pharmaceuticals, Inc., received a $16.1 million CPRIT New Company Product Development Award (DP160014) in May 2016 to support the development of novel drugs for rare pediatric cancers and other cancers by focusing on treatments that interrupt the final steps of the signaling cascade.

224. Obesity is one of the major risk factors of cancer, but the underlying mechanisms are not well known. Interleukin-15 (IL-15) is a known stimulator of immune cells and studies suggest that plasma IL-15 levels are negatively correlated with body mass index (BMI). Recently small nucleolar RNAs (snoRNAs) have been implicated as biomarkers for several cancers. Researchers including CPRIT Scholar Leng Han, Ph.D., Department of Biochemistry and Molecular Biology at The University of Texas Health Science Center at Houston, and CPRIT Scholar Zhi Tan, M.D., Ph.D., Department of Pathology, Baylor College of Medicine, profiled snoRNAs in serum from obese human donors, and discovered that lab models that overexpressed SNORD46 developed obesity and had impaired anti-tumor immunity. As reported in *Cell Metabolism* on June 16, 2023, the team used a snoRNA power inhibitor to block SNORD46 which resulted in anti-obesity effects and improved anti-tumor immunity of chimeric antigen receptor (CAR) NK cell therapy. This data highlights the importance of snoRNAs in obesity and in the immune response, demonstrating their therapeutic potential. The University of Texas MD Anderson Cancer Center received two CPRIT Academic Research grants (RP180259, RP200423). The University of Texas Health Science Center at Houston recruited Dr. Han in 2015 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR150085). Baylor College of Medicine recruited Dr. Tan in 2022 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR220039).

225. Translation regulation is the process of turning RNA into proteins and is critical in the early development of mammalian embryos. Up until now, scientists have had limited knowledge about what happens immediately after an egg is fertilized. A new technology developed by a team from The University of Texas at Austin, including CPRIT Scholar Can Cenik, Ph.D., assistant professor in the Department of Molecular Biosciences, allows researchers to study translation in careful detail in single cells and embryos. Ribo-ITP uses a specially designed micro-fluidic chip to isolate fragments of RNA which are in the process of being read by ribosomes to produce proteins. The research, published in *Nature* on June 21, 2023, revealed which genes are translationally regulated as an egg matures and is fertilized. The team integrated their measurements with proteomics data -- a large-scale study of proteins -- and discovered that ribosome occupancy in germinal vesicle-stage oocytes is the predominant determinant of protein abundance in the zygote. This study demonstrates the type of new biological insights that can be expected from the application of Ribo-ITP, which will help to answer fundamental questions in translational control relevant to samples with limited input amounts, including embryonic tissues and cancer stem cells. The University of Texas at Austin recruited Dr. Cenik from Stanford University School of Medicine in August 2018 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR180042).

226. Immune checkpoint inhibitors effectively target advanced malignancies but also predispose patients to immune-related adverse events like immune-mediated colitis (IMC). Previous studies suggest fecal microbiota transplantation (FMT), which delivers healthy human donor stool to a recipient, can help restore the gut microbiome balance and improve treatment responses. In the largest case series to date, researchers at The University of Texas MD Anderson Cancer Center led by Yinghong Wang, M.D., Ph.D., Department of Gastroenterology, Hepatology and Nutrition, and CPRIT Scholar Robert Jenq, M.D., associate professor, Department of Genomic Medicine, evaluated FMT in 12 patients with refractory IMC

who failed to respond to standard first-line corticosteroids and second-line treatments. The results, published in *Science Translational Medicine* on June 14, 2023, reported that ten patients (83%) achieved symptom improvement and 92% achieved IMC clinical remission. The researchers noted significant increases in specific bacterial signatures that may play a role in improving the immune response. This study demonstrated the promise of FMT as a therapeutic strategy to better manage toxicities associated with checkpoint blockade. The University of Texas MD Anderson Cancer Center recruited Dr. Jenq in September 2016 from the Memorial Sloan-Kettering Cancer Center with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR160089).

227. Despite significant clinical advancement with the use of immune checkpoint blockade (ICB) in non-small cell lung cancer (NSCLC), there are still a major subset of patients that develop adaptive/acquired resistance. In this study Don Gibbons, M.D., Ph.D., professor, Department of Thoracic/Head and Neck Medical Oncology at The University of Texas MD Anderson Cancer Center, and colleagues sought to understand which immune cells were contributing to resistance and attempt to modify them in a way to improve response to ICB therapy. Therapeutically the researchers found that the addition of anti-Ly6C to the combination of anti-PD-1/CTLA-4 was capable of complete tumor eradication. The data, published in *Frontiers in Immunology* on June 28, 2023, supports that immunotherapy resistance is associated with infiltrating monocytes and that controlling monocytes can enhance the therapeutic potential of ICB. The University of Texas MD Anderson Cancer Center received two $900,000 CPRIT Academic Research grants (RP150405, RP200235) in 2015 and 2020, and a $5.98 million CPRIT MIRA grant (RP160652) in 2016.

228. The adult human breast is comprised of an intricate network of epithelial ducts and lobules that are embedded in connective and adipose tissue. Researchers at The University of Texas MD Anderson Cancer, University of California, Irvine and Baylor College of Medicine set out to study the many breast non-epithelial cell types that remain understudied. With non-epithelial cell types being understudied, the team was driven to develop an atlas to establish a baseline for typical cell function and uncover cell interactions that may lead tissue toward disease. The data published in *Nature* on June 28, 2023, reported that the team used single-cell and spatial genomic methods to profile more than 714,000 cells from 126 women. The study revealed significant differences in breast tissue composition and cell states that were dependent upon ethnicity, age, and menopause status. From this data, the team created the comprehensive Human Breast Cell Atlas, the world's largest map of normal breast tissue, providing an unprecedented understanding of mammary biology that may help identify therapeutic targets for diseases such as breast cancer. "We are thrilled to see the completion of this monumental seven-year project," said senior corresponding author Nicholas Navin, Ph.D., chair of Systems Biology at MD Anderson. "We expect this tool will be highly useful for anyone studying breast cancer and other diseases such as mastitis, as well as breast development and lactation failure." The University of Texas MD Anderson Cancer Center received a $4.9 million CPRIT Core Facility Support Awards grant (RP180684) in August 2018 to establish an Integrated Single Cell Genomics (SCG) Core Facility at The MD Anderson Cancer Center.

229. Lung cancer causes an estimated 25% of cancer deaths. Early detection improves prospects of survival, but fewer than half of all U.S. cases are among people who are eligible for screening under U.S. Preventive Services Task Force (USPSTF) guidelines. Researchers at The University of Texas MD Anderson Cancer Center have developed a blood-based test which can predict an individual's risk of dying from lung cancer when combined with a personalized risk model. According to new data published on June 28, 2023, in the *Journal of Clinical Oncology*, a blood-based four-protein panel (4MP), when combined with a lung cancer risk model (PLCOm2012), can better identify those at high risk of dying from lung cancer than the current USPSTF criteria. "This simple blood test has the potential to save lives by determining the need for lung cancer screening on a personalized basis," said co-corresponding author Samir Hanash, M.D., Ph.D., professor of Clinical Cancer Prevention. "Given the challenges associated with CT as a frontline screening method for lung cancer and the fact that most individuals diagnosed with the disease do not meet current guidelines, there is an urgent demand for an alternative approach." The University of Texas MD Anderson Cancer Center received a $799,085 CPRIT Academic research grant (RP180505) in February 2018 to help reduce mortality associated with lung cancer through more effective screen-

ing strategies.

230. The ability to map the trafficking for thousands of endogenous proteins simultaneously in living cells would reveal biology currently invisible to both microscopy and mass spectrometry. Human DNA contains genetic instructions that guide the formation of proteins, which are crucial for the structure and functioning of our bodies. However, understanding the entire collection of proteins within a cell or a specific area, known as the proteome, is challenging because of its complex nature. To help decipher this complexity, Alice Ting, Ph.D., professor, Department of Genetics at Stanford Medicine, led the development of a new method, called TransitID, for tracking the complete activity of proteins in living cells. CPRIT Scholar Steven Boeynaems, Ph.D., assistant professor, Department of Molecular and Human Genetics at Baylor College of Medicine, and team reported this novel method in a paper published June 28, 2023, in *Cell*. TransitID allows researchers to combine the strengths of both microscopy and mass spectrometry proteomics by looking at living samples and seeing all the proteins at once. Tracking proteins at this level could reveal information about how cells communicate which in turn could lead to applications for research into various diseases and treatments, including cancer and neurodegenerative diseases. Baylor College of Medicine recruited Dr. Boeynaems in August 2022 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR220094).

231. Glioblastoma (GBM) represents the most common primary brain tumor. Although antiangiogenics, a treatment that stops tumors from growing their own blood vessels, are used in the recurrent setting, they do not prolong survival. Andrew Brenner, M.D., Ph.D., professor of medicine at The University of Texas Health Science Center at San Antonio initiated a trial of 25 patients to enhance the options for treatment of GBM. "The average survival for a newly diagnosed GBM is 20 months, and that's only a four-month improvement in survival from 2005, when we began following surgery with chemotherapy and radiation," said Dr. Brenner. In this trial, treatment consisted of a standard-of-care chemotherapy called bevacizumab (Avastin) combined with a small-molecule fatty acid synthase inhibitor called TVB-2640 (Denifanstat) in 25 patients with recurrent, high-grade GBM. Side effects such as rashes, dry eye and fatigue were mild, and researchers noted an improvement in six-month progression-free survival. This data, published in *Clinical Cancer Research* on July 1, 2023, supports the initiation of a larger multicenter trial of TVB-2640 plus bevacizumab in this population. The University of Texas MD Anderson Cancer Center received a $4.5 million CPRIT Core Facility Support Awards grant (RP130397) to develop a new Proteomics and Metabolomics Core to advance key projects.

232. LGR4, LGR5, and LGR6 are three related membrane receptors (proteins that are found on the surface of cells) with the ability to influence multiple, often diverse, functions or traits in organ development and the formation of tumors. Loss-of-function mutations in *LGR4* in humans is associated with low bone density, abnormal female reproductive systems and other traits while knockout of *Lgr4* in the mouse led to developmental defects with phenotypes similar to those of human mutation. Previously, Qingyun Liu, Ph.D., professor and director, IMM-Center for Translational Cancer Research, and colleagues at The University of Texas Health Science Center at Houston, showed that the R-spondin (RSPO) ligands and the LRG5 complex does not interact with RNF43/ZNRF3 whereas LRG4 interacts with ZNRF3/ZNRF3, even without RSPO. In this study, the team provided new evidence revealing that LGR4 and LGR5 display distinct configurations on the cell surface when probed by monovalent and bivalent ligands and proposed models that depict quaternary arrangements of LGR4 with RSPO and RNF43/ZNRF3 and of LGR5 with RSPO furin domain. The findings, published in *Scientific Reports* on July 4, 2023, reinforce the notion that LGR4 and LGR5 signals via different mechanisms in Wnt/β-catenin signaling and provide a glimpse of LGR4 and LGR5 configurations on the cell surface that has not been revealed by crystallography or cryo-EM analysis. The University of Texas Health Science Center at Houston received two CPRIT Academic Research grants (RP190542, RP220169) totaling $3.05 million.

233. Every day, roughly 350 patients are expected to die from lung cancer, making it the leading cause of cancer-related death in the U.S. To obtain a more comprehensive understanding of lung cancer development, treatment, and outcomes, CPRIT Scholar Christopher Amos, Ph.D., professor and chief, Department of Medicine, and colleagues at Baylor College of

Medicine examined various epidemiological factors and psychiatric comorbidities in primary and secondary lung cancer. This cross-sectional, case–control study aimed to answer the research question of whether the prevalence and impact of smoking-related behaviors, psychiatric comorbidities, and other epidemiological factors differ between primary and secondary lung cancer patients compared to light smoking and matched smoking controls This is the first study to report key epidemiological information in lung cancer from the "All of Us" research program, which focuses on recruiting historically underrepresented individuals. As reported in *Nature* on July 5, 2023, the results from this analysis demonstrated that primary lung cancer patients have significantly higher odds of having comorbid substance use disorder, insomnia, bipolar disorder, disorder caused by alcohol, depressive disorder, and anxiety when compared to their LSC-1 controls. Secondary lung cancer patients had significantly higher odds of having substance use disorder, insomnia, and anxiety compared to their LSC-2 controls. Understanding the relationship between lung cancer, smoking, and psychiatric disease may help oncologists collaborate closely with mental health professionals to provide well-rounded, comprehensive care to lung cancer patients. Baylor College of Medicine recruited Dr. Amos in August 2017 with a $6 million Recruitment of Established Investigators grant CPRIT grant (RR170048).

234. Secretion systems, which are bacterial cell envelope-located protein complexes, are used by bacteria to promote infection. The GspD secretin is the outer membrane channel of the bacterial type II secretion system (T2SS) which secretes diverse toxins that cause severe diseases such as diarrhea and cholera. With T2SS's diverse substrate functions and close relevance to diseases, knowing its structure and working mechanism are important for understanding bacteria functions and developing antimicrobial strategies. Corresponding author, Zhao Wang, Ph.D., assistant professor, Department of Biochemistry and Molecular Biology at Baylor College of Medicine, and fellow researchers investigated two types of secretins discovered so far in *Escherichia coli*, $GspD_{\alpha}$, and $GspD_{\beta}$. The team determined four in situ structures of the T2SS secretin: both the inner and outer membrane structures of $GspD_{\alpha}$ and $GspD_{\beta}$. $GspD_{\alpha}$ exists in an unstable form on the inner membrane, but forms firm and stable connections with the outer membrane. The $GspD_{\beta}$ multimer exists on the inner membrane in wild-type *E. coli*, and $GspD_{\beta}$ on the outer membrane exists together with GspS. These results, published in *Nature Communications* on July 7, 2023, indicate that the $GspD_{\alpha}$ multimer is not integrated into the bacterial inner membrane. Instead, it only forms a loose connection with significant mobility, facilitating its further transportation to the outer membrane. The data add to the knowledge of the membrane interactions of the T2SS secretins and their outer membrane targeting process, providing a comprehensive model for the secretin biogenesis process of *Proteobacteria*. Baylor College of Medicine received a $5.38 million CPRIT Core Facility Award (RP190602) in 2019 to add new technologies to the two CryoEM Cores which will provide 3-D cellular structure at molecular resolution, allowing researchers to visualize how cancer impacts the molecular interactions within the living cell.

235. Financial toxicity (FT) refers to the personal economic burden experienced by individuals with cancer. This burden manifests in various ways, including non-adherence to treatment and the development of psychological distress related to financial concerns. Researchers from The University of Texas MD Anderson Cancer Center piloted a Spanish version of the Economic Strain and Resilience in Cancer (ENRICh) FT measure using qualitative cognitive interviews and surveys to evaluate the acceptability and appropriateness of the Spanish language instrument for assessing FT. The team also set out to conduct exploratory analyses of the impact of insurance status and English language proficiency on FT outcomes for un-/under-insured English-speaking Hispanics and insured English-speaking Hispanics receiving ambulatory oncology care at a public healthcare safety net hospital in the Houston metropolitan area. The results, published in *Frontiers in Psychology* on July 10, 2023, revealed that lower education and income were accompanied by low access to health insurance. Un- or under-insurance was a significant predictor of FT, and while language acculturation was not found to be an independent risk for FT in exploratory analysis, further exploration of the differences among lower and higher English proficiency in additional diverse subpopulations continue to be warranted. The University of Texas Medical Branch at Galveston received a $6 million CPRIT Multi-Investigator Research grant (RP160674) in August 2016. The University of Texas Southwestern Medical Center received a $1.5 million CPRIT Early Clinical Investigator grant (RP210140) in August 2021.

236. Contraception options, especially for females, have consisted of hormone manipulation or a barrier method. However, a hormone-based contraception for males may not be a feasible option due to unwanted physiological changes. Researchers from Baylor College of Medicine, seeking to find a way to develop a non-hormonal male contraceptive pill, targeted reproductive tract-specific proteins known to be required for male fertility. Serine protease 37 (PRSS37) is a sperm-specific protein that when ablated in mice renders them sterile. Corresponding author Martin M. Matzuk, Ph.D., professor and chair of the Department of Pathology & Immunology, and colleagues sought to examine the molecular sequelae of PRSS37 loss to better understand its molecular function. As reported in *Scientific Reports* on July 14, 2023, using Prss37 KO mice and proteomics confirmed that PRSS37 is essential for male fertility and demonstrated that fertility can be rescued using a humanized PRSS37 protein in a mouse model that was generated in the laboratory. These findings further validate the pursuit of PRSS37 as a target for non-hormonal male contraception and the creation of a novel tool for contraceptive evaluation. Baylor College of Medicine received a $4 million CPRIT Core Facility Support Awards grant (RP210227) in August 2018 to facilitate comprehensive multiomic studies in preclinical models.

237. Receptor tyrosine kinases (RTKs) are important proteins in our cells that regulate various cellular processes. They are typically activated through a precise sequence of intracellular phosphorylation events starting with a tyrosine residue on the activation loop (A-loop) of the kinase domain (KD). They act like switches, turning on or off specific signaling pathways that control functions like cell growth and development. However, additional control is exerted by intracellular amino acid sequences peripheral to KD. The modus operandi of these regions varies across different receptors and can lead to both down- and up-regulation of kinase activity. As reported in *Communications Biology* on July 14, 2023, this disruption can lead to the development of various diseases, such as cancer, where the uncontrolled activation of RTKs can drive abnormal cell growth and tumor formation. Thus, understanding the roles of these interactions will help suggest alternative routes for therapeutic intervention outside inhibition of kinase activity. The University of Texas MD Anderson Cancer Center received a $5.96 million CPRIT Multi-Investigator Research Awards grant (RP180813) in August 2018 to increase the probability of long-term survival for BRCA positive cancer patients.

238. Patients with advanced or metastatic disease often undergo genomic sequencing to identify alterations that may affect therapeutic decision-making and provide additional approved or investigational options. However, a large percentage of alterations detected in patient samples have not been previously experimentally or clinically characterized, may not appear within these knowledge bases, and fall within the unknown or uncertain classification (variants of unknown significance, VUS). To address the real-time need for determining whether a variant is likely to be functionally significant and therapeutically actionable, the The University of Texas MD Anderson Precision Oncology Decision Support (PODS) team created a tiered actionability scheme. Corresponding author Funda Meric-Bernstam, M.D., chair of the Department of Investigational Cancer Therapeutics, and colleagues aimed to assess the oncogenic potential of VUS in actionable genes. They utilized a functional genomics platform employing two cell lines, MCF10A and BaF3, to measure the impact of genetic alterations on cell viability, particularly under conditions where cells are not dependent on external growth factors. Altogether these data, published in *NPJ Precision Oncology* on July 15, 2023, demonstrate that functional annotations relying on experimental data cannot be replaced by predicted functionality by proximity and protein features, as 63% of VUS classified as Potentially actionable were not functionally validated in the systems assessed. However, the PODS tiered VUS actionability scheme does add value in stratifying alterations more likely to be functionally significant: 37% of the Potentially actionable variants had a functionally significant effect in the functional genomics platform. This information would be important to take into consideration for an individual patient. Therefore, genomic annotation of VUS may identify additional patients that benefit from emerging therapeutics. The University of Texas MD Anderson Cancer Center received a $6 million CPRIT Core Facility Support Awards grant (RP150535) in May 2015.

239. Tissues such as the liver, kidney, and intestine carry out diverse biological functions. A division of labor among cells within these tissues is spatially organized into "zones" that follow a unique set of instructions written in their genes to perform specialized tasks. Liver zonation is dynamic and can change during development, aging, and disease, making

it important to measure changes in zonal boundaries and gene expression patterns under different biological conditions. The quantification of important features within a tissue and understanding how they are spatially organized are necessary for this kind of analysis, but it is labor-intensive and difficult to do manually while maintaining precision and accuracy. Tao Wang, Ph.D., assistant professor, Peter O'Donnell Jr. School of Public Health | Center for Genetics of Host Defense at The University of Texas Southwestern Medical Center, and colleagues addressed this challenge by developing a deep-learning-based quantification method called the "Tissue Positioning System" (TPS), which can automatically analyze zonation in the liver lobule as a model system. The data, published in *eBioMedicine* on July 12, 2023, reported that TPS was able to determine the expression pattern of reporter mice with zone-specific expression and mice with undefined, sparse expression patterns. Any measurable tissue feature such as cell size, subcellular structures, inflammatory cells, lipid droplets, cell proliferation, or cell death can be integrated into TPS in a modular fashion. The design principles of TPS could be generalized to other tissues to explore the biology of zonation. The University of Texas Southwestern Medical Center was awarded three CPRIT Academic Research grants: a $900,000 grant (RP190208) in August 2019, a $237,501 grant (RP220614) in September 2022, and a $1.3 million CPRIT Academic Research grant (RP230330) in February 2023.

240. Multiple myeloma (MM) is the second most common hematologic malignancy and leads to osteoclast (OCL) activation and bone lesions in 80% of patients. Current treatments that target osteoclast function only partially inhibit osteolytic bone disease and are accompanied by side effects such as osteonecrosis (bone death) of the jaw. Alternative therapies that specifically intercept the osteoclastogenic factors that are generated at the MM-OCL interface are needed to improve treatment outcome. Gabriel Pagnotti, Ph.D., assistant professor, Department of Endocrine Neoplasia and Hormonal Disorders – Research at The University of Texas MD Anderson Cancer Center, and team previously demonstrated that MMP-13 is a critical osteoclastogenic factor that is highly expressed by human MM cells. This data, published in *Nature Communication*s on July 17, 2023, suggests that MMP-13 promotes c-Src signaling via a PD-1H-dependent process. In MM patients, OCLs express checkpoint molecules such as PD-L1 and IDO that may contribute to T-cell inhibition and immune suppression. These findings identify a role of PD-1H in bone biology separate from its known immunoregulatory functions and suggest that targeting the MMP-13/PD-1H axis could be a potential approach for treating myeloma-associated osteolysis. The University of Texas MD Anderson Cancer Center recruited Dr. Theresa Guise from Indiana University School of Medicine with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR190108) in November 2019.

241. An increasing number of patients are being treated with CAR T cell therapy; however, real-world toxicity continues to remain a significant challenge to its widespread adoption. The potent systemic immune activation responsible for the success of CAR T cells also drives the life-threatening toxicity of cytokine release syndrome (CRS), neurotoxicity, and impaired hematopoietic recovery that impose significant morbidity and mortality. CPRIT Scholar Christopher Flowers, M.D., M.S., Department of Lymphoma – Myeloma at The University of Texas MD Anderson Cancer Center, and team have previously shown that allogeneic umbilical cord blood-derived (UCB) regulatory T cells (Tregs) can resolve inflammation and treat acute and immune-mediated lung injuries. In this study, the researchers hypothesized that adjunct therapy with UCB-derived Treg cells may resolve the undesirable inflammation responsible for CAR T cell therapy-associated toxicity. The results were published in *Cells* on July 18, 2023, and provided proof of concept for adjunct therapy with UCB Treg cells to mitigate the hyper-inflammatory state induced by CAR T cells in a xenogeneic lymphoma model without interfering with the CAR T cells' on-target anti-tumor activity. This data supports further exploration of adjunct therapy with UCB Treg cells in high-risk patients with B-cell lymphoma/leukemia who are prone to developing cytokine release syndrome (CRS). The University of Texas MD Anderson Cancer Center recruited Dr. Flowers in August 2019 from Emory University School of Medicine with the support of a $6 million CPRIT grant (RR190079).

242. Uterine fibroids (UFs) are benign tumors of the uterus with an estimated prevalence of ~70% among women of reproductive age. Multiple risk factors have been identified that contribute to the development of UFs, including the harmful

environmental exposure to substances such as endocrine-disrupting chemicals (EDCs). Treatment options are limited and the most common one is hysterectomy. However, the specific mechanisms through which biological pathways are disrupted remain poorly understood. Here, researchers presented evidence demonstrating that developmental exposure to EDCs targets the inflammatory pathways in myometrial stem cells (MMSC), the cell source for UFs. As reported in *International Journal of Molecular Sciences* on July 19, 2023, targeting MLL1 and HDAC epigenetic regulators can reverse notable changes in the expression of inflammatory responsive genes in the MMSCs from Eker rats exposed to EDCs. These findings revealed that early-life exposure to EDCs increases the risk of UF development by reprogramming the epigenome toward the activation of inflammatory pathways. This preclinical study can help researchers better understand the impact of developmental exposure insults on human health. The University of Texas MD Anderson Cancer Center received a $6 million CPRIT Core Facility Support Awards grant (RP120348) in November 2011 to enhance the Molecular Biology Facility Core (MBFC) at Science Park by adding an Illumina HiSeq 1000 and its associated equipment to support next-generation sequencing.

243. Estrogen receptor (ER) is a key transcription factor (the proteins involved in converting DNA into RNA) regulating expression of genes in normal mammary gland development and ER-positive (ER+) breast cancer. Treatment for ER+ breast cancer typically involves endocrine therapy, like tamoxifen, which targets the estrogen receptor. However, many patients eventually develop resistance to this treatment, leading to disease progression and poor outcomes. Corresponding author Rachel Schiff, Ph.D., professor, Department of Molecular and Cellular Biology at Baylor College of Medicine, and colleagues focused on a specific protein, FOXA1, which regulates how the estrogen receptor binds to the genetic material (chromatin) in cells. Through experiments using mice with human breast cancer, the researchers found that high levels of FOXA1 promoted the spread of ER+ breast cancer to other parts of the body. Mechanistically, FOXA1 caused changes in how the estrogen receptor interacts with chromatin, leading to alterations in the activated genes. This change in gene activation resulted in the production of proteins that drive cancer metastasis. These findings, published in *Cell Reports* on July 18, 2023, suggest that inhibiting the interaction between FOXA1 and the estrogen receptor could be a potential strategy to prevent and treat endocrine-resistant ER+ breast cancer. Developing more potent drugs that target the estrogen receptor and potential epigenetic interventions (modifying how genes expression without changing the underlying DNA sequence) may be promising approaches for future treatments. Baylor College of Medicine received two CPRIT Core Facility Support Awards grant (RP180672, RP200504) in August 2018 and 2020, respectively, totaling $9.17 million to purchase high-end equipment that will help identify new therapeutic targets and novel drugs. Baylor College of Medicine received a $900,000 CPRIT Individual Investigator grant (RP190398) in 2019.

244. Appendix cancer is a rare gastrointestinal cancer with limited available treatment options due to the lack of preclinical models. Surgery and heated intraperitoneal (IP) chemotherapy is the current standard of care, but it is not appropriate for patients with a large tumor burden. Researchers led by CPRIT Scholar John Paul Shen, M.D., hypothesized that IP paclitaxel, which is safe and effective in other cancers, would also be effective in appendix cancer, since these tumors are in the peritoneal space. This study, published in *Cancer Research* on July 11, 2023, demonstrated the promising therapeutic potential of IP paclitaxel. In three different lab models of appendix cancer, weekly IP paclitaxel significantly reduced tumor growth and had fewer side effects than intravenous chemotherapy. Given the established safety record of IP paclitaxel in gastric and ovarian cancers, and lack of effective chemotherapeutics for AA, these data support the evaluation of IP paclitaxel in a prospective clinical trial patients with metastatic appendix cancer. The University of Texas MD Anderson Cancer Center recruited Dr. Shen in 2018 from the University of California, San Diego with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR180035).

245. Triple negative breast cancer (TNBC) constitutes 10-15% of all breast tumors. The current standard of care is multiagent chemotherapy, which is effective in only a subset of patients. CPRIT Scholar Matthew Ellis, MB BChir, Ph.D., professor, Department of Molecular and Cellular Biology at Baylor College of Medicine, and fellow researchers are developing a strategy to predict the response of TNBC to chemotherapy, which would help physicians decide on the appropriate patient

treatment on an individual basis. The researchers used a laboratory assay called Kinase Inhibitor Pulldown Assay, or KIPA, to search for proteins they could target to control tumor growth. As reported in *Cancer Research Communications*, on July 20, 2023, the team searched for these proteins in 43 frozen tumor biopsies that were part of the previous Clinical Proteomic Tumor Analysis Consortium (CPTAC)-TNBC study. Although their research for these kinases did not produce valuable candidates, the assay captured seven non-kinase proteins, specifically purine-binding proteins, that completely responded to treatment. "The purine binding signature could help identify a subset of TNBC patients who should receive investigational therapy from the outset rather than an ineffective standard chemotherapy approach," said co-corresponding author Dr. Ellis. Baylor College of Medicine recruited Matthew Ellis, MB BChir Ph.D., in 2014 with the support of a $6 million CPRIT Recruitment of Established Investigators Award (RR140033). Baylor College of Medicine received two CPRIT Core Facility Awards (RP170005, RP210227) in 2016 and 2021, respectively, for a total of $8.9 million to support the BCM Mass Spectrometry Proteomics Core.

246. CPRIT Scholar Jun Wu, Ph.D., assistant professor, Department of Molecular Biology at The University of Texas Southwestern Medical Center, and colleagues have developed a new stem cell-based embryo model for studying early human development, tissue formation, and differentiation, offering valuable contributions to the field of developmental biology and regenerative medicine. Dr. Wu noted that generating peri-gastruloids, primitive embryonic structures with the potential to form many of the different cell types of the body, is an important process because researchers can mimic and study the complex processes that occur during gastrulation and early organ formation. The model, described in *Cell* on July 20, 2023, could impact a wide range of diseases and conditions that involve early human development, such as certain types of cancer or neurological disorders, as well as disease modeling and drug testing. "Studying peri-gastruloids allows researchers to gain insights into how abnormalities or genetic mutations can impact the early stages of human development. This knowledge can be used to model and understand developmental disorders or diseases that arise during early embryonic development. Additionally, peri-gastruloids can serve as a platform for testing the efficacy and safety of potential drugs or therapies targeting these conditions," Dr. Wu explained. The University of Texas Southwestern Medical Center recruited Dr. Wu from the Salk Institute for Biological Studies in 2017 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR170076).

247. Acute myeloid leukemia (AML) is a type of blood and bone marrow cancer characterized by an excess of immature white blood cells and by a high rate of therapy resistance. Unfortunately, 40–50% of AML patients have primary refractory disease or relapse shortly after remission. Since cellular lineages can impact resistance to therapy, it is critical to delineate the lineage composition of AML cells at the time of therapy resistance. To understand why therapy resistance occurs in AML, CPRIT Scholar Andy Futreal, Ph.D., Department of Genomic Medicine at The University of Texas MD Anderson Cancer Center, and colleagues applied scATAC-seq profiling to 22 AML bone marrow aspirates from eight patients who had become resistant to treatment. They studied the developmental pathway of AML cells at the time of therapy resistance using advanced single-cell analysis. The team proposed that the acquisition of a differentiation spectrum not only contributes to the generation and maintenance of leukemic stem cells, but it may also create distinct barriers for therapeutic responses ultimately leading to resistance and persistence of AML. The results, published in *Communications Biology* on July 21, 2023, revealed a complex lineage architecture of therapy-resistant AML cells. These cells showed characteristics of stem and progenitor cells, which are early stages of blood cell development, as well as features of more mature blood cells. The resistant AML cells had a range of characteristics spanning different stages of cell development. Based on these findings, the researchers propose that using drugs that reprogram AML cells into a uniformly differentiated state (a state resembling more mature blood cells) as a potential approach to overcome therapy resistance. The University of Texas M.D. Anderson Cancer Center recruited Dr. Futreal in 2011 with the support of a $7 million CPRIT Recruitment of Established Investigators grant (R1205). The University of Texas Health Science Center at Houston received a $4.42 million CPRIT Core Facility Support Awards grant (RP180734) in August 2018 to support the UTHealth Cancer Genomics Core research.

248. RAD51C is a known breast, ovarian, and prostate cancer susceptibility gene associated with treatment resistance, but research has not yet identified its protein structure or the significance of certain mutations. Using CRISPR/Cas9-edited cells with RAD51C mutations, researchers led by John Tainer, Ph.D., and CPRIT Scholar Katharina Schlacher, Ph.D., Department of Cancer Biology at The University of Texas MD Anderson Cancer Center, generated the protein's crystal structure and identified associated DNA replication functions. The study uncovered distinct regions for binding to the DNA repair protein CX3, emphasizing RAD51C's role in cancer-relevant DNA replication pathways. This builds upon previous results from the Schlacher lab showing that having a RAD51C mutation in addition to a BRCA2 mutation was a strong driver of cancer progression in lab models. The data, published in *Nature Communications* on July 24, 2023, indicate that cancer variant testing could be expanded to include DNA replication and related functions for a comprehensive understanding of the potential defects of damaging mutations. It also highlights the potential for using RAD51C mutations in patient risk stratification and treatment response predictions. The University of Texas MD Anderson Cancer Center recruited Katharina Schlacher, Ph.D., in 2014 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (R1312) and two CPRIT Academic Research grants (RP180463, RP180813) in 2018 totaling $6.5 million.

249. Metastatic lung cancer is the leading cause of cancer-related mortality worldwide primarily due to the formation of metastatic lesions, which induce multi-organ failure. Phosphorylation is a chemical modification involving the addition of phosphate groups, specifically mediated by the KRAS pathway. Phosphorylation of the DICER1 enzyme by the KRAS pathway causes its nuclear translocation in human primary lung tumors, suggesting a potential role in metastatic behavior in lung cancer. Researchers led by Swathi Arur, Ph.D., Department of Genetics at The University of Texas MD Anderson Cancer Center, sought to determine whether DICER1 is phosphorylated in human lung adenocarcinomas (LUADs). The team performed immunohistochemistry analysis using anti-phospho-DICER1 and anti-phosphorylated ERK antibodies on 88 LUAD tumors including 38 (~43%) samples with KRAS oncogenic mutations and 50 (~57%) without KRAS oncogenic mutations. The data, published in *Science Advances* on July 26, 2023, identified phosphorylated DICER1 as a biomarker for early metastatic disease and suggests the enzyme may be a potential therapeutic target. The researchers propose that the increased tumor cell plasticity because of lineage reprogramming may be the underlying mechanism through which phosphorylated nuclear DICER1 drives late-stage tumor progression. The University of Texas MD Anderson Cancer Center received a $4.9 million CPRIT Core Facility Support Awards grant (RP180684) in August 2018 to establish an Integrated Single Cell Genomics (SCG) Core Facility at The MD Anderson Cancer Center.

250. Approximately 20-30% of all diagnosed breast cancers are characterized by an overexpression of the human epidermal growth factor receptor 2 (HER2) gene. HER2–targeted treatments have improved survival rates in HER2+ breast cancer patients, yet poor responsiveness remains a major clinical obstacle. Recently, HER2+ breast cancer cells, both resistant and responsive to HER2–targeted therapies, have demonstrated sensitivity to poly–(ADP–ribose) polymerase (PARP) inhibition, independent of DNA repair deficiencies. This study, published in *Biomedicines* on July 25, 2023, investigated the potential of glucose metabolism and cellular proliferation as indicators for assessing the response of HER2+ breast cancer cells to the novel combination of niraparib and trastuzumab. The researchers observed that cellular proliferation, rather than glucose metabolism, emerged as a more suitable metric to assess the response of combination–targeted therapies in breast cancer. The results demonstrate the potential use of cellular proliferation as an indicator in assessing response to the novel treatment combination. PDX tissue was collected by Baylor College of Medicine's Patent–Derived Xenograft core and Advanced *In Vivo* Models Core which is supported by CPRIT Core Facilities Support grant (RP170691).

251. The TP53 gene is a high-frequency target of mutations in human cancers and plays a critical role in regulating various cellular processes, including transcription, DNA synthesis and repair, cell cycle regulation, senescence, and apoptosis (cell death). Mutations in TP53 can disrupt these functions, leading to genetic instability and an increased risk of cancer development. Several tripartite motif (TRIM) proteins are known to regulate cell growth and cell cycle transition. However, the relationship between TRIM family genes and TP53 mutations in cancer remains unknown. In this study, researchers analyzed the links between TP53 mutations and TRIM family proteins and then evaluated the role of TRIM family

proteins in cancer patients with TP53 mutation. As reported in *Cancers* on July 26, 2023, TRIM family members may play a crucial role in the TP53-mediated upregulation of cell-cycle-specific progression genes. These findings suggest that p53 may regulate TRIM family members through specific miRNAs and provide a novel perspective on the TRIM family functions in cancers. The University of Texas Health Science Center at Houston received a $4 million CPRIT Research Training grant (RP210045) in May 2021, to establish a unique collaborative Biomedical Informatics, Genomics, and Translational Cancer Research Training Program (BIG-TCR).

252. Chimeric antigen receptor (CAR) T cell therapy has emerged as a promising approach for cancer treatment in which T cells are engineered to recognize a specific target on tumor cells. However, the systemic immune activation responsible for the efficacy of CAR T cell treatment may cause life-threatening toxicities. Ken Chen Ph.D., professor, Department of Bioinformatics and Computational Biology, and fellow researchers at The University of Texas MD Anderson Cancer Center investigated mechanisms that may be associated with resistance to CAR-NK (natural killer) cell therapy. Using laboratory models of lymphoma, they evaluated cells that expressed either CAR19 alone, IL-15 alone, or both CAR19 and IL-15 to investigate the ability of IL-15 to activate NK cells and to enhance their potency and persistence. The team discovered loss of metabolic fitness in CAR NK cells is a critical mechanism of resistance, with infused cells gradually losing the ability to compete with tumor cells for nutrients, leading to tumor relapse. The study, published on July 26, 2023, in *Science Advances*, demonstrates that engineering CAR NK cells to express interleukin-15 (IL-15) enhances the cells' metabolic fitness and provides a longer-lasting anti-tumor response. The University of Houston received a $1.17 million CPRIT Academic Research Award grant (RP180466) in February 2018. The University of Texas MD Anderson Cancer Center received an $898,997 CPRIT Individual Investigator Research Awards for Computational Biology grant (RP180248) in February 2018.

253. Pyroptosis is an inflammatory cell death that is often associated with prominent tissue inflammation. It mainly occurs in myeloid cells upon microbial infection, as well as in tumor cells under certain circumstances, such as the colon tumor cells treated with chemotherapy drugs. Gasdermin D (GSDMD) is the first gasdermin protein to be identified as a pyroptosis mediator, a factor that plays a role in mediating programmed cell death. GSDMD-mediated pyroptosis often triggers severe tissue inflammation during infections, immune diseases, or even cancers. In the study published in *Cell Death & Disease* on July 26, 2023, the researchers used a TetOn system to selectively express the killer fragment GD-NT in tumor cells to determine whether GD-NT is under regulation as well as the mechanisms involved. Interestingly, they found that the cytolytic activity of GD-NT was negatively regulated by the AMP-activated protein kinase (AMPK) and AMPK activation rendered tumor cells resistant to GD-NT-mediated pyroptosis. Therefore, the researchers concluded that GSDMD is a potent mediator of pyroptosis and a potential target of pyroptosis regulation. Baylor College of Medicine received a $5 million CPRIT Core Facility Awards grant (RP170005) in September 2016 to support cancer researchers with state-of-the-art proteomics and metabolomics technologies.

254. Medulloblastoma is the most common type of malignant pediatric brain tumor with group 4 medulloblastomas (G4 MBs) accounting for 40% of cases. However, the molecular mechanisms that underlie this subgroup are still poorly understood. CPRIT Scholar Michael Taylor, M.D., Ph.D., director of the Pediatric Neuro-Oncology Research Program at Texas Children's Hospital and at Baylor College of Medicine, and colleagues applied linked-read sequencing to perform a comprehensive analysis of medulloblastoma genomes. The researchers identified both rare and novel mutational events in G4 medulloblastomas. As reported in *Frontiers in Oncology* on July 28, 2023, the team also generated TELL-Seq (27) libraries for 4 of the tumor samples and validated the somatic SVs detected by 10X-LR. Using these datasets, they aim to expand the understanding of medulloblastoma biology by identifying previously uncharacterized structural variation. Identification of SVs can be used to guide diagnosis, personalize the selection of chemotherapies and monitor patient response to treatment highlighting the importance of developing highly sensitive, low-cost genomic assays which could eventually be used in routine clinical practice. The minimal input required by linked-read technologies makes them an appealing option for clinical diagnosis particularly when tumors are small or occur in regions which are surgically inaccessible but can still be biopsied. Baylor College of Medicine recruited Dr. Taylor with the support of a $6 Million CPRIT Recruitment of

Established Investigators grant (RR220051) in May 2022.

255. Osteosarcoma (OS) is a type of primary malignant bone tumor that is most commonly seen in children and adolescents. Osteosarcoma primarily metastasizes to the lungs, where FAS ligand (FASL) is constitutively expressed (active without the need for external stimuli). The prognosis of patients with metastatic disease at diagnosis or poor responders to standard neoadjuvant treatment has remained static, largely due to the lack of robust biomarkers to distinguish them from others. Using one of the largest osteosarcoma cohorts to date, John Hicks, M.D., Ph.D., DDS, professor of Pathology & Immunology and Pediatrics at Baylor College of Medicine, and colleagues comprehensively profiled FAS promoter methylation and expression in OS patients and cell lines. DNA methylation is an epigenetic regulation wherein methyl groups are added to the cytosine of cytosine-guanine dinucleotides (CpG sites). This modification of CpG sites, particularly in regions called CpG islands (CGIs), is a crucial mechanism influencing gene transcription. The methylation of CGIs is significant in the regulation of downstream gene expression by impacting the accessibility of transcription factors and other components involved in gene regulation. The team also used an orthotopic xenograft mouse model of OS and observed the decreased formation of lung metastases in mice injected with 5-aza treated metastatic LM7 cells. The results published in *International Journal of Molecular Sciences* on July 29, 2023, suggest that DNA methylation of CGI shore sites may regulate FAS expression and constitute a potential target for osteosarcoma therapy, utilizing demethylating agents currently approved for the treatment of other cancers. Baylor College of Medicine received a $277,968 CPRIT Multi-Investigator grant (RP101335-C4) in June 2010.

256. Approximately 60% of patients with colorectal cancer (CRC) with wild-type KRAS, NRAS, and BRAF genes (RASWT) do not respond to cetuximab treatment. In this study, CPRIT Scholar John Paul Shen, M.D., Department of Gastrointestinal Medical Oncology at The University of Texas MD Anderson Cancer Center, and colleagues sought to discover novel biomarkers to predict response to anti-EGFR (epidermal growth factor receptor) antibody treatment in CRC and to understand mechanisms of resistance to anti-EGFR therapy. The team used transcriptomic profiles from three clinical and two preclinical cohorts treated with cetuximab to assign consensus molecular subtypes (CMS), which provides a more comprehensive understanding of CRC beyond traditional histopathological features, to each sample and correlated with outcomes. The researchers found that CMS can predict response to anti-EGFR therapy. The data, published in *JCO Precision Oncology* on July 24, 2023, suggest that CRC transcriptional profiles, when used to assign CMS, provide additional ability to predict response to anti-EGFR therapy relative to using tumor sidedness alone. The University of Texas MD Anderson Cancer Center recruited Dr. Shen in 2018 from the University of California, San Diego with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR180035).

257. The Cancer Genome Atlas Pan-Cancer analyses revealed TP53 as the most commonly mutated gene in human cancers. Patients with p53-mutant tumors usually have a worse prognosis and respond poorly to treatment. In this study, CPRIT Scholar Yong Li, Ph.D., professor, Department of Medicine – Epidemiology & Population Science and colleagues applied artificial intelligence (AI)-powered virtual screening to identify small-molecule compounds that specifically restore the wild-type p53 conformation from p53-Y220C. From 10 million compounds, the AI algorithm selected a chemically diverse set of 83 high-scoring hits, which were subjected to several experimental assays using cell lines with different p53 mutations. The data was published in *Frontiers in Oncology* on August 1, 2023. The team identified one compound, H3, that preferentially killed cells with the p53-Y220C mutation compared to cells with other p53 mutations. Furthermore, H3 reduced tumorigenesis in a mouse xenograft model with p53-Y220C-positive cells. These results highlight the potential use of AI-powered drug screening to investigate individual p53 mutants in the future. Baylor College of Medicine recruited Dr. Li in 2019 from the Cleveland Clinic Lerner College of Medicine with the support of a $6 million Recruitment of Established Investigators grant (RR190043).

258. Triple-negative breast cancer (TNBC) is a devastating disease accounting for 15% to 20% of all breast cancer but has limited therapeutic options. Corresponding author Feng Yang, Ph.D., assistant professor, Department of Molecular & Cellular

Biology, and a team of researchers from Baylor College of Medicine, previously reported that the enzyme MAPK4 is highly expressed in a large fraction of TNBC but is resistance to certain therapies. Since there is no drug to specifically block MAPK4, the team explored a different approach. The data, published in *PLOS Biology* on August 2, 2023, reported that the researchers identified a strategy that can potentially control MAPK4-promoted growth in TNBC and other cancers. "We showed that blocking both AKT and PDK1 effectively repressed MAPK4-induced cancer cell growth, suggesting a potential therapeutic strategy to treat MAPK4-dependent cancers, such as a subset of TNBC, prostate and lung cancer," Dr. Yang said. Baylor College of Medicine received two CPRIT Individual Investigator grants (RP130651, RP200439) totaling $1.45 million in 2012 and 2020, respectively.

259. Early detection of localized pancreatic cancer improves survival outcomes but detecting indolent tumors, or potentially inconsequential tumors, can lead to overdiagnosis. Intraductal papillary mucinous neoplasms (IPMN) are abnormal growths in the pancreas and are bona fide precursor lesions of pancreatic ductal adenocarcinoma (PDAC), but little is known about their pathogenesis and progression. Marta Sans, Ph.D., Department of Translational Molecular Pathology, and fellow researchers from The University of Texas MD Anderson Cancer Center set out to identify the molecular features driving IPMN development and differentiation. The team used spatial transcriptomic profiling on pancreatic tissue samples and identified NKX6-2 as an important transcription factor driving gastric differentiation of IPMN, which is a marker of biological indolence. As reported in *Cancer Discovery* on August 4, 2023, further investigation showed that NKX6-2 overexpression resulted in slow-growing cancer in preclinical models, while NKX6-2 loss was associated with an aggressive gene signature and changes in the behavior of cells within the tissue. This study highlights NKX6-2 as a potential biomarker to assist with risk stratification of patients with pancreatic cancer precursor lesions allowing for more targeted and effective interventions. The University of Texas MD Anderson Cancer Center received a $4 million CPRIT Research Training grant (RP210028) in May 2021 to instruct postdoctoral fellows for careers in translational cancer research.

260. The rapid emergence of the COVID-19 pandemic was met with efforts to develop first-in-class mRNA vaccines for SARS-CoV-2. These vaccines have spared countless human lives; however, they have also revealed challenges including their high cost of development and rapid virus evolution which rendered first-generation vaccines ineffective. Nirmatrelvir (Paxlovid) diminishes the morbidity and mortality associated with SARS-CoV-2 infection, but its impact may be limited given that main protease (M^{pro}) mutations causing nirmatrelvir resistance have already been observed in the clinic, underscoring the likely continual need to develop new inhibitors to keep pace with evolving viral strains. CPRIT Scholar Reuben Harris, Ph.D., professor at The University of Texas Health Science Center at San Antonio and colleagues developed an alternative approach in which DNA-encoded chemistry technology (DEC-Tec) can be used to discover inhibitors of M^{pro}. The data, published in *Nature* on August 4, 2023, demonstrate that DEC-Tec is a powerful and efficient method for discovering inhibitors of important viral targets, and it has the advantage of avoiding biases related to the chemical matter. The rapid mutation and selection of novel viral strains puts a continual burden on the need to synthetically "evolve" better drugs to keep pace. The researchers contend that DECLs are an important tool aimed at preserving human health in the face of future pandemics. Baylor College of Medicine received a $6 million CPRIT Core Faculty Support Awards grant (RP160805) to develop a Preclinical Candidate Discovery Core (PCDC). The University of Texas Health Science Center at San Antonio recruited Dr. Harris in 2022 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR220053).

261. Triple-negative breast cancer (TNBC) is an aggressive tumor that accounts for ~10%–15% of all breast cancer subtypes and has a bad prognosis. Several staging and classifying systems have been developed due to the variability of different types of breast cancer. Due to high heterogeneity, personalized treatment has become a new strategy. Zhongming Zhao, Ph.D., M.S., professor, School of Biomedical Informatics, and Aman Chandra Kaushik, Ph.D., both from The University of Texas Health Science Center at Houston, scanned the Cancer Cell Line Encyclopedia (CCLE) and Genomics of Drug Sensitivity in Cancer (GDSC) databases for potential drugs using human breast cancer cell lines and drug sensitivity

data. Understanding the interaction between a cell line and a specific drug will eventually allow for tailored treatment for specific cancer patients. The results, published in *Frontiers in Molecular Bioscience* on August 4, 2023, demonstrate the transcriptional effects of derivatives (screened against approved drugs) across a pool of cell lines. The proposed biomarkers and drug sensitivity analysis will provide potential candidates for future clinical investigation. The University of Texas Health Science Center at Houston received two CPRIT Academic Research grants (RP180734, RP210045) in 2018 and 2021 for a total of $8.4 million to establish a unique collaborative Biomedical Informatics, Genomics, and Translational Cancer Research Training Program (BIG-TCR), located at UTHealth.

262. Many cancers are initiated by mutations that develop in DNA. Additional mutations frequently form, driving tumors to grow and spread, and become resistant to treatment. CPRIT Scholar Ping Mu, Ph.D., assistant professor, Department of Molecular Biology at The University of Texas Southwestern Medical Center, and his colleagues sought to understand why these mutations appeared so quickly. The researchers looked for genetic differences in the cells of prostate cancer tumors and discovered that loss of a gene known as SYNCRIP in prostate cancer tumors unleashes cellular machinery that creates random mutations throughout the genome that drive resistance to targeted treatments. Published in *Cancer Cell* on August 14, 2023, that data suggested that SYNCRIP serves as a brake for a major member of the APOBEC protein family, known as APOBEC3B, keeping its activity in check. When SYNCRIP is lost, APOBEC3B's function becomes uncontrolled, causing it to create random mutations throughout the genome. When the researchers genetically altered cells to remove APOBEC3B, they did not accumulate mutations, even in the absence of SYNCRIP, confirming that their roles are linked. "This study paves the way for innovative strategies to fix the broken 'brake' for mutagenesis in cancer and curb resistance to treatments," said Dr. Mu. The University of Texas Southwestern Medical Center recruited Dr. Mu in August 2017 with the support of a $2 million CPRIT grant (RR170050); recruited Dr. Xiaoling Li in August 2017 with the support of a $2 million CPRIT grant (RR170079); and received three CPRIT Academic Research grants totaling $5.9 million (RP220473, RP190208, RP220309) in February 2022, August 2019, and November 2015, respectively.

263. Interferon Stimulating Gene 15 (ISG15) was first identified as an interferon (IFN) responsive gene and plays a crucial role in protein modification and regulation within cells. ISG15 is a ubiquitin-like protein that is activated by an E1 enzyme (Uba7). Despite its biological importance, the molecular basis by which Uba7 catalyzes ISG15 activation and transfer to UBE2L6 is unknown as there is no available structure of Uba7. Shaun Olsen, Ph.D., Department of Biochemistry & Structural Biology at The University of Texas Health Science Center at San Antonio, and colleagues presented cryo-EM structures of human Uba7. The team reported extensive biochemical analysis of these structures which reveal the key determinants of Uba7-catalyzed ISG15 activation and thioester transfer to UBE2L6. Further, they showed that these key molecular determinants are crucial for ISG15 function in cells as mutation leads to reductions of global and MDA5-specific ISGylation in human cell-based studies. The results were published in *Nature Communications* on August 8, 2023. The University of Texas Health Science Center at San Antonio recruited Dr. Sung in 2018 with a $6 million CPRIT grant (RR180029), Dr. Olsen in 2020 with a $4 million CPRIT grant (RR200030), and Dr. Wasmuth in 2022 with a $2 million CPRIT grant (RR220068).

264. Bile acids are crucial in breaking down and absorbing fats. However, in excessive amounts, they can damage the liver. Corresponding author Yi Zhu, Ph.D., Department of Pediatrics at Baylor College of Medicine, and colleagues investigated whether dimethyl sulfoxide (DMSO) could diminish bile acid production and subsequently protect the liver in mice. The team's results, published in *MDPI Biology* on August 9, 2023, showed that DMSO effectively reduced bile acid production in mouse primary hepatocytes and *in vivo*. Yet, DMSO failed to protect the liver in two separate mouse models with liver damage induced or partially induced by excess bile acids. Notably, while DMSO decreases hepatic bile acid levels in healthy mice, the body appears to counterbalance this effect under disease conditions, resulting in persistent liver damage. These results underscore the need to reconsider treating DMSO as a mere inert solvent and prompts further exploration to identify more effective therapeutic strategies for the prevention and treatment of bile-acid-associated liver diseases. Baylor College of Medicine received a $4 million CPRIT Core Facility Support Awards grant (RP210227) in August 2018 to facilitate comprehensive multiomic studies in preclinical models.

265. Endometrial carcinoma (EC) is the most common gynecologic malignancy in developed nations. EC-specific mortality has steadily worsened over the past 10 years and has been attributed to the increasing incidence of aggressive EC histotypes, particularly among Black and Hispanic women. However, failure rates associated with traditional treatments remain unacceptably high. To identify potential new endometrial carcinoma targets, CPRIT Scholar Bing Zhang, Ph.D., professor, Department of Molecular and Human Genetics at Baylor College of Medicine, and fellow researchers explored in detail the role of mutations called in-frame indels in the PIK3R1-AKT pathway that have been associated with worse cancer outcomes. The researchers hypothesized that in-frame indels eliminate PIK3R1's ability to suppress cancer progression. Phosphorylated AKT1 is thought to activate pathways that help cancer grow. Analysis of the 138 prospectively collected endometrial carcinoma tumors and 20 normal endometrium samples confirmed published findings from the team's recent exploratory studies and provided biological insights relevant to potential therapeutic strategies. The results, published in *Cancer Cell* on August 10, 2023, reported a second key finding that MYC activity, which has a direct role in the initiation and maintenance of tumorigenesis, can potentially be used as a biomarker for triaging EC patients to metformin treatment. The team found that real-world metformin treatment results in lower levels of MYC activity in EC patients with T2D across both their current and previous EC cohorts. "Altogether, our findings suggest that PIK3R1 in-frame indel mutations are potential markers of the AKT inhibition response and might be used to identify patients who could respond to AKT inhibitors, moving a step toward future improved clinical applications," Dr. Zhang said. Baylor College of Medicine recruited Dr. Zhang in 2016 with a $4 million CPRIT Recruitment of Rising Stars grant (RR160027).

266. The prognosis of high-grade gliomas, such as glioblastoma multiforme (GBM), is extremely poor due to the highly invasive nature of these aggressive cancers. While NF-κB-inducing kinase (NIK) activity is primarily controlled at the post-translational level, suggesting that modifications after the synthesis of the protein influence its function, Raquel Sitcheran, Ph.D., associate professor, Department of Cell Biology and Genetics at Texas A&M University Health Science Center, and colleagues showed that NIK (MAP3K14) is upregulated at the transcriptional level in invading cell populations. GBM cells with high induction of NIK gene expression demonstrate characteristics of collective invasion, facilitating invasion of neighboring cells. NIK and NF-κB dysregulation are highly correlated with the induction of disease and malignancies. Several studies have demonstrated an increase in NIK expression in various cancer models, including breast cancer, lymphomas, pancreatic cancer, gastric cancer, and GBMs. This study has demonstrated that NIK has a role in promoting brain tumor cell invasiveness and tumor growth *in vivo* through regulation of mitochondrial dynamics, which plays a crucial role in maintaining cellular function and homeostasis, and metabolic homeostasis. As supported by the data published in *Scientific Reports* on August 11, 2023, the inhibition of NIK may prove a promising therapeutic target for primary as well as recurrent, invasive or metastatic tumors. Texas A&M University System Health Science Center received a $200,000 CPRIT High Impact/High Risk grant (RP160842) in May 2016.

267. In the colorectal cancer (CRC) tumor microenvironment, cancerous and precancerous cells continuously experience mechanical forces associated with peristalsis, an involuntary muscle movement that occurs in your digestive system. Because mechanical forces like stress and strain can positively impact cancer progression, corresponding author Shreya Raghavan, Ph.D., assistant professor, Department of Biomedical Engineering at Texas A&M University, and colleagues explored the hypothesis that peristalsis may also contribute to malignant progression in CRC. To do this, the researchers leveraged their peristalsis bioreactor. As published in *Cellular and Molecular Bioengineering* on August 11, 2023, the researchers found that peristalsis associated forces drive malignant progression of CRC via ROCK, YAP1, and Wnt-related mechanotransduction. Texas A&M University System Health Science Center received a $6 million CPRIT Texas Regional Excellence in Cancer Award (RP230204) in February 2023 to create a regional center of excellence in cancer research (TREC) to address unmet needs in cancer prevention and treatment at the regional and national levels.

268. Proper characterization of cancer cell states within the tumor microenvironment is a key to accurately identifying matching experimental models and the development of precision therapies. Computational deconvolution of tumors may be applied in conjunction with physical separation methods, such as single-cell RNA sequencing. However, these

technologies present technical challenges, variabilities, increase cost, and limit throughput. To construct the cancer cell state map of breast cancer, corresponding author Aleksandar Milosavljevic, Ph.D., chair in Molecular Genetics at Baylor College of Medicine, and colleagues developed the XDec Simplex Mapping (XDec-SM) reference-optional deconvolution method that maps tumors and the states of constituent cells, which provide insight into interactions between cancer cell states and the surrounding tumor microenvironment. As reported in *PLOS Computational Biology* on August 14, 2023, this approach bridges the cellular and tissue layers of biology in an innovative, conceptually simple way that can be applied to cancer and non-cancer tissues alike. To empower the community to use this method, the team made the XDec-SM code available online and as an R package under a free open-source license. Baylor College of Medicine received a $4.7 million CPRIT Core Facility Support Awards grant (RP170691) in 2017 to unify existing "patient-derived xenograft" (PDX) programs, to develop at least six new PDX programs, specifically rare pediatric and adult tumors, and to provide infrastructure to expand services.

269. Ductal carcinoma *in situ* (DCIS) is a known precursor of breast cancer, but genomic understanding of disease progression and recurrence has been limited due to the challenges associated with single-cell sequencing to formalin-fixed paraffin-embedded (FFPE) samples that have been archived over many years. Researchers led by Nicholas Navin, Ph.D., director, CPRIT Single Cell Genomics Center, and professor, Department of Bioinformatics and Computational Biology at The University of Texas MD Anderson Cancer Center, developed Arc-well, a high-throughput single-cell DNA-sequencing method that is compatible with FFPE materials. The team profiled 40,330 single cells from cell lines, a frozen tissue, and 27 FFPE samples from breast, lung, and prostate tumors stored for 3–31 years to validate their method. The researchers reported in *Cell* on August 15, 2023, that they were able to track genomic changes in matched samples from premalignancy to invasive recurrence, showing they were genetically related. Arc-well has broad potential applications for studying existing collections of FFPE and frozen samples to provide further insights into copy number diversity in various cancers and in normal tissues. The University of Texas MD Anderson Cancer Center received a $4.9 million CPRIT Core Facility Support Awards grant (RP180684) in August 2018 to establish an Integrated Single Cell Genomics (SCG) Core Facility at The MD Anderson Cancer Center.

270. Glioblastoma (GBM) stem cell-like cells (GSCs), a subpopulation of highly tumorigenic GBM cells, are critical for tumor development and therapeutic resistance. Long noncoding RNAs (lncRNAs), which regulate gene expression, can have tumor-promoting effects, but it is unclear if they play a role in GSCs to drive treatment resistance. Researchers, including CPRIT Scholar Nidhi Sahni, Ph.D., assistant professor of Epigenetics and Molecular Carcinogenesis at The University of Texas MD Anderson Cancer Center, used CRISPR interference along with multi-omic analysis of The Cancer Genome Atlas to identify a post-transcriptional role for lncRNAs in promoting GSC proliferation and tumorigenesis as well as enhancing treatment resistance. They discovered lncRNAs regulate specific DNA damage repair pathways that allow GSCs to survive double-strand breaks caused by radiation therapy. The findings, published in *Science Advances* on August 4, 2023, suggest that inhibiting this lncRNA-mediated process could sensitize GSCs to treatment with radiation or homologous recombination deficiency targeted therapy, meriting further research as a potential therapeutic strategy. The University of Texas MD Anderson Cancer Center recruited Dr. Sahni in 2015 with the support of a $2 million CPRIT Recruitment grant (RR160021); and recruited Dr. Xu in 2016 with the support of a $2 million CPRIT Recruitment grant (RR160097). Baylor College of Medicine received a $2 million CPRIT Academic Research grant (RP230285) in 2023.

271. Fatty acid metabolism remodeling is essential in the tumor microenvironment to support tumor formation and cancer progression. Fatty acid synthase (FASN) inhibition has been viewed as an effective approach to limit tumor growth since most proliferating cancer cells rely on active *de novo* lipogenesis (DNL) to generate new membranes for daughter cells. However, to date, none of the FASN inhibitors have been approved for cancer treatment. Ralph DeBerardinis, M.D., Ph.D., distinguished chair, Department of Pediatrics at The University of Texas Southwestern Medical Center, and colleagues reported that their stable isotope tracing assays show that GSK2194069, as a FASN inhibitor, completely blocks *de novo* fatty acid synthesis in multiple cancer cell lines. Moreover, as a lipase inhibitor, orlistat is an FDA-approved drug to treat

obesity, but it has also been reported to inhibit FASN. The researchers confirmed that orlistat completely inhibited *de novo* fatty acid synthesis and orlistat treatment impaired cell proliferation in H460 cells. This data was published in *Cell Reports* on August 12, 2023. The University of Texas Southwestern Medical Center received a $6 million CPRIT Multi-Investigator Research Awards grant (RP180778) in August 2018.

272. Vertebrate craniofacial development relies on a complex and tightly regulated series of tissue growth and fusion, and even minor disruptions to this intricate process can lead to birth defects, the most common of which is nonsyndromic cleft lip and palate (NSCLP). In a previous study, CPRIT Scholar George Eisenhoffer, Ph.D., associate professor, Department of Genetics at The University of Texas MD Anderson Cancer Center, and colleagues identified FOS, a protein coding gene which has roles in oncogenic processes such as tumor growth and progression, as a candidate regulator of NSCLP through family-based association studies, yet its specific contributions to oral and palatal formation are still poorly understood. This study investigated the role of fos during zebrafish craniofacial development through genetic disruption and knockdown approaches. The findings, published in *Frontiers in Cell and Developmental Biology* on August 16, 2023, demonstrated that perturbation of fos has detrimental effects on oral epithelial and CNCC-derived tissues, suggesting that it plays a critical role in zebrafish craniofacial development and a potential role in NSCLP. The University of Texas MD Anderson Cancer Center recruited Dr. Eisenhoffer in 2014 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR140077).

273. Glioblastoma (GBM) is the most common and aggressive primary brain tumor. The treatment of GBM has limited clinical progress over the past decade, partly due to the lack of effective drug delivery strategies across the blood-brain-tumor barrier. Zhenpeng Qin, Ph.D., associate professor, Departments of Mechanical Engineering and Bioengineering at The University of Texas at Dallas, and colleagues analyzed the intratumoral blood-brain-tumor barrier heterogeneity in human GBM and characterized two genetically engineered models in female mice. The results, published in *Nature Communications* on August 15, 2023, showed that pulsed laser modulates the blood-brain-tumor barrier permeability (optoBBTB) and enhances the delivery of paclitaxel, a chemotherapy drug, in these two models. "The tumors shrank in size, and we expanded survival by more than 50%," Dr. Qin said. "We hope this will lead to expanded therapeutic options for treating diseases in the brain and central nervous system." This breakthrough suggests that by using such techniques to enhance drug delivery across the BBTB, many potent anti-cancer drugs that researchers previously deemed ineffective for treating brain tumors like GBM could be re-evaluated and repurposed. The University of Texas at Dallas received two CPRIT Academic Research grants (RP190278, RP210236) in 2019 and 2021 totaling $1.15 million, and a $3.58 million Core Facility Support Awards grant (RP180670) in 2018 to significantly expand the capabilities of preclinical imaging resources that are currently available for UT Dallas scientists.

274. Health disparity is a substantial socioeconomic challenge. Ongoing large-scale single-cell studies aim to create a genetically unbiased reference and to avoid the Eurocentric biases in previous human genetic studies. Single-nucleotide variants (SNVs) are changes at specific positions in a DNA sequence that can help classify and explain differences in disease susceptibility across populations, but how the resulting profiles depend on the cell's genetic background remains understudied. Nicholas Navin, Ph.D., professor, Department of Systems Biology at The University of Texas MD Anderson Cancer Center, and colleagues developed Monopogen, a computational tool that enables researchers to maximize the genetic information from available single-cell sequencing data, which can lead to immediate benefits on genetic ancestry mapping, association analysis using current large-scale single-cell atlas data, and somatic clonal lineage delineation. This study, published in *Nature Biotechnology* on August 17, 2023, has shown that single-cell sequencing data can potentially be used as a resource to determine the genetic ancestry of study samples and to identify risks of complex diseases in different populations, informing better prevention and treatment strategies. The University of Texas MD Anderson Cancer Center received a $4 million CPRIT Research Training grant (RP210028) in May 2021 and a $4.9 million CPRIT Core Facility Support Awards grant (RP180684) in August 2018 to establish an Integrated Single Cell Genomics (SCG) Core Facility.

275. Single-cell and single-nuclei RNA-sequencing (scnRNA-seq) technologies have revolutionized researchers' ability to quantify cell types and cell states in healthy and disease tissues. Although these tissue profiling technologies provide cell-type-specific information at unprecedented resolution, their widespread adoption in clinical settings has been prevented by technical and financial challenges. In this study published in *Genome Biology* on August 1, 2023, co-corresponding author, Pavel Sumazin, Ph.D., associate professor, Department of Pediatrics at Baylor College of Medicine, and colleagues devised SQUID, a computational approach to predict the single-cell RNA composition of a tumor sample using only the data of the bulk analysis of the sample. SQUID can reveal if chemoresistant cells are in the tumor sample and the chemotherapy they are sensitive to. "Even the best methods were not able to predict cancer treatment outcomes, but SQUID anticipated treatment outcomes for both types of pediatric cancer we work with, neuroblastoma and acute myeloid leukemia. This represents a significant advance in the field because methods to predict bulk composition had not worked well before," said Dr. Sumazin. The team has increased RNA analysis accuracy that is relevant academically and clinically, and this approach requires a relatively small extra effort and cost. Baylor College of Medicine received two Academic Research grants (RP180674, RP230120) in 2018 and 2023, totaling $7.3 million.

276. γ-Aminobutyric acid type A (GABAA) receptors mediate fast inhibitory signaling in the brain and are targets of numerous drugs and endogenous neurosteroids. Neuroteroids regulate neuronal activity in the central and peripheral nervous systems and are altered by stress, pregnancy, the ovarian cycle, neural development, and aging. Their dysregulation can result in neurological and psychiatric disorders. One neurosteroid, allopregnanolone, is the first FDA-approved drug to treat post-partum depression. Ryan Hibbs, Ph.D., Department of Neuroscience at The University of Texas Southwestern Medical Center and colleagues sought to find how positive modulators potentiate GABA activation. The team combined cryo-electron microscopy (cryo-EM) studies with electrophysiology and molecular dynamics (MD) simulations. Their findings, published in *Nature Communications* on August 22, 2023, support a mechanism by which allopregnanolone potentiates channel activity and suggest the dominant mechanism for sulfated neurosteroid inhibition is through pore block. The University of Texas Southwestern Medical Center received a $5.5 million CPRIT Core Facility Support Awards grant (RP170644) in August 2017 to advance the Cryo-EM Core Facility and establish a Service for Single-Particle structure determination.

277. Increased expression of the human telomere reverse transcriptase (hTERT) in tumors promotes tumor cell survival and diminishes the survival of patients. Understanding conditions that can influence the rates at which deamination occurs in DNA sequences is important for uncovering the reasons behind mutations in the promoter region of the hTERT gene, which plays a role in cellular aging and telomere maintenance. Corresponding author Lawrence C. Sowers, Ph.D., Department of Pharmacology and Toxicology at The University of Texas Medical Branch at Galveston, and colleagues explored the conditions that modulate deamination rates to gain insights into the origins of these mutations and their implications in cellular processes. The team developed an approach using deep DNA sequencing to investigate deamination mutations in the C-rich strand. The study, published in *Biomolecules* on August 25, 2023, revealed that deamination rates did not vary substantially across the 46 cytosines examined, and the two mutation hotspots were not deamination hotspots. The appearance of mutational hotspots in tumors is more likely the result of the selection of sequences with increased promoter binding affinity and hTERT expression. The University of Texas Medical Branch at Galveston received a $4 million CPRIT Research Training grant (RP170593) in November 2016.

278. Triple-negative breast cancer (TNBC), a highly aggressive breast cancer subtype, accounts for 10–20% of all breast cancers. Because the molecular mechanisms underlying TNBC metastasis remain unclear, Jeanne Kowalski, Ph.D., professor, Department of Oncology in Dell Medical School and co-lead of Quantitative Oncology for the Livestrong Cancer Institutes, and colleagues performed whole-exome sequencing (WES) analysis of primary TNBC. The team investigated the mutational landscapes of primary TNBC tumors and their matched recurrent tumors and compared the mutational profiles of primary tumors that had recurrence to those that remained recurrence-free. Published in *Genes* on August 25, 2023, the results revealed that the primary tumors and metastatic lesions had similar mutational landscapes. However, they

also found that mutations in COL17A1, LAMC3, and MMP27 were enriched only in recurrent tumors. MUC3A was the most frequently mutated gene in the dataset. This study led to the identification of previously unexplored, metastasis-specific, actionable targets (i.e., MUC3A, COL17A1, LAMC3, and MMP27) that can be further validated and developed for the treatment of metastatic TNBC. The University of Texas at Austin received a $6 million CPRIT recruitment grant (RR160093) in 2016, which supported this research.

279. Bisphosphonates have been commercially available since 1977 for the treatment of various bone diseases, such as osteoporosis, Paget's disease, hypercalcemia, and cancer bone lesions. Bisphosphonates contain phosphate groups that enable the drug to bind to the bone mineral hydroxyapatite, where the drug is delivered to osteoclasts through their bone resorptive activity. Researchers, including William Putnam, Ph.D., professor of Pharmacy Practice and Pharmaceutical Sciences at Texas Tech University Health Sciences Center, tested the immune modulatory effects of the pegylated liposomal alendronate (PLA), a potent amino-bisphosphonate, as an immunotherapeutic agent for cancer, in comparison with a standard of care immunotherapy, a PD-1 immune checkpoint inhibitor. The results, published in *Biomolecules* on August 28, 2023, demonstrated that both PLA and anti-PD1 were well tolerated. The team reported that PLA is an efficacious immunotherapy in a mouse model of aggressive melanoma with an established tumor microenvironment. The beneficial effects of PLA on macrophage and T cell functionality suggest potential synergy with other immunotherapies. Texas Tech University Health Sciences Center received a $2.5 million CPRIT Core Facilities Support Awards grant (RP170003) in 2016 to upgrade the Core laboratory and expand the research capacity and capability to meet clinical pharmacology needs.

280. Hepatocellular carcinoma (HCC) is the most common primary liver cancer arising from hepatocytes (liver cells). HCC is a highly fatal disease; chronic liver inflammation plays a key role in the development of HCC. Race/ethnicity plays a vital role in determining incidence, mortality and survival rates, but little is understood of the molecular mechanism underlying the HCC racial disparity between African American (AA)/Black and White patients. Zhao Lai, Ph.D., assistant professor, Department of Research, Molecular Medicine at The University of Texas Health Science Center at San Antonio, and colleagues analyzed global gene expression between AA/Black and White HCC patients and identified the activation of a key inflammatory pathway in AA/Black tumors. Ginger extract (GE) is known for its anti-inflammatory properties. GE inhibited proliferation of HCC cells, and the data, published in *Cancers* on August 27, 2023, suggest that HCC cell lines from AA/Black patients responded better to GE compared to those from White and Asian patients. These findings suggest that AA/Black HCC patients might benefit from holistic dietary approach which includes ginger. The University of Texas Health Science Center at San Antonio received a $3.7 million CPRIT Core Facility Support Awards grant (RP160732) in May 2016 to establish the UTHSCSA Cancer Genome Sequencing and Computation Core.

281. Immune-checkpoint blockade (ICB) therapy has been a breakthrough discovery in cancer treatment. However, only a limited number of patients benefit from it because of intrinsic and adaptive resistance mechanisms. Molecular chaperone HSP70s are attractive targets for cancer therapy, but their substrate broadness and functional non-specificity have limited their role in therapeutical success. Here, CPRIT Scholar Guo-Min Li, Ph.D., professor and director of the Reece A. Overcash, Jr. Center for Research on Colon Cancer at The University of Texas Southwestern Medical Center, and fellow researchers provide a strategy for cancer therapy by specifically targeting on DNAJA2. Tumor cells depleted of DNAJA2 or chaperone-mediated autophagy (CMA) factor LAMP2A exhibited elevated levels of centriolar satellite proteins, which causes aberrant mitosis. This activates the cGAS-STING pathway to enhance ICB therapy response in tumors derived from DNAJA2-deficient cells. Although dysfunction of chaperone-mediated autophagy (CMA) has a similar effect, the researchers believe that targeting DNAJA2 is more feasible than inhibiting the CMA pathway, as the latter will likely cause cellular toxicity and therapeutic resistance. As reported in *Nature Communications* on August 28, 2023, the data suggests DNAJA2 as a potential target to enhance cancer immunotherapy, thereby providing strategies to advance HSPs-based cancer therapy. The University of Texas Southwestern Medical Center recruited Dr. Li with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR160101) in September 2016.

282. Genetic crossovers – the exchange of DNA between pairs of chromosomes from each parent – are required for accurate chromosome segregation during meiosis (cell division). However, the mechanisms underlying the formation of these crossovers are poorly understood. Researchers led by CPRIT Scholar Francesca Cole, Ph.D., Department of Epigenetics and Molecular Carcinogenesis, The University of Texas MD Anderson Cancer Center, used genetic dissection to map the frequency and distribution of crossover points in mouse models to provide insight into this process. The researchers discovered two unique intermediate steps that occur prior to recombination. Additional data revealed the DNA mismatch repair protein MLH3 as a pivotal structural component required to form the junctions involved in recombination. These findings, published in *Molecular Cell* on August 17, 2023, increase the understanding of how genes are transferred during meiosis. The University of Texas MD Anderson Cancer Center recruited Dr. Cole from the Memorial Sloan-Kettering Cancer Center with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (R1213) in 2012.

283. CAR T cell therapy, a type of cellular immunotherapy that changes T cells so they can recognize and attack cancer, would benefit from knowledge of the fate of the cells *in vivo*. This requires the permanent labelling of CAR T cell products and their pooling in the same microenvironment. CPRIT Scholar Pawel Mazur, Ph.D., Department of Experimental Radiation Oncology at The University of Texas MD Anderson Cancer Center, and fellow researchers report a cell-barcoding method for the multiplexed longitudinal profiling of cells *in vivo* using single-cell RNA sequencing (scRNA-seq). The method, which the team named "shielded-small-nucleotide-based scRNA-seq" (SSN-seq), is compatible with both 3′ and 5′ single-cell profiling, and enables the recording of cell identity, from cell infusion to isolation. By using SSN-seq to track the dynamics of the states of CAR T cells in a tumor-rechallenge mouse model of leukemia, they found that SSN-seq may aid the development of adoptive cell therapies. The results were published in *Nature Biomedical Engineering* on August 31, 2023. The University of Texas MD Anderson Cancer Center recruited Dr. Mazur in 2016 from Stanford University with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members (RR160078), received a $4 million CPRIT Research Training grant (RP210028) in May 2021, and received a $998,000 CPRIT Individual Investigator grant (RP220391) in February 2022.

284. Bromodomain-containing protein 4 (Brd4) is overexpressed and functionally implicated in various myeloid malignancies. However, the role of Brd4 in normal hematopoiesis (blood cell production) remains largely unknown. Utilizing an inducible Brd4 knockout mouse model, Cheng-Ming Chiang, Ph.D., Departments of Biochemistry and Pharmacology at The University of Texas Southwestern Medical Center, and colleagues found that deletion of Brd4 (Brd4Δ/Δ) in the hematopoietic system impairs hematopoietic stem cell (HSC) self-renewal and differentiation, which associates with cell cycle arrest and cessation of cell division. This study, published in *EMBO Reports* on August 31, 2023, unveils an important role of BRD4 in HSC/HPC function by preventing H3 clipping and suppressing senescence gene expression. The University of Texas Health Science Center at San Antonio received a $3.7 million CPRIT Core Facility Support Awards grant (RP160732) in May 2016. The University of Texas Southwestern Medical Center received a $900,000 CPRIT Academic Research grant (RP180349) in 2018 and an $864,000 CPRIT Academic Research grant (RP190077) in 2019.

Together . . .
Texans Conquer Cancer

Cancer Prevention & Research
Institute of Texas

1701 North Congress Avenue, Suite 6-127
Austin, TX 78701
512.463.3190

To view grants online or learn more:

cprit.texas.gov

YouTube @CPRITTEXAS