CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Published Research Findings

A summary of research findings published by CPRIT grantees
September 1, 2023 – August 31, 2024.

For Fiscal Year 2024

1. Non-small cell lung cancer (NSCLC) patients have benefitted from anti-PD-1 immune checkpoint inhibitors; however, the 5-year survival rate is approximately 8%. To identify novel tumor-driven therapies, corresponding author 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 studied a group of mouse models of lung cancer that were resistant to anti-PD-1 therapy. They compared these models to those that responded well to the treatment and discovered that resistant tumors had an increase in an enzyme called autotaxin (ATX) and its byproduct, lysophosphatidic acid (LPA).

The study, published in the Journal of Clinical Investigation on September 1, 2023, also found that combining an ATX inhibitor with anti-PD-1 therapy not only slowed tumor growth but also caused tumor shrinkage. ATX was linked to inflammatory genes in many lung cancer patients, indicating its role in helping tumors resist treatment. These findings suggest that targeting the ATX/LPA pathway could make anti-PD-1 treatments more effective for NSCLC patients. Researchers should conduct further preclinical studies to support this combined treatment approach.

The University of Texas MD Anderson Cancer Center received two CPRIT Academic Research grants (RP160652, RP200235) in 2016 and 2020 totaling $6.9 million.

2. CRISPR tiling screens are a powerful tool used to find mutations that enhance the normal function of genes or proteins, which is important in cancer treatment. To simplify the analysis of CRISPR tiling screens, CPRIT Scholar Han Xu, Ph.D., Department of Epigenetics and Molecular Carcinogenesis at The University of Texas MD Anderson Cancer Center, and colleagues developed ProTiler, a computational method that maps protein regions linked to increased sensitivity to CRISPR-knockout.

The team focused on P300/CBP genes, which are frequently mutated in human cancers. They discovered that mutations are scattered throughout the coding sequences, including in a specific region called the TAZ2 domain. Using ProTiler, they analyzed CRISPR tiling screens of p300/CBP in cells and found that mutations in the TAZ2 domain led to increased histone acetylation, which may boost protein function. Published in Nature on September 2, this study may represent the first class of cancer-associated p300/CBP GOF mutations. Since the presence of TAZ2 mutations are common in various cancer types, these findings suggest a promising therapeutic strategy for treating cancers with these specific mutations.

The University of Texas MD Anderson Cancer Center recruited Dr. Xu in 2016 from the Broad Institute with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160097).

3. CRISPR systems linked to the Cas13 protein differ from the more familiar Cas9 systems by targeting RNA instead of DNA. RNA serves as the “instruction manual” for translating DNA’s genetic code into proteins. This makes Cas13 systems particularly promising for combating RNA-based viruses. However, the large size of Cas13 proteins and their non-specific RNA cleavage (breaking of RNA molecules into smaller fragments) upon target activation limit the adeno-associated viruses (AAVs) based delivery of Cas13 systems for therapeutic applications.

CPRIT Scholar Yang Gao, Ph.D., assistant professor of biosciences at Rice University, and team

addressed these limitations by studying Cas13bt3, a compact version of Cas13 suitable for AAV delivery. They used a cryo-electron microscope to map the structure of the CRISPR system to generate data and then processed it into a three-dimensional model. The structural insights surprised the team and helped explain how the system works.

Armed with this knowledge, researchers refined the system to improve its precision. Tests in living cells showed that the engineered CRISPR system became more effective at pinpointing its target while maintaining strong RNA-editing abilities. The results highlight how these detailed structural findings were key to fine-tuning the system for better specificity and performance. This advancement, published in Nature Communications on September 20, paves the way for more precise RNA-targeting therapies.

“My lab is a structural biology lab,” Dr. Gao said. “What we are trying to understand is how this system works. So part of our goal here was to be able to see it in three-dimensional space and create a model that would help us explain its mechanism.”

Rice University recruited Dr. Gao in 2019 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR190046). Baylor College of Medicine received a $5.38 million CPRIT Core Facility Support Awards grant (RP190602) in August 2019 to add new technologies to the two CryoEM Cores in the Texas Medical Center.

4. Glioblastoma (GBM) is a malignant grade 4 tumor which invades nearby regions of the brain. The tumors consist of multiple cell populations, including self-renewing glioblastoma stem cells (GSCs) and microglia, the primary immune cells of the central nervous system. In this study, Wen-Hao Hsu, M.Sc., Department of Cancer Biology at The University of Texas MD Anderson Cancer Center, and colleagues from Northwestern University identified the protease inhibitor TFPI2 as a critical factor linking these cell populations and their harmful behaviors, like the ability of GSCs to self-renew and the tendency of microglia to suppress the immune response. The data, published in Nature Immunology on September 4, reveals that TFPI2 causes microglia to suppress immune activity instead of mounting an immune response and supports therapeutic targeting of TFPI2 as an effective strategy for GBM.

The University of Texas MD Anderson Cancer Center received a $4 million CPRIT Research Training grant (RP210028) in May 2021 to provide a comprehensive learning environment focused solely on cancer, to position trainees for successful careers in cancer research.

5. Systemic lupus erythematosus (SLE) is an autoimmune disorder that affects multiple organs. The most severe organ manifestations of SLE occur in Lupus nephritis (LN), where regulatory T cells (Tregs), that normally reduce inflammation are defective, fewer in number, and contribute to disease progression.

CPRIT Scholar Christopher Flowers, M.D., M.S., Department of Lymphoma/Myeloma at The University of Texas MD Anderson Cancer Center, and colleagues hypothesized that treatment with allogeneic, healthy Tregs derived from umbilical cord blood (UCB) may stop this inflammatory process and protect against kidney damage. As reported in Frontiers in Immunology on September 5, the study showed that UCB-Tregs can reduce inflammation in SLE, decrease harmful auto-antibody production, resolve damaged organs, and improve kidney function. This suggests

that UCB-Tregs therapy could be a promising treatment for lupus nephritis in the clinical setting.

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 Recruitment of Established Investigators grant (RR190079).

6. Scientists are currently studying histone deacetylase inhibitors (HDACi) for the treatment of both solid and blood malignancies. Although they do not fully understand how HDACi treatments trigger T cells to fight tumors, HDACi influences several aspects of the immune response that help combat cancer. To design effective treatments combining HDACi with immunotherapy, it is important to understand their direct effects on T cells.

In this study, CPRIT Scholar S. Gail Eckhardt, M.D., director of the Livestrong Cancer Institutes, and chair of the Department of Oncology at The University of Texas at Austin, and colleagues analyzed T cell responses in patients treated with OKI-179 (bocodepsin) in a phase I dose-escalation study, together with in vitro and in vivo mouse models.

Published in Frontiers in Immunology on September 6, the in vivo data revealed that stopping OKI-179 during immunotherapy resulted in superior anti-tumor responses compared to continuous treatment. These findings suggest that OKI-179 can enhance the immune system's ability to fight tumors by making tumor cells more recognizable to the immune system, increasing the presence of MHC that help present antigens to immune cells, boosting the number of T cells in the blood, and improving the balance between regulatory T cells (which suppress immune responses) and cytotoxic T cells (which kill cancer cells). These findings suggest that treatment schedules should account for acute T cell effects when combined with immunotherapies to fully harness tumor-specific T cell responses in patients.

The University of Texas at Austin recruited Dr. Eckhardt in September 2016 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR160093).

7. Viral protein U (Vpu), a key HIV-1 protein, plays a key role in several processes important for the virus functions in the infected cells. Previous observations show that this protein forms stable molecules called oligomers in aqueous solution, but details about these oligomers are unknown.

Co-corresponding author Steven J. Ludtke, Ph.D., professor, Department of Biochemistry and Molecular Pharmacology at Baylor College of Medicine, and colleagues used protein engineering, size exclusion chromatography, cryoEM, and electron paramagnetic resonance (EPR) spectroscopy to better understand the nature of the soluble oligomers. Published in Scientific Reports on September 6, the data provides new fundamental information about the size and nature of oligomeric interactions. This study not only confirms with high confidence that in aqueous environment Vpu forms stable oligomers, but also reports for the first time on structural character of these oligomers.

Baylor College of Medicine received a $5.38 million CPRIT Core Facility Support Awards grant (RP190602) in August 2019 to add new technologies to the two CryoEM Cores in the Texas Medical Center.

8. Alzheimer's Disease (AD) continues to be a leading cause of death in the United States. Studies have shown that there are existing ethnic/racial differences in developing cognitive impairment, yet there are few reports investigating biological, behavioral, and lifestyle factors that lead to neurodegeneration in populations more heavily burdened by cognitive decline. Researchers from the University of North Texas Health Science Center at Fort Worth hypothesized that mitochondrial health - how well the mitochondria in cells produce energy - may hold greater biological importance in the development of age-related disease for individuals with Hispanic/Latino ancestry.

Corresponding author Nicole R. Phillips, Ph.D., Department of Microbiology, Immunology & Genetics at the University of North Texas Health Science Center at Fort Worth, and team compared the predictability of a DNA marker, 8-oxo-guanine (8oxoG), which indicates oxidative stress and mitochondrial dysfunction, to assess the risk for cognitive decline in Mexican American (MA) and non-Hispanic White (NHW) participants. The results confirm MAs, especially females, exhibit higher levels of oxidative damage in mitochondrial DNA compared to NHWs. As reported in Nature on September 7, these findings suggest that differences in mitochondrial function may contribute to the higher burden of cognitive decline observed in certain ethnic/racial populations, highlighting the importance of understanding these biological factors in neurodegenerative diseases like Alzheimer's.

The University of North Texas Health Science Center at Fort Worth received a $3.9 million CPRIT Research Training grant (RP210046) in May 2021 to implement a well-designed recruitment plan to recruit and train underrepresented minorities and disadvantaged scholars.

9. In a group of neurodegenerative diseases like Alzheimer's, called tauopathies, abnormal deposits of tau protein in the brain contribute to disease progression. Researchers have discovered that acetylation, a chemical modification of lysine residues on tau protein, can influence how these proteins clump together into harmful structures called amyloids. In this study, researchers from The University of Texas Southwestern Medical Center found that specific patterns of acetylation around amyloid-forming regions of tau can either promote or inhibit the formation of these toxic clumps.

This study, published in Structure on September 7, revealed that understanding these molecular mechanisms is crucial for developing therapies that target tau-related diseases effectively. Corresponding author Lukasz A. Joachimiak, Ph.D., Center for Alzheimer's and Neurodegenerative Diseases and Department of Biochemistry at The University of Texas Southwestern Medical Center, reported that the data lays the groundwork for understanding the various structural polymorphs seen in a disease.

The University of Texas Southwestern Medical Center received a $5.5 million CPRIT Core Facility Support Awards grant (RP170644) in August 2017 to establish a new Cryo-Electron Microscopy Core Facility and Service for Structure Determination at UT Southwestern Medical Center.

10. Patients treated for head and neck cancers frequently develop oral mucositis, an inflammation of the mucosa which causes painful sores in the mouth. This often leads to difficulty eating, weight loss, and readmission or prolonged hospital stays to manage pain or infections.

CPRIT Scholars Bing Zhang, Ph.D., and Andre Catic, M.D., Ph.D., from Baylor College of Medicine, and colleagues investigated the impact of oral microbial features on the severity of oral mucositis during and after treatment for patients with squamous cell carcinoma of the head and neck. The team investigated how the cancer-related gene KRAS affects protein regulation in cells and how changes in this process can lead to resistance to treatments targeting KRAS. The research, published in Science on September 8, revealed that specific microbiome features of the oral microbiome play a role in the severity of oral mucositis progression. These findings show that oncogenic KRAS is critical for protein quality control in cancer cells and suggest the potential to personalize treatment plans with tailored microbiome interventions.

Baylor College of Medicine recruited Dr. Catic in 2014 with the support of a $2 million Recruitment of First-Time, Tenure-Track Faculty Members grant (RR140038), and recruited Dr. Zhang in 2016 with the support of a $4 million Recruitment of Rising Stars grant (RR160027). BCM also received three Academic Research grants (RP160283, RP180672, RP230285) totaling $13 million. Texas A&M University System Health Science Center received a $6 million CPRIT Core Facility Support Awards grant (RP150578) in May 2015.

11. Endometrial carcinoma (EC) is the most common gynecologic malignancy in developed nations, with the incidence steadily increasing over the past decade. The mortality rate from EC has worsened, particularly due to the increasing incidence of more aggressive forms of the cancer, especially among Black and Hispanic women.

As reported in Cancer Cell on September 11, CPRIT Scholar Bing Zhang, Ph.D., co-led a comprehensive analysis of EC using proteogenomic data, which combines protein and genetic information. This study identified new potential targets for drug development, demonstrating the value of the Clinical Proteomic Tumor Analysis Consortium (CPTAC) dataset for scientific discovery.

Through four key findings, Dr. Zhang and his colleagues demonstrated the ability of proteogenomic analysis to increase understanding of EC tumor biology, and identified molecular and imaging markers that researchers can investigate to guide patient stratification for more precise treatment of EC. The team developed a method to measure two protein peptides that help the immune system recognize and attack harmful cells, determined that a diabetes drug metformin may help treat a certain kind of cancer in patients who have a high level of a protein called MYC, even if they do not have diabetes, discovered that a common mutation in EC involving the PIK3R1 gene increases activity AKT protein activity, which is often linked to cancer, and showed that computer deep learning can accurately identify different subtypes and mutations of EC from tissue images. The results suggest that this technology could be useful for quick and precise cancer diagnosis.

Baylor College of Medicine recruited Dr. Zhang to Texas from Vanderbilt University School of Medicine with a $4 million CPRIT Rising Star Scholar Award (RR160027) in 2016.

12. The gut microbiome is a diverse community of trillions of microbes, including bacteria, living in human intestines, affecting not only gut health but also the health of organs outside of the gut. However, scientists do not fully understand the exact ways these microbes affect other parts of the body.

"L. reuteri is one of such bacteria that can affect more than one organ in the body," said co-corresponding author Sara Di Rienzi, Ph.D., assistant professor of molecular virology and microbiology at Baylor College of Medicine. "Researchers have found that these bacteria reduce gut inflammation in adult humans and rodent models, suppress bone loss in animal models of osteoporosis and in a human clinical trial, promote skin wound healing in mice and humans and improve social behavior in six mouse models of autism spectrum disorder." Although L. reuteri can promote social behavior and wound healing, this requires signaling by the hormone oxytocin.

To find out how this happens, first author Heather Danhof, Ph.D., assistant professor of molecular virology and microbiology at Baylor, and team reviewed single-cell RNA-Seq datasets of the intestinal epithelium. They discovered that oxytocin genes are active in the intestines of mice, macaques, and humans. Using fluorescence microscopy, the team visualized the presence of oxytocin in human intestinal tissues, demonstrating that oxytocin acts as an intestinal hormone. The results of this study were published in Gut Microbes on September 12. The team is now working to identify potential treatments for autism spectrum disorders to gain a new understanding of the connection between oxytocin produced in the gut, social behavior, and the brain.

Baylor College of Medicine received a $5.17 million CPRIT Core Facility Support Award (RP180672) in August 2018 to purchase high-end equipment that will more than double the current detection capabilities.

13. The intestinal barrier is a semipermeable structure that allows essential nutrients to pass through and helps with immune sensing, while blocking harmful molecules and bacteria. Intestinal barrier dysfunction leads to inflammation and allows pathogens to trigger the innate immune response, the body's first line of defense against germs. Although initiating the innate immune response restores intestinal homeostasis, its hyperactivation can lead to autoimmune and neurodegenerative disorders.

Similar to the protective mucus layer in mammalian guts, Drosophila (fruit flies) have a structure called the peritrophic matrix in their intestines. In this study, co-corresponding author Hamed Jafar-Nejad, M.D., Department of Molecular & Human Genetics at Baylor College of Medicine, and a team of international researchers found that loss of Drosophila N-glycanase 1 (Pngl) in a specific intestinal cell of fruit flies compromised developmental progression. This led to a widespread increase in the breakdown of fats in the body, which affected the normal progression of development and ultimately resulted in death. Published in Nature on September 13, the data shows that Pngl plays a crucial role in forming the intestinal barrier in young fruit flies (larvae). When Pngl is missing, defects in this barrier occur, leading to serious issues. Interestingly, the lethality linked to gut barrier defects in Pngl mutants mostly stems from factors other than bacterial infections.

Texas A&M University System Health Science Center received a $5.95 million CPRIT Core Facility Support Awards grant (RP150578) in May 2015 to expand and enhance the capabilities of the Combinatorial Drug Discovery Program (CDDP).

14. HIV-1, the most common type of Human Immunodeficiency Virus, attacks the body's immune system by destroying CD4 cells, which help fight infections. The virus spreads both through cell-free infection and more efficiently through direct cell-to-cell infection. While current treatments effectively block cell-free HIV-1, they are less effective against cell-to-cell transmission. Thus, development of an effective way to block cell-cell transmission of HIV-1 could have potential advantages for HIV-1 prevention and therapy.

In this study published in Frontiers in Immunology on September 14, co-corresponding author Jason Kimata, Ph.D., associate professor, Department of Molecular Virology and Microbiology at Baylor College of Medicine, and team used live cell microscopy and imaging flow cytometry, to demonstrate that engineered GPI-anchored proteins attached to T cells, can transfer to immune cells called iDCs when co-cultured. They observed this transfer using specific protein markers. Additionally, they found that a protein inhibitor, GPI-scFv X5, effectively blocks the transmission of HIV-1 between cells. This data provides further support that therapies based on GPI-scFv could be a promising strategy to control HIV-1 and work towards a functional cure.

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 more than double the current detection capabilities.

15. Human papillomavirus (HPV) is the most common sexually transmitted infection and is associated with many types of cancers, particularly affecting Hispanics. An HPV vaccine is available for individuals ages 9 - 45 that can prevent up to 90% of HPV-associated cancers. Eva Moya, Ph.D., professor in the Department of Social Work at The University of Texas at El Paso, led a study to understand why HPV vaccine rates might be lower in heavily Hispanic areas. The team set out to examine the impact of theory-based factors (i.e., the Health Belief Model), culture-based factors that may be unique to Hispanics of Mexican American origin, and trusted sources of information on HPV-vaccine acceptance (HPV-VA) and HPV-vaccine uptake (HPV-VU).

The team used a cross-sectional study design with an online questionnaire to explore the factors affecting their decision to get the vaccine from a community sample of Hispanic (mostly female) adults between the ages 18–65 residing in El Paso. As reported in BMC Public Health on September 14, the findings support that theory-based factors would be associated with HPV-VA and showed that several factors impacted vaccine acceptance, including household size, primary language, community involvement, trust in the government, and beliefs about health. Where people got their information about HPV and their perception of the vaccine's safety also played significant roles. By understanding what influences vaccine decisions, health professionals can design better strategies to encourage more people in underrepresented communities to have the HPV vaccination.

The University of Texas at El Paso received a $5.88 million CPRIT Texas Regional Excellence in Cancer Award (RP210153) in August 2021 to provide junior faculty with research programs in Hispanic cancer disparities.

16. Nanomedicines, drugs carried by tiny particles, have shown promise in treating various diseases, including cancer. Some of these drugs have proven more effective and less

toxic than their traditional counterparts. For instance, clinicians have effectively used a drug called nanoparticle-albumin-bound paclitaxel (nab-paclitaxel) for certain hard-to-treat cancers since 2005. Despite these successes, the medical community has been slow to embrace such treatments, largely due to concerns about how the liver processes nanoparticles.

A research team led by CPRIT Scholar Wen Jiang, M.D., Ph.D., associate professor of radiation oncology at The University of Texas MD Anderson Cancer Center, investigated therapeutic blockade of the protein known as MARCO, found in macrophages - cells responsible for filtering out foreign substances - including nanoparticles, as a possible strategy to avoid drug clearance. They recently discovered that younger patients might respond less effectively to such treatments because younger livers more efficiently filter the bloodstream, which helps limit toxins in the blood but also filters out beneficial treatments. The data, published in Nature Nanotechnology on September 18, revealed that when researchers blocked MARCO in young mice, the nanomedicines became more effective. This discovery highlights the significance of age in determining the effectiveness of certain treatments and underscores the need for treatments tailored to patients' unique physiological profiles.

The University of Texas Southwestern Medical Center recruited Dr. Jiang in 2018 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR180017).

17. Fundus cameras enable doctors to assess the retina in a non-invasive, radiation-free fashion. Retinal blood vessels are some of the most studied structures in fundus photographs and are useful in the diagnosis and prognosis of retinal diseases and can indicate conditions like diabetes, glaucoma, and hypertension.

In this work, published in Scientific Reports on September 15, researchers proposed a novel strategy, synthetic optical coherence tomography angiography (OCT-A), to create better images of these blood vessels from fundus images. Instead of training a fully convolutional neural network (FCNN) to identify vessels from manually drawn maps, they trained it to create images similar to OCT-A scans. Corresponding author Luca Giancardo, Ph.D., associate professor, McWilliams School of Biomedical Informatics at The University of Texas Health Science Center at Houston, and colleagues trained an FCNN to map a fundus image to an en face OCT-A image. Quantitative and qualitative evaluations against state-of-the-art vessel segmentation models demonstrated improved accuracy in mapping retinal blood vessels and simplified the process of creating retinal datasets.

The University of Texas Health Science Center at Houston received a $5.84 million CPRIT Core Facility Support Awards grant (RP170668) in August 2017 to create a Data Science and Informatics Core for Cancer Research.

18. Mass spectrometry (MS)-based shotgun proteomics is the primary method for identifying and quantifying proteins in biomedical research. However, studies have provided limited information on protein isoforms due to data analysis challenges.

To address this challenge, CPRIT Scholar Bing Zhang, Ph.D., Department of Molecular and Human Genetics at Baylor College of Medicine, and colleagues developed SEPepQuant, a new method based on graph theory to better identify and quantify protein isoforms. By analyzing both simulated and real experimental data, SEPepQuant showed significant improvements over existing methods, offering more detailed isoform-level information and identifying hundreds of isoform-level regulation events. This analysis, published in Nature Communications on September 19, enhances the understanding of protein isoform regulation in normal and disease processes. Researchers expect SEPepQuant to have broad applications to biological and translational research to boost scientific discoveries.

Baylor College of Medicine recruited Dr. Zhang in February 2016 with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR160027).

19. Researchers have developed a method using heavy water to label molecules in the body, combined with a technique called liquid chromatography coupled with mass spectrometry (LC-MS), to study how proteins change over time in living organisms. Benchmark mass spectrometry data is crucial to compare and validate the effectiveness of newly developed techniques and algorithms.

In this work, principal investigator William K. Russell, Ph.D., professor, Department of Biochemistry and Molecular Biology at The University of Texas Medical Branch at Galveston, and colleagues developed a heavy water-labeled LC-MS dataset from the murine liver for analyzing protein turnover rates. They found that while higher resolutions offered more detailed data, the number of identified peptides and the accuracy of turnover rate estimations decreased. As reported in Scientific Data on September 19, the team used this dataset to develop and validate a new algorithm called d2ome+. This approach helps improve understanding of protein dynamics in the body.

The University of Texas Medical Branch at Galveston received a $3.5 million CPRIT Core Facility Support Awards grant (RP190682) in August 2019 to provide state-of-the-art mass spectrometry technologies, expertise, and support for Texas cancer investigators.

20. Chromosomal aberrations are common in cancer and developmental syndromes, yet researchers haven't been able to identify their origin. In this study, researchers from Baylor College of Medicine and colleagues provided a detailed view of the earliest events leading to the development of cancer and of potential new ways to prevent it.

The team discovered that losing the protein SETD2 or its marker leads to abnormal chromosomal bridges during cell division. Further examination of the chromosome structure revealed the formation of isochromosomes, which are unusual chromosomal errors with mirror-imaged or inverted symmetry. Ruhee Dere, Ph.D., associate professor of medicine at the Center for Precision Environmental Health at Baylor College of Medicine, and colleagues showed that a key epigenetic mark, H3K36me3, and its regulator, the tumor suppressor SETD2, help maintain genomic integrity by preventing isochromosome formation. The results, published in Proceedings of the National Academy of Sciences on September 18, reveal that isochromosomes could play a critical role in developing chemotherapy resistance.

Baylor College of Medicine received a $1.05 million CPRIT Individual Investigator grant (RP220332) in February 2022 to provide an innovative approach to exploit a susceptibility in clear cell renal cell carcinoma (ccRCC).

21. The CRISPR-Cas13 system is a technique for editing RNA to alter protein sequences without modifying the cell's DNA. However, the large size of Cas13 proteins and their tendency to cut RNA non-specifically have limited their use, especially with virus-based delivery methods. In this study, CPRIT Scholar Yang Gao, Ph.D., assistant professor, Department of BioSciences at Rice University, and team explored a smaller version of Cas13, called Cas13bt3, which is suitable for delivery using adeno-associated viruses (AAV). AAVs are single-stranded DNA viruses that don't cause disease in humans and need helper viruses for replication and productive infection.

Using cryo-electron microscopy, the team detailed the structure of Cas13bt3 in its active state. Guided by the structure, the team engineered Cas13bt3 variants and discovered that adding an RNA-binding domain to Cas13a enhances its ability to cut RNA and improves RNA detection sensitivity. The study, published in Nature Communications on September 20, revealed that by carefully modifying the parts of Cas13 that bind to RNA, scientists can adjust its activity for different purposes, making it more versatile for various applications.

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). Baylor College of Medicine received a $5.4 million CPRIT Core Facility Support Awards grant (RP190602) in August 2019.

22. Appendiceal cancer is a rare, understudied disease with no FDA approved treatments. These tumors have historically been treated with chemotherapy designed for colon cancer, but recent research shows that appendiceal adenocarcinoma is quite different from colon cancer at the molecular level, notably rare adenomatous polyposis coli (APC) mutation. This is important because the absence of this mutation may make appendiceal cancer more responsive to a class of drugs called taxanes, which are effective in treating other types of gastrointestinal cancers.

CPRIT Scholar John Paul Shen, Ph.D., assistant professor, Department of Gastrointestinal Medical Oncology at MD Anderson Cancer Center, and colleagues completed a single-center retrospective study of 13 patients with metastatic appendiceal adenocarcinoma, treated with taxane chemotherapy. The results were promising, with a median overall survival of 8.8 months. The team evaluated the progress of 10 patients: three showed a positive response to the treatment, four had their disease stabilize, and three experienced disease progression (30% response rate, 70% disease control rate). The results, published in The Oncologist on September 20 (Volume 28, Issue 12), show that the activity of taxane-based chemotherapy in appendiceal adenocarcinoma support further clinical investigation of taxane therapy in appendiceal adenocarcinoma.

The University of Texas MD Anderson recruited Dr. Shen from the University of California, San Diego in 2018 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR180035).

23. Medulloblastoma is the most common malignant brain tumor in children, accounting for 20-25% of pediatric malignancies in high-income countries (HICs) with large variations in incidence in low- and middle-income countries (LMICs). Patients with this diagnosis require craniospinal radiotherapy (CSI); however, treatment planning for CSI is complex and time-consuming, especially for resource-constrained centers.

To alleviate demanding workflows, researchers from The University of Texas MD Anderson Cancer Center and colleagues successfully automated the pediatric CSI planning pipeline in previous work. In this study, published in Frontiers in Oncology on September 22, the team validated their CSI autosegmentation and auto planning tool on a large dataset from St. Jude Children's Research Hospital. The results indicate that this algorithm works well adjusting to differing patient populations. Automating the contouring and planning workflow for pediatric CSI has the potential to increase treatment planning efficiency and global access to high-quality radiation therapy.

The University of Texas MD Anderson Cancer Center received a $4 million CPRIT Research Training grant (RP210028) in May 2021 to provide a comprehensive learning environment focused solely on cancer, to position trainees for successful careers in cancer research.

24. Multifocal tumor growth and late metastatic spread to other tissues are characteristic of early-stage invasive lobular breast cancer (ILC). Researchers believe that ILC cells initiate metastases by leaving the breast through blood and lymphatic channels early in the disease, eventually growing in distant tissues.

Using in vitro ILC models, researchers, including CPRIT Scholar Suzanne D. Conzen, M.D., Department of Internal Medicine at The University of Texas Southwestern Medical Center, showed that activating the glucocorticoid receptor (GR), which responds to stress hormones, slows down ILC cell growth. As published in Cancers on September 22, the data also revealed that GR expression in ILC cells reduced the growth of the main tumor but unexpectedly increased the spread to bones and other tissues. This suggests that GR-related gene activity may play a role in unusual characteristics of ILC biology.

The University of Texas Southwestern Medical Center recruited Dr. Conzen in May 2019 from the University of Chicago with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR190037).

25. DNA base editors are advanced tools that can precisely modify specific DNA sequences without causing double-stranded breaks. Using components from CRISPR systems together with other enzymes, DNA base editors convert specific parts of DNA using enzymes called deaminases, fused to a programmable DNA-binding protein for targeted nucleotide conversion. However, the most widely used TadA deaminases lack control once inside living cells.

In this study, researchers from Rice University and Baylor College of Medicine developed a split adenine base editor (sABE) that uses a method called chemically induced dimerization (CID) to control the activity of TadA-8e, an enzyme involved in the editing process. They successfully used this method to edit the PCSK9 gene with high precision. This approach, published in Nature Com-

munications on September 11, allows for controlled DNA base editing in living organisms, potentially benefiting a wide range of research and medical applications.

The University of Texas Health Science Center at Houston received a CPRIT Core Facility Support Awards grant (RP180734) in August 2018 to establish the UTHealth Cancer Genomics Core.

26. Glioblastoma (GBM), a highly aggressive brain cancer, contains heterogeneous cells that invade surrounding brain tissue, causing cancer growth and spread. However, scientists do not fully understand the molecular mechanisms that enable these GBM cells to disperse throughout the brain.

In this study, researchers from The University of Texas MD Anderson Cancer Center studied patient tumor samples and found that a protein called GlialCAM, normally active in healthy brain cells, plays a key role in GBM cell behavior. High levels of GlialCAM make tumor cells stick together and grow within the tumor core. In contrast, GBM cells with low levels of GlialCAM are better at invading surrounding brain tissue along blood vessels and white matter. The data, published in The Journal of Neuroscience on September 18, highlight the importance of GlialCAM and related proteins in controlling how GBM cells grow and spread, which could lead to new treatment strategies.

The University of Texas MD Anderson Cancer Center received a $3.4 million CPRIT Core Facility Support Grant (RP170628) in August 2017 to create an integrated Flow Cytometry and Cell Imaging Core (FCCIC) facility at the MD Anderson Cancer Center, Science Park.

27. Patients with TP53-mutant acute myeloid leukemia (AML) have an extremely poor prognosis and, essentially, do not respond to available medications, including the combination of venetoclax and hypomethylating agents. Researchers led by Bing Carter, Ph.D., and Michael Andreeff, M.D., Ph.D., both from the Department of Leukemia at The University of Texas MD Anderson Cancer Center, have identified a new potential therapeutic target called the epichaperome complex, which is present in high levels in TP53-mutant AML cells.

The team found that targeting epichaperomes with the selective inhibitor PU-H71 had significant anti-leukemia effects in AML cells and stem cells with TP53 mutations, but not in normal bone marrow stem cells. They demonstrated that combining PU-H71 with venetoclax enhanced the treatment in a xenograft model. The results, published in Blood on September 21, suggest that inhibiting epichaperome function is essential for targeting TP53-mutant AML and could improve response to venetoclax while preventing resistance.

Texas A&M University Health Science Center Institute of Biosciences and Technology received a $4.68 million CPRIT Core Facility Support Awards grant (RP190581) in 2019. Texas A&M University System Health Science Center received a $4 million CPRIT Core Facility Support Awards grant (RP200668) in 2020 for renewal funding of the Gulf Coast Consortium (GCC) Combinatorial Drug Discovery Program (CDDP).

28. Neuroblastoma is a pediatric cancer of the sympathetic nervous system (a network of nerves that helps your body activate its “fight-or-flight” response), and often involves high levels of GD2, which can help cancer cells survive and spread. Doctors treat patients with relapsed neuroblastoma with Dinutuximab and other anti-GD2 antibodies in combination with chemotherapy. However, studies have shown that some neuroblastomas are negative for GD2. It is important to identify patients with tumor cells with low GD2 levels since these patients may not benefit from this therapy and may experience toxicity.

A team of scientists from Texas Tech University Health Sciences Center, including C. Patrick Reynolds, M.D., Ph.D., Cancer Center Director for the School of Medicine, developed a method to measure how much dinutuximab binds to neuroblastoma cells and how many of these cells in the bone marrow have GD2. In the study published in the Journal of Clinical Medicine on September 27, the team created a multi-color flow cytometry test that uses other antibodies to identify neuroblastoma cells in mixed cell samples. This method can help identify patients who are unlikely to respond to anti-GD2 therapy, improve understanding of clinical trial results, and guide treatment options for neuroblastoma patients.

Texas Tech University Health Sciences Center received a $1.2 million CPRIT Individual Investigator Research Awards for Cancer in Children and Adolescents grant (RP200432) in February 2020.

29. Fusion oncoproteins (FOs) are abnormal molecules formed by the fused parts of two proteins, and spontaneously form condensates inside cells that promote cancer development. However, it is not clear whether this clustering is a general property of FOs.

Researchers, including CPRIT Scholar Nidhi Sahni, Ph.D., associate professor, Department of Epigenetics and Molecular Carcinogenesis at The University of Texas MD Anderson Cancer Center, sought to uncover whether formation of these cellular condensates is a common property of the FOs associated with diverse cancers. The team assembled a database of the amino acid sequences of several thousand FOs and tested 166 of them for condensate formation in cells. They used this information as a launchpad to predict the behavior of other fusion oncoproteins. “By obtaining a grasp of the underlying mechanisms, we are setting the stage for potential innovative therapeutic approaches against fusion oncoprotein-driven cancers,” said corresponding author Richard Kriwacki, Ph.D., Department of Structural Biology at St. Jude Children’s Research Hospital. The findings, published in Nature Communications on September 28, 2023, provide valuable insights into how FOs contribute to cancer.

The University of Texas MD Anderson Cancer Center recruited Dr. Sahni from the Dana Farber Cancer Institute in November 2015 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160021). MD Anderson also received a $900,000 Individual Investigator grant (RP220292) in February 2022.

30. When single muscle cell building blocks (myoblasts) come together, they merge to create large, multi-nucleated muscle fibers, creating our skeletal muscles. Myomaker, a protein found specifically in skeletal muscle, is essential for this process. In this study, Eric N. Olson, Ph.D., professor, Department of Molecular Biology, and fellow researchers at The University of

Texas Southwestern Medical Center, examined the structures of mouse Myomaker (mMymk) and Ciona robusta Myomaker (cMymk) using cryogenic electron microscopy.

The analysis demonstrated that Myomaker's ability to connect as pairs (dimers) and bind to fats (lipids) is crucial for the protein's ability to help muscle cells fuse together. The findings, published in Nature Structural & Molecular Biology on September 28, emphasize how important it is for Myomaker proteins to interact across cell boundaries to facilitate the fusion of muscle cells, providing structural and functional insights into how muscle cells fuse to form skeletal muscles.

The University of Texas Southwestern Medical Center received a $5.5 million CPRIT Core Facility Support Awards grant (RP170644) in 2017 to establish a New Cryo-Electron Microscopy Core Facility and Service for Structure Determination. UT Southwestern also received a $1.13 million CPRIT Individual Investigator Research Awards for Cancer in Children and Adolescents (RP200103) in 2020.

31. Cancer cells can take an enzyme, called APOBEC3B - which normally fights viruses - and instead randomly alter the cancer cell's own DNA. This leads to random mutations that can make cancer more powerful. About 20% of breast cancer tumors produce an excess of APOBEC3B, which results in poor patient outcomes and increased resistance to therapies. Researchers, including CPRIT Scholar Kyle Miller, Ph.D., professor, Department of Molecular Biosciences at The University of Texas at Austin, and CPRIT Scholar Reuben Harris, Ph.D., professor and chairman, Department of Biochemistry & Structural Biology at The University of Texas Health Science Center at San Antonio, discovered that APOBEC3B targets specific DNA regions called R-loops, which are involved in protein production.

In this study, published in Nature Genetics on September 21, the team discovered that these R-loops are more likely to have mutations caused by APOBEC3B. "Cancer is an evolutionary process," said Dr. Miller. "Each cell is experimenting and whatever cell is the most efficient is the one that's going to survive in the tumor and branch out. A therapy might have a great effect on a tumor, but those few cells that are able to mutate and escape that therapy, they're the ones that become resistant, they're the ones that metastasize, and those are the ones that kill patients." Developing a drug that modifies the number of R-loops in a cell's DNA might counteract the harmful effects of APOBEC3 in cancer cells.

The University of Texas Health Science Center at San Antonio recruited Dr. Harris in 2022 with the support of a $6 million Recruitment of Established Investigators grant (RR220053). The University of Texas at Austin recruited Dr. Miller in 2011 with the support of a $2 million Recruitment of First-Time, Tenure-Track Faculty Members grant (R1116), and received a $1.05 million Individual Investigator grant (RP220330) in 2022 to understand how bromodomain proteins suppress DNA damage and promote genome integrity.

32. In a new study, researchers discovered that altering certain molecular interactions could lead to new strategies for treating prostate cancer and related diseases. The study, led by scientists at Mays Cancer Center at The University of Texas Health Science Center at San Antonio, focused on androgen receptors (AR), which are protein molecules that help control the devel-

opment of male sexual characteristics, essentially by turning genes on or off as necessary.

The data, published in Molecular Cell on September 21, showed that genetic and chemical methods weaken or strengthen AR activity. Both disrupting and elevating these interactions impaired AR transcriptional activity. The team proposed that AR interactions must be at an optimal level for proper function and that alterations could contribute to diseases.

“Our results provide molecular insights for potential therapeutic strategies to treat prostate cancer and other AR-involved diseases by targeting AR multivalent interactions,” said CPRIT Scholar Zhijie “Jason” Liu, Ph.D., associate professor, Mays Cancer Center and the Institute of Biotechnology of the Department of Molecular Medicine at UT Health San Antonio. “Collectively, our results suggest that disruption of the fine-tuned AR protein multivalent interactions might underlie AR-related human pathologies. AR multivalent interactions could be pharmacologically targeted to treat prostate cancer and other AR-involved diseases.”

The University of Texas Health Science Center at San Antonio recruited Dr. Liu in 2015 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160017).

33. Many patients with relapsed/refractory (R/R) large B cell lymphoma initially respond well to CAR T cell therapy targeting CD19, but most of these patients do not experience lasting effects. To understand why, researchers from The University of Texas MD Anderson Cancer Center including Linghua Wang, M.D., Ph.D., associate professor in the Department of Genomic Medicine, used single-cell RNA sequencing to create a large dataset of CAR T cells used to treat 59 patients with R/R large B cell lymphoma to uncover the underlying resistance mechanisms. The researchers identified characteristics of CAR T cells among the patient population after three months of treatment.

The results, published in Cancer Cell on September 21, showed that patients who achieved a complete response had higher expression of genes from the glycolysis pathway compared to those who did not. This single-cell atlas of CD19 CAR T cells is now publicly available for further research and validation.

The University of Texas MD Anderson Cancer Center received a $900,000 CPRIT Individual Investigator grant (RP200385) in August 2020 to improve efficacy in CAR T-cell therapy in relapsed/refractory diffuse large B-cell lymphoma patients.

34. Tumor mutational burden (TMB) refers to the number of gene mutations that occur in the genome of a cancer cell. Scientists previously found that tumors with many mutations responded better to immunotherapy drugs known as checkpoint inhibitors. However, understanding how TMB influences tumor immunity has been challenging in lung cancer models. addressable using genetically

To study this, a team of researchers led by CPRIT Scholar Esra Akbay, Ph.D., Department of Pathology at The University of Texas Southwestern Medical Center, used genetically engineered

mouse models (GEMMs) of lung cancer and introduced a variant of DNA polymerase-E (POLE) ^{P286R} that causes high mutation rates in lung epithelial cells. Adding this variant to existing lung cancer models significantly increased their TMB. The data, published in Cancer Cell on September 28, showed that the loss of p53 and the presence of heterogeneous mutations contribute to immune resistance in a GEMM of lung cancer. This research helps to clarify the role of TMB in shaping tumor immunity and resistance to treatment.

The University of Texas Southwestern Medical Center recruited Dr. Akbay in 2016 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160080).

35. Antibiotics have significantly extended the human lifespan and are one of the most crucial medical breakthroughs of the 20th century. However, the overuse and inappropriate use of antibiotics in humans and livestock has resulted in a rise of antibiotic-resistant bacteria and the emergence of multidrug-resistant organisms (MDROs). To combat this, it is essential to understand how bacteria develop resistance to the further development of new drugs.

FTIR (Fourier transform infrared spectroscopy) is a technique that analyzes bacterial cells and identifies molecules by their unique absorption patterns in the infrared spectrum. An international team of scientists, led by Vanderlei S. Bagnato, Ph.D., professor, Biomedical Engineering at Texas A&M Engineering, developed a method to better analyze and classify FTIR data obtained from samples of Staphylococcus aureus using machine learning algorithms. Published in MDPI Antibiotics on September 30, the data demonstrated that spectral analysis allows scientists to identify and characterize molecules based on their unique absorption or emission patterns in the infrared spectrum. This possibility allows scientists to identify which antibiotics contribute the most to resistance, offering insights into how these resistances develop and aiding in the creation of new drugs.

Texas A&M Engineering Experiment Station recruited Dr. Bagnato in 2022 with the support of a $6 million Recruitment of Established Investigators grant CPRIT (RR220054).

36. Colorectal cancer (CRC) remains a significant contributor to cancer-related mortality despite a variety of treatment options including surgery, chemotherapy, and targeted agents, which improve short-term outcomes depending on disease stage. However, survival rates with metastasis remain low. A promising strategy involves using dendritic cell (DC) vaccines to boost the immune system against tumor-derived blood vessels that support tumor growth.

In this report, researchers led by Devin B. Lowe, Ph.D., associate professor, Department of Immunotherapeutics & Biotechnology at Texas Tech University Health Sciences Center, targeted tumor-derived pericytes, which are cells that surround blood vessels in tumors and can influence tumor growth, progression, and therapy resistance. The team used an alpha type-1 polarized DC vaccine (αDC1) in a mouse model of CRC. The pre-clinical data, published in Frontiers in Immunology on October 2, demonstrate that the αDC1 vaccine can trigger immune responses that destroy tumor blood vessels and enhance the activity of cytotoxic T cells, disrupting the blood vessels that supply the tumor, further weakening the tumor. This work suggests that αDC1 vac-

cines could be a promising strategy for improving CRC treatment strategies.

Texas Tech University Health Sciences Center received a $6 million CPRIT Texas Regional Excellence in Cancer Award grant (RP210154) in August 2021 to study new anti-cancer drugs and cancer immunotherapy and to recruit outstanding junior faculty to West Texas who will study cancer drug development.

37. More than half of prostate cancer patients treated with androgen deprivation therapy (ADT) will experience significant cognitive decline. Although evidence suggests that ADT can induce profound cognitive impairment, many of the studies include small sample sizes or are mostly observational.

To identify potential new therapeutic targets for the treatment of cognitive impairment after ADT, David Morilak, Ph.D., director, Center for Biomedical Neuroscience, and colleagues from The University of Texas Health Science Center at San Antonio, investigated the effects of androgen deprivation on cognition in rats. The team then tested the potential efficacy of vortioxetine, an FDA-approved antidepressant, in restoring impaired cognition after ADT, and investigated mechanisms that might contribute to these effects.

The results of these experiments, published in Translational Psychiatry on October 3, revealed that vortioxetine reversed the cognitive deficits caused by ADT, particularly in areas related to hippocampal function and visuospatial cognition. This suggests that vortioxetine is a relatively safe, well-tolerated drug and has the potential for treating cognitive impairment associated with ADT in prostate cancer survivors.

The University of Texas Health Science Center at San Antonio received a $900,000 CPRIT Individual Investigator grant (RP180055), a $4 million CPRIT Research Training Award (RP170345), and a $3.68 million Core Facility Support Awards grant (RP160732).

38. Sodium-calcium exchangers (NCX) are proteins found throughout the body that help regulate the levels of calcium inside cells. Calcium is crucial for communication between cells, and NCXs help keep calcium levels in balance. Dysfunctions of NCXs are associated with many health issues, including cardiac hypertrophy, arrhythmia, and brain damage after a stroke. Despite extensive investigations, scientists do not fully understand the detailed structure and function of eukaryotic NCX1.

In this study, corresponding author Youxing Jiang, Ph.D., chair, Department Biomedical Science at The University of Texas Southwestern Medical Center, and colleagues used cryo-EM to visualize the structures of human cardiac NCX1 in both inactivated and activated states. This revealed the molecular basis underlying the complex regulation of NCX1. The team demonstrated that the interactions between the TM domain and the regulatory domain inside the cell determine the activity of NCX. The results, published in Nature Communications on October 4, provide new insights into its complex regulation

The University of Texas Southwestern Medical Center received a $5.5 million CPRIT Core Facil-

ity Support Awards grant (RP170644) in 2017 to establish a new Cryo-Electron Microscopy Core Facility and Service for Structure Determination at UT Southwestern Medical Center.

39. Mutations in the BRCA1 gene increase the risk of breast and ovarian cancer. BRCA1 works in conjunction with an essential partner gene, BARD1, to safeguard against cancer, but researchers have debated how this happens for years. One vital function of BRCA1, known as E3 ligase activity, helps regulate key proteins involved in DNA repair and other biological processes. However, in 2011, researchers concluded that the E3 ligase activity wasn't necessary for BRCA1's ability to prevent cancer. This conclusion remained at odds with the fact that many BRCA1 mutations seen in patients fall within the E3 ligase domain of BRCA1.

In a new study, Weixing Zhao, Ph.D., assistant professor, Department of Biochemistry & Structural Biology at The University of Texas Health Science Center at San Antonio, and colleagues revisited this conclusion by creating robust BRCA1-BARD1 reactions in the lab. As reported in Molecular Cell on October 8, the researchers discovered that the mutant previously thought to lack E3 ligase activity retained significant activity, challenging the established belief that BRCA1 does not require this activity for suppressing tumor formation. The researchers then identified a truly inactive mutant and demonstrated that this E3 ligase activity is crucial for DNA repair and tumor suppression.

"This essentially not only allowed us to finally put underlying assumptions that had gone unquestioned for decades to the test," Dr. Zhao said, "but we also sifted through a bunch of mutations to find the one that really shuts down the E3 ligase activity. With this specific non-working mutant, our experiments clearly demonstrated that this enzyme is crucial in several stages of DNA repair." The data will help researchers to identify women who are at an increased risk of developing breast and ovarian cancer and help in the development of appropriate treatment.

The University of Texas Health Science Center at San Antonio received a $250,000 CPRIT High Impact/High Risk grant (RP210102) in August 2021 to study the key functions of BRCA1 and to provide the foundation for formulating new treatment regimens.

40. Pancreatic ductal adenocarcinoma (PDAC) cells require a lot of nutrients in the form of sugars, amino acids, and lipids. Particularly, amino acids are critical for cancer growth and, as intermediates, connect glucose, lipid and nucleotide metabolism. Yangzom D. Bhutia, DVM, Ph.D., Department of Cell Biology and Biochemistry at Texas Tech University Health Sciences Center, and colleagues investigated the role of SLC38A5 (SN2/SNAT5), a neutral amino acid transporter, in PDAC growth and proliferation.

The team used a gene editing technique, CRISPR/Cas9, to reduce the levels of SLC38A5 in PDAC cells and observed its effects in both cell lines and mice. The data, reported in Scientific Reports on October 6, show that SLC38A5 is significantly increased in PDAC cells and that its overexpression is associated with poorer survival in patients. Additionally, the data shows that SLC38A5 is functional and essential for PDAC growth and proliferation. The team demonstrated for the first time the importance of SLC38A5 in PDAC and its potential as a target for future treatment.

Texas Tech University Health Sciences Center received a $6 million CPRIT Texas Regional Excellence in Cancer Award grant (RP210154) in August 2021 to study new anti-cancer drugs and cancer immunotherapy and to recruit outstanding junior faculty to West Texas who wish to study cancer drug development.

41. Doctors diagnose more than a thousand cases of T cell acute lymphoblastic leukemia (T-ALL) in the United States every year, and about half of these are pediatric cases. Chemotherapy exists for T-ALL patients, but it comes with side effects, including neurological toxicity, cognitive impairment, and metabolic disorders, as well as the possibility of developing resistance to the treatment.

A research team led by CPRIT Scholar Lauren Ehrlich, Ph.D., professor of molecular biosciences at The University of Texas at Austin, have found a link between myeloid cells (a blood cell that originates in the bone marrow) and T-ALL. The researchers discovered that T-ALL cells must adhere to myeloid cells to survive. The data, published in Nature Communications on October 7, revealed that this attachment happens through cell surface receptors called integrins, which activate a signaling pathway involving two proteins, FAK and PYK2. When the researchers blocked those proteins, the T-ALL cells also died. “Most research on T-ALL has been focused on mutations in the genome of the leukemia cell,” Dr. Ehrlich said. “And that’s an angle that sets us apart from most leukemia research. We’re showing how the tumor microenvironment supports leukemia growth and survival.” This data suggests a potential new target for T-ALL therapies.

The University of Texas at Austin received a $1.2 million CPRIT Academic Research grant (RP180073) in 2018 to determine which myeloid cells and associated signals support multiple subtypes of T-cell leukemia. UT Austin recruited Dr. Ehrlich in 2010 with the support of a $2 million Recruitment of First-Time, Tenure-Track Faculty Members grant (R1003).

42. Most cancer drugs work by attaching to a specific protein that drives cancer growth, blocking the function of the protein. These drugs often fail because of a weak attachment to the protein. CPRIT Scholar Ku-Lung (Ken) Hsu, associate professor of chemistry at The University of Texas at Austin, and fellow researchers focused on designing drugs that stay attached to the protein. Typically, researchers create covalent drugs that are good at binding to cysteine—one of 20 amino acids that make up proteins—because it has the highest tendency to share electrons and form a bond.

The team has developed a new method called sulfur-triazole exchange chemistry, SuTEx, that targets other amino acids, tyrosine and lysine, while avoiding cysteine and focusing on compounds that can form a stable covalent bond with underexplored nucleophile sites on proteins. As reported in Nature Communications on October 7, researchers engineered natural building blocks of nucleic acids, called purines, into a chemical probe for measuring RNA-binding activity in proteins. In particular, the new high-content discovery platform, PACCE, allows scientists to discover which proteins and regions bind to RNA, aiding in the development of therapies for previously “undruggable” targets.

The University of Texas at Austin recruited Dr. Hsu from the University of Virginia in 2022 with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR220063).

43. In recent years, researchers have used CRISPR-based targeting systems to develop cutting-edge synthetic transcription factors, which are proteins involved in the process of converting DNA into RNA. Most of these tools are built with materials of nonhuman origin, which may come with unwanted side effects. “Many human diseases are driven by problems with too little of a gene being produced,” said CPRIT Scholar Isaac Hilton, Ph.D., assistant professor, Departments of Biosciences and Bioengineering at Rice University. “You encounter these health issues where people don’t make enough of a certain protein or gene product, and in those cases, unfortunately there are often few therapeutic options.”

To address this issue, Rice University bioengineers developed a tool that activates silent or insufficiently expressed genes using human-derived proteins that naturally enable cells to turn on specific genes in response to mechanical cues. The tool, CRISPR-DREAM (or DREAM for short), is smaller, more effective, and less toxic to medically useful cell types than other state-of-the-art technologies used to control gene expression. According to the study published in Nature Methods on October 9, the DREAM tool could enable better and safer gene and cell therapies and more accurate disease models to address disorders, including epilepsy and some forms of cancer.

Rice University recruited Dr. Hilton in 2017 from Duke University with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR170030).

44. High grade glioma (HGG) is a class of brain tumors that are highly aggressive in nature. Treatment of HGG with radiotherapy (RT) is highly variable from patient to patient due to differences in cellular architecture and tumor micro-environment. CPRIT Scholar Thomas Yankeelov, Ph.D., professor, Department of Biomedical Engineering and director of the Center for Computational Oncology, and Karen Willcox, Ph.D., director of the Oden Institute for Computational Engineering and Sciences, both at The University of Texas at Austin, and fellow researchers developed a methodology to create data-driven predictive digital twins to help improve overall survival by adjusting and optimizing RT plans for each patient.

The digital twin is a mathematical model initialized with population-level clinical data and then personalized for each patient using Bayesian model calibration. This model helps predict how a patient will respond to treatment and provides doctors with personalized treatment recommendations. The results, published in Frontiers in Artificial Intelligence on October 11, reveal that using these optimized RT plans can delay tumor progression and reduce side effects compared to standard RT treatments.

The University of Texas at Austin recruited Dr. Yankeelov in 2015 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR160005). UT Austin received a $1.2 million CPRIT Individual Investigator Research Awards for Computational Biology grant (RP220225) in 2022.

45. Hetero-pentameric Cys-loop receptors are an important group of receptors in our nervous system that help transmit and process signals between nerve cells. It is unclear how neurotransmitters activate these receptors due to the lack of high-resolution structural information in

the activated open state. Their dysfunction causes or are associated with a myriad of neurological disorders, including Alzheimer's disease, schizophrenia, epilepsy, and autism as well as locomotive problems.

In this study, scientists have obtained detailed images of a major Cys-loop receptor called α1β GlyR, found in the adult human central nervous system, which is essential for inhibiting nerve signals in our brain. Through cryo-EM analysis, the team captured the structure of α1emβem GlyR both with and without the presence of glycine. These findings, published in Nature Communications on October 11, provide a foundation for understanding how receptors in the Cys-loop family adapt and operate in various situations, potentially aiding in the development of treatments for related neurological disorders.

The University of Texas Southwestern Medical Center received a $5.5 million CPRIT Core Facility Support Awards grant (RP170644) in 2017 to establish a new Cryo-Electron Microscopy Core Facility and Service for Structure Determination at UT Southwestern Medical Center.

46. The APOBEC3A family of enzymes normally helps combat infections but can also cause mutations in human cancer. Thus, blocking APOBEC3A with inhibitors could be a new way to treat cancer by blocking gene mutation, slowing tumor evolvability, and preventing drug resistance and metastasis. Two family members, A3A and A3B can change parts of DNA in a way that can lead to cancer and worsen the disease. Recent studies have also shown that A3A can cause cancer in mice.

An international team of researchers, including CPRIT Scholar Reuben Harris, Ph.D., professor and chairman, Department of Biochemistry & Structural Biology at The University of Texas Health Science Center at San Antonio, used X-ray crystallography to determine how to inhibit high-resolution structures of wildtype A3A/hairpin effectively. They found that 3-nt hairpin loops with TTC (or TTFdZ) are preferred A3A substrates and inhibitors. As reported in Nature Communications on October 11, further enhancement of such inhibitors may lead to new treatments that slow cancer progression and improve outcomes for patients with A3A-driven tumors.

The University of Texas Health Science Center at San Antonio recruited Dr. Harris in 2022 with the support of a $6 million Recruitment of Established Investigators grant (RR220053).

47. Stimulator of interferon genes (STING) plays a crucial role on our body's defense system by detecting the presence of foreign DNA inside cells, which helps defend against pathogens and cancer. CPRIT Scholar Xiaochen Bai, Ph.D., Department of Biophysics at The University of Texas Southwestern Medical Center, and colleagues reported the discovery of a class of STING agonists that show potent antitumor activity. They used a combination of techniques to find and understand how this activator, called NVS-STG2, works. NVS-STG2 binds to a specific part of STING, helping it form larger structures, a process known as oligomerization. This oligomerization enhances STING's ability to activate immune responses. The data, published in Nature Chemical Biology on October 12, reported that NVS-STG2 can trigger strong STING-mediated immune responses in cells and has potent anti-cancer effects in animal models.

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 grant (RR160082); and received a $4 million CPRIT Core Facility Support Awards grant (RP220582) in 2022 to establish new Cryo-EM Core Services to Drive Cancer Research and Drug Discovery.

48. In 2022, there were an estimated 60,000 new cases and approximately 50,000 deaths due to pancreatic cancer (PC). Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal of all cancers and scientists estimate it will be the second highest cause of cancer-related mortality by 2030. Researchers have linked the tumor microbiome (TM), the microbes in the tumor environment, to pancreatic cancer prognosis; specific microbes can confer tumor resistance to therapies. Knowledge of the TM at time of diagnosis could help tailor treatment based on microbial composition. However, it is difficult to define the TM prior to surgical resection.

Researchers from The University of Texas MD Anderson Cancer Center led by Florencia McAllister, M.D., Department of Clinical Cancer Prevention, reported the results of a pilot study to test feasibility of analyzing the bacteria and fungi in pancreatic tumors using a method called Endoscopic Ultrasound-Fine Needle Aspiration (EUS-FNA) biopsy. In this study, patients underwent EUS-FNA biopsy of pancreatic adenocarcinoma. As reported in Frontiers in Immunology on October 13, the team analyzed the samples and was then able to characterize the TM in biopsies. They found that the TM identified in these biopsy samples matched those from surgical specimens, suggesting that EUS-FNA biopsy is a feasible way to characterize the pancreatic TM prior to surgical resection.

The University of Texas MD Anderson Cancer Center received a $2 million CPRIT Academic Research grant (RP200173) in 2020 to study the role of gut and tumor bacteria in modulating the tumor microenvironment and tumor growth.

49. Osteoimmune diseases, such as apical periodontitis (AP), are prevalent, often painful, inflammatory conditions resulting in bone loss and reduced quality of life. There is growing evidence that the nociceptive fibers, nerves responsible for sensing pain, have a role in controlling disease progress. Substances released during inflammation or by harmful bacteria can activate these nerves.

An international team of researchers wanted to understand how these pain-sensing nerves influence the inflammatory processes in the context of bone loss due to root canal infections. Using a mouse model with AP, the team found that nociceptive nerves directly affect bone-maintaining cells and the immune response, at least in part, leading to an increase in the activity of genes involved in inflammation. These data, published in Scientific Reports on October 16, highlight how pain-sensing nerves contribute to the development of AP and show the complex changes occurring during the disease. The results further confirm that the network of nerves around our teeth significantly impacts disease progression.

The University of Texas Health Science Center at San Antonio received a $4 million CPRIT Core Facility Awards grant (RP220662) in 2022 for cutting-edge technologies that will facilitate new discoveries at the CPRIT-funded UTHSA Cancer Genome Sequencing and Computation Core.

50. Cells are the most essential component of life, which respond to stimuli, reproduce, process information, and carry out various chemical activities. Single-cell analysis (SCA) provides information on each cell which helps us understand processes such as stem cell activity or tumor progression. Single-cell RNA sequencing (scRNA-seq) provides a powerful tool for analyzing the complexity of biological tissues by identifying and grouping different cell types.

Researchers set out to identify the gene signature, which are combinations of genes associated with a particular condition or biological process, and to simplify bulk RNA-seq data by removing noise (irrelevant information). Co-corresponding author Zhongming Zhao, Ph.D., chair and professor for Precision Health at The University of Texas Health Science Center at Houston, and fellow researchers used scRNA-seq data from rare intestinal cell type in mice consisting of 23,630 features, 1872 cells, and 9 classes.

The team developed a new framework for gene signature detection to address the “drop-out” problem, where certain genes may not be accurately detected in some cells. As reported in MDPI: Mathematics on October 17, the data revealed that their method effectively identified differentially expressed stronger gene signatures and up-regulated markers in the single-cell RNA sequencing data.

The University of Texas Health Science Center at Houston received two CPRIT Core Facility Support Awards grants (RP170668, RP180734) totaling $10.2 million in 2017 and 2018 to create a Data Science and Informatics Core for Cancer Research (DSICCR) and to establish the UTHealth Cancer Genomics Core, which will provide state-of-the-art sequencing facilities and timely bioinformatics service and training.

51. Coinfections, where multiple pathogens infect a host at the same time, happen regularly in the natural world. Hosts are exposed to multiple pathogens over the course of their life, either simultaneously or sequentially. Researchers often design experiments with a set order and timing for these infections but rarely check if changing the sequence affects the outcome. However, it is important to know how the order of infection changes the outcomes of coinfection because humans experience all sequences of infection.

The purpose of this study, published in Pathogens on October 17, was to understand how the order of infections impacts the result, focusing on the impact of intestinal parasite infection on murine gammaherpesvirus-68 (MHV68) infection and latency. Tiffany A. Reese, Ph.D., Departments of Immunology and Microbiology at The University of Texas Southwestern Medical Center, and fellow researchers asked whether the sequence of coinfection led to different outcomes. In previous reports, where the team infected with gammaherpesvirus first, followed by intestinal parasite, they found that parasite challenge increased reactivation of the virus. In the current study, the team found that when mice were infected with a parasite before the virus, there was an increase in viral infection in tissue-resident macrophages (immune cells) during both the acute and chronic phases of herpesvirus infection. During the chronic phase of infection, the coinfected mice had more latent viral infections in these immune cells and reactivated more herpesvirus. This work suggests that parasitic infections exacerbate chronic herpesvirus infection. Importantly, the timing of coinfection plays a crucial role in how parasitic infections can reactivate chronic herpesvirus infections.

The University of Texas Southwestern Medical Center received a $900,000 CPRIT Individual Investigator grant (RP200118) in 2020.

52. Cervical cancer is a human papillomavirus (HPV)-related cancer that often responds well to radiation treatment, but some patients develop resistance. To find out why, researchers at The University of Texas MD Anderson Cancer Center analyzed data from 101 cervical cancer patients undergoing chemoradiation between September 2015 and March 2022 and studied the bacteria present in their tumors. The data, published in Cancer Cell on October 19, revealed that a particular bacterial species, Lactobacillus iners (L. iners), made cancer cells resistant to radiation by altering their metabolic pathways. The researchers showed that introducing L. iners to cancer cells in the lab also caused resistance to treatment.

“These lactic acid-producing bacteria are seemingly responsible for changing signaling pathways by priming cancer cells to use lactate instead of glucose to fuel growth and proliferation from oxidative stress following radiation therapy,” said corresponding author Lauren Colbert, M.D., assistant professor in the Department of Radiation Oncology. “This is potentially paradigm shifting, and we currently are working on novel approaches to target these specific intratumoral bacteria. We are hopeful that these efforts will lead us to approaches that can benefit patients across several types of cancer.” The results also revealed that L. iners have functions inside of tumors that are not present in healthy patients, suggesting that these bacteria may change before cancer develops.

The University of Texas Health Science Center at Houston received a $4.4 million CPRIT Core Facility Support Awards grant (RP180734) to establish the UTHealth Cancer Genomics Core, which will provide state-of-the-art sequencing facilities and timely bioinformatics service and training.

53. Somatic copy number alterations (SCNAs) are changes in the number of physical copies of a given genomic region and are common in human cancers, contributing to the formation of cancer. Most computational methods for identifying SCNAs from DNA sequencing analyze tumor samples individually, but cancer cells often change their chromosome numbers as they evolve. The chromosomal instability and abnormal chromosome numbers are associated with cancer drug resistance and metastasis.

An international team of researchers, including CPRIT Scholar Peter Van Loo, Ph.D., professor, Department of Genetics at The University of Texas MD Anderson Cancer Center, developed a new algorithm and software tool, Refphase, to better analyze SCNAs. Refphase uses a technique called multi-sample reference phasing, comparing multiple tumor samples from the same patient against a reference sample. This provides the team with detailed insights into the differences between cancer genomes and helps catalog various evolutionary events within tumors. The results, published in Computational Biology on October 23, show that Refphase can accurately detect SCNAs and the variations within a tumor, compare SCNA patterns between primary and metastatic tumors from the same patient, and uncover previously hidden genetic imbalances in low-purity samples. This new algorithm helps researchers understand common genetic patterns that may

drive cancer development or progression across different types of cancer.

The University of Texas MD Anderson Cancer Center recruited Dr. Van Loo in November 2020 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR210006).

54. When the normal chemical tagging of DNA gets disturbed, it's called DNA methylation deregulation at partially methylated domains (PMDs). This abnormal alteration affects the regulation of genes and is associated with various biological processes, including aging and cancer, yet the underlying molecular basis and resulting biological consequences remain unresolved.

In this study, CPRIT Scholar Yun Huang, Ph.D., and Yubin Zhou, M.D., Ph.D., both with the Institute of Biosciences and Technology at Texas A&M University, and fellow researchers report that the TET2 gene plays a role in the rearrangement of tightly packed DNA (heterochromatin) within the nuclei of aging HSPCs (the stem cells that give rise to other blood cells). This suggests that TET2 contributes to the functional decline of aged HSPCs. Researchers found that reverse transcriptase inhibitors can help restore normal function in these aging stem cells by reducing overactive genes. The data, published in Nature Aging on October 26, improves scientists' understanding of how DNA methylation and changes in DNA packaging work together, which is crucial for protecting genetic stability in stem cells. These results offer hope for treating conditions in the elderly population, such as unexplained anemia, and reducing the incidence of aggressive myeloid leukemias.

Texas A&M University System Health Science Center received a $250,000 High Impact/High Risk grant (RP210070) in August 2021 to engineer smart therapeutic T cells by delivering durable and controllable cell-based immunotherapy against cancer. Texas A&M University Health Science Center recruited Dr. Huang in 2014 from the La Jolla Institute for Immunology with a $1.8 million First-Time, Tenure-Track Faculty Member grant (RR140053).

55. Researchers at Baylor College of Medicine and collaborating institutions have discovered a potential new treatment for triple-negative breast cancer (TNBC) that could lead to novel therapies and improved outcomes for this devastating cancer. TNBC tumors usually have more immune cells that protect the tumor rather than fight it, making immunotherapies ineffective. The team targeted a protein called eIF4A with the small molecule drug Zotatifin, which suppresses tumor cell growth by inhibiting the production of several tumor-promoting proteins, making the tumors more responsive to immunotherapy. The results, reported in The Journal of Clinical Investigation on October 24, revealed that Zotatifin also stimulated an interferon response, which improved the immune microenvironment of the tumor.

"TNBC tumors are typically 'cold tumors,' meaning they have more immune cells that protect the tumor than cells that fight the tumor," said corresponding author Jeffrey Rosen, Ph.D., professor of molecular and cellular biology and member of the Dan L Duncan Comprehensive Cancer Center at Baylor. "This in turn makes immunotherapies ineffective in most TNBC as these therapies depend on having immune cells that would attack the tumor. Zotatifin changed cold tumors into 'hot tumors' carrying more cancer-fighting immune cells. This change sensitized the tumors to a

type of immunotherapy called immune checkpoint blockade and improved the treatment."

The team encountered an additional positive outcome; the use of Zotatifin allows for lowering the dose of chemotherapy. Patients can now receive half the dose of chemotherapy when combined with the small inhibitor and achieve good survival benefits while reducing toxicity. These studies have provided an important foundation for submission of an investigational new drug application to the FDA to facilitate the next stage of clinical trials for TNBC and potentially other cancer types that also require chemotherapy.

Baylor College of Medicine received a $950,000 CPRIT Individual Investigator grant (RP220468) in 2022 to study the new therapeutic vulnerability in triple-negative breast cancer, eIF4A. Baylor College of Medicine received three CPRIT Core Facility Support Awards (RP170005, RP180672, RP210227) in 2017, 2018, and 2021 totaling $14 million.

56. Homologous recombination (HR) is a DNA repair mechanism that plays a critical role in maintaining the integrity of the genome. Defects in HR DNA repair (HRD) can lead to cancer development and produce therapeutic vulnerabilities. However, only a small fraction of patients with hereditary breast or ovarian cancers has BRCA1/2 mutations, which are involved in HRD repair.

Researchers led by CPRIT Scholar Nidhi Sahni, Ph.D., associate professor, Department of Epigenetics and Molecular Carcinogenesis at The University of Texas MD Anderson Cancer Center, sought to identify other genetic factors involved in HR defects. They calculated data across tumors from The Cancer Genome Atlas to identify tumors that were either positive or negative for HR defects. The data, published in Cell Reports Medicine on October 30, revealed that approximately 75% of tumors with a positive HR score did not have defects in known HR genes. The team identified nearly 100 candidate HR-related genes. They also discovered that RNA-binding protein (RBP) genes, which help manage RNA in cells, play a significant role in HR repair. This study adds to previous research providing further insights into specific RBPs and their role as novel drivers of HR deficiency. These findings have implications for the development of targeted therapies and interventions.

The University of Texas MD Anderson Cancer Center recruited Dr. Sahni in November 2015 from the Dana-Farber Cancer Institute with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160021).

57. Therapeutic T-cells, a type of immune cell used in immunotherapy, are less effective because the tumor microenvironment lacks sufficient positive signals for T-cell activity and contains an excess of inhibitory signals that suppress their function. This imbalance hampers the ability of T-cells to effectively target and eliminate cancer cells within the tumor.

Researchers from Baylor College of Medicine previously showed that modifying T cells with constitutively active IL7 receptor (C7R) improved the survival, growth, and anti-tumor activity of T-cells expressing chimeric antigen receptors (CARs), and C7R-modified GD2. To determine if this modification could also help T-cells that recognize tumors through their natural T-cell recep-

tors (TCRs), corresponding author Cliona M. Rooney, Ph.D., professor, Department of Pediatrics-Hem-Onc Cell and Gene, and team tested its effects in Epstein–Barr virus (EBV)-specific T-cells (EBVSTs) that have produced clinical benefits in patients with EBV-associated malignancies. EBV plays a role in several cancers including about 30% of Hodgkin and non-Hodgkin lymphomas.

As reported in the International Journal of Molecular Sciences on October 31, C7R enhanced the growth and specificity of these EBV-targeting T-cells in the lab and improved their ability to fight tumors in a mouse model. These promising results have led to a clinical trial to test C7R-modified T-cells in patients with difficult-to-treat EBV-positive lymphoma.

Baylor College of Medicine received a $4 million CPRIT Research Training grant (RP160283) in November 2015.

58. Nucleotide excision repair (NER) is a major DNA repair system that repairs significant DNA damage. Defects in NER can lead to xeroderma pigmentosum (XP), an inherited skin cancer-prone disorder causing extreme sun sensitivity. A specific type of NER, called transcription-coupled nucleotide excision repair (TC-NER), focuses on repairing DNA damage in actively transcribed genes, including non-coding genes.

Two University of Texas Southwestern Medical Center researchers, including CPRIT Scholar Guo-Min Li, Ph.D., Department of Radiation Oncology, discovered that chaperone-mediated autophagy (CMA), a process that selectively removes damaged proteins, also helps regulate TC-NER in the nucleus. Heat shock proteins (HSPs), including DNAJA2, are crucial for maintaining protein homeostasis in normal and stressed conditions, such as UV exposure. The data, published in Cell Discovery on October 31, show that DNAJA2 deficiency makes cells more vulnerable to damage from UV radiation and impairs their ability to recover normal gene activity. This study has not only identified DNAJA2 as an essential factor for TC-NER, but also provided insights into the molecular mechanism. Understanding these molecular interactions sheds light on the intricate ways by which cells repair damaged DNA during transcription.

The University of Texas Southwestern Medical Center recruited Dr. Li in September 2016 from the Norris Comprehensive Cancer Center, University of Southern California Keck School of Medicine with support from a $6 million CPRIT Recruitment of Established Investigators grant (RR160101).

59. The primary treatment for high-grade serous ovarian cancer (HGSC) has been a combination of taxanes and platinum-based drugs for more than two decades. Despite this treatment, HGSC still has a high overall mortality rate, because it's often diagnosed at a late stage and quickly becomes resistant to chemotherapy. Relapse is a major issue in treating patients with ovarian cancer, so it's crucial to study the molecular changes related to therapy response to identify novel actionable targets.

Principal investigator, Livia Schiavinato Eberlin, Ph.D., associate professor of surgery at Baylor College of Medicine, and team used desorption electrospray ionization mass spectrometry (DESI-MS) to examine tissue samples from HGSC patients before and after neoadjuvant chemother-

apy (NACT). They compared patients with poor responses (PR) to those with excellent responses (ER) to NACT. The findings, published in NPJ Precision Oncology on November 3, revealed distinct metabolic differences in the tumor-rich areas compared to the surrounding tissue both before and after therapy. Based on these metabolic changes, the researchers developed a predictive model that predicts patients' responses to chemotherapy with 75% accuracy. This groundbreaking work not only enhances the understanding of how ovarian cancer responds to chemotherapy at the metabolic level. It also paves the way for new treatment strategies and the possibility of personalized treatment plans based on these metabolic signatures.

Baylor College of Medicine received a $240,190 CPRIT Individual Investigator Research Awards for Clinical Translation grant (RP180381) in February 2018.

60. Cancer and heart disease are the two leading causes of death in the United States. As the incidence of both diseases continues to rise, an increasing number of radiation oncology patients will present with cardiac-implantable electronic devices (CIEDs), posing challenges for radiation therapy. One challenge is obtaining high-quality CT and cone beam CT (CBCT) images for radiation planning. Contouring these devices and overriding their density is crucial for ensuring accurate dose calculations, precise treatment delivery, and overall patient safety.

Laurence E. Court, Ph.D., professor, Department of Radiation Physics - Patient Care at The University of Texas MD Anderson Cancer Center, and colleagues aimed to improve the contouring accuracy of cardiac pacemakers by improving their visualization using deep learning models. In this study, GAN-based models were effective tools for improving pacemaker visualization in kV imaging, simplifying the contouring process.

The data, published in the Journal of Imaging on November 8, report that this approach reduced the time needed for implant delineation and increased accuracy. Enhanced visualization on daily CBCT scans could streamline adaptive treatment planning, making it faster and easier to re-plan when necessary. This method can potentially work for other implant devices, like defibrillators, cardiac loopers, and breast expanders.

The University of Texas MD Anderson Cancer Center received two CPRIT Academic Research grants (RP200395, RP210028) in 2020 and 2021 totaling $4.9 million.

61. Fluorine is the most chemically reactive element and is useful in making drugs more effective by increasing their absorption and prolonging their lifespan. However, attaching fluorine to drugs is challenging since current processes often require expensive chemicals, are dangerously reactive, and don't work well. Researchers at Rice University discovered a new, simpler method using common, inexpensive elements: iron and sulfur.

CPRIT Scholar Julian West, Ph.D., assistant professor, Department of Chemistry, and colleagues found that when they shine light on iron and sulfur, they interact and erupt with enough energy to break apart carboxylic acid molecules, which then frees up fluorine atoms for use elsewhere. Published in Nature Chemistry on November 13, the study revealed that not only can the light-activated reaction work to free up fluorine from carboxylic acids, but it can incorporate it into alkenes

 common building blocks for pharmaceuticals and other chemical products. “Alkenes are most commonly used to help put the drugs together because they can be transformed into many different things, like a foundation that more complex parts can be built on,” Dr. West said. “If you want to add a different fluorine piece, just put in a different carboxylic acid.”

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).

62. Systematic transcriptome profiling in human cells has revealed that the cells actively use more than 70% of all the information coded in our DNA under certain conditions. The human genome contains thousands of non-canonical open reading frames (ORFs), segments of a DNA or RNA molecule with the potential for translation into a protein, including microproteins. Many transcripts in the human transcriptome are classified as noncoding RNA (ncRNA) because they lack ORFs that are recognizable by traditional methods.

Recent studies have indicated that some microproteins have tumor-suppressive functions in colorectal cancer (CRC), but their role in cancer remains largely unknown. To provide further insight, a team of researchers led by CPRIT Scholar Yiwen Chen, Ph.D., associate professor, Department of Bioinformatics and Computational Biology, and CPRIT Scholar Han Xu, Ph.D., Department of Epigenetics and Molecular Carcinogenesis at The University of Texas MD Anderson Cancer Center, used an integrated multiomic approach to identify non-canonical ORFs that may be functionally relevant in CRC. They identified a long noncoding RNA-encoded microprotein, SMIMP (SMC1A-interacting microprotein), that has tumor-promoting function in vivo and is associated with poor prognosis. This study, published in Nature Structural & Molecular Biology on November 6, emphasizes the importance of further research of the functional roles of non-canonical ORFs for potential novel therapeutic targets.

The University of Texas MD Anderson Cancer Center recruited Dr. Chen in 2014 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR140071) and recruited Dr. Xu in 2016 the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160097). Baylor College of Medicine received two CPRIT Core Facility Support Awards (RP170005, RP210227) in 2017 and 2021 totaling $14 million.

63. Rice University’s Biotech Launch Pad is developing an implantable electrocatalytic on-site oxygenator (ecO2) device to autonomously administer and regulate therapeutics for the patient. A study, led by a team of researchers, including CPRIT Scholar Omid Veiseh, Ph.D., associate professor of bioengineering and faculty director of the Rice Biotech Launch Pad, published on November 9 in Nature Communications. The study details the development of the rechargeable ecO2 device, which produces oxygen to keep cells alive inside an implantable “living pharmacy.” Cell-based therapies have potential to treat many different types of diseases including endocrine disorders, autoimmune syndromes, cancers, and neurological degeneration, but the survival of these cells for extended periods is necessary to produce effective treatments. The current treatment options to deliver oxygen to cells, however, require bulky equipment and have

limited oxygen production and regulation.

“Oxygen generation is achieved here through basic water splitting and precisely regulated using a battery powered and wirelessly controllable electronic system; however, the next iterations of this device will have wireless charging, which means that this could potentially last the full life of the patient,” said Dr. Veiseh. “This breakthrough technology has the potential to reshape the landscape of disease treatment and the future of research and development in the field of cell-based therapies. We are working toward advancing this technology into the clinic to bring it one step closer to those in need.”

Rice University recruited Dr. Veiseh from the Massachusetts Institute of Technology with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160047) in 2016.

64. Cronkhite-Canada syndrome (CCS) is a rare, non-inherited disease that causes abundant cystic polyps in the intestine, along with symptoms such as hair and nail loss and changes in skin pigmentation. The cause of CCS, which mainly affects individuals in middle to late adulthood, has been difficult to interpret due to the rareness of the disease.

To better understand CCS, a team of researchers, including co-author Mary Estes, Ph.D., professor and chair, Department of Molecular Virology and Microbiology at Baylor College of Medicine, created human intestinal organoids (HIOs), or mini guts, from intestinal stem cells of two patients with CSS. The team discovered that CCS HIOs are highly proliferative and have increased numbers of enteroendocrine cells that produce serotonin, a chemical that carries messages between nerve cells. As reported in The Journal of Clinical Investigation on November 1, the data suggests a link between local serotonin production and control of intestinal cell proliferation. This work provides a new mechanism to explain the progression of CCS. It also illustrates the important contribution of HIO cultures can help understand the cause of CSS and in the identification of novel therapies.

Baylor College of Medicine received two CPRIT Core Facility Support Award grants (RP180672, P200504) in 2018 and 2020 totaling $9.1 million. Texas A&M University System Health Science Center received two CPRIT Core Facility Support Awards grants (RP150578, RP170719) in 2015 and 2017 totaling $11.7 million.

65. Rhabdomyosarcoma (RMS) is a pediatric malignancy of the muscle that starts as a growth of cells in soft tissue. Over the last two decades, studies have identified many genes that drive the development of RMS or suppress its growth. One key pathway involved is the Notch signaling pathway, particularly the gene NOTCH1, which is crucial for regulating muscle stem cells. If the muscle loses NOTCH1, its ability to regenerate decreases, especially as we age. However, the maintenance or regulation of NOTCH1 in normal and malignant cells is unclear. Understanding how normal muscle cell development is disrupted in RMS could lead to better treatments.

In this study, CPRIT Scholar Myron Ignatius, Ph.D., assistant professor, Department of Molecular Medicine at The University of Texas Health Science Center at San Antonio, and fellow research-

ers discovered a novel mechanism where the protein SNAI2, normally known for turning genes off, activates rather than represses NOTCH1. The team found that SNAI2 works together with another protein, CTCF, by binding to a specific DNA region near NOTCH1, which is essential for the expression and the survival of RMS cells. The results, published in Molecular and Cellular Biology on November 17, revealed that SNAI2 is necessary for maintaining NOTCH1 levels by regulating the 3D structure of chromatin, the material that makes up chromosomes.

The University of Texas Health Science Center at San Antonio recruited Dr. Ignatius in 2016 from Massachusetts General Hospital/Harvard Medical School with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160062). UTHSCA received a $4 million CPRIT Research Training grant (RP170345) in November 2016 to train individuals committed to cancer research and prevention in the basic science, translational, and clinical areas of research.

66. A multi-Center study co-led by CPRIT Scholar Carlos L. Arteaga, M.D., professor of Internal Medicine, director of the Harold C. Simmons Comprehensive Cancer Center, and associate dean of Oncology Programs at The University of Texas Southwestern Medical Center, has found a new targeted therapy for a difficult-to-treat form of breast cancer that has become resistant to other treatments and has no curative options. As reported in the November 14, issue of the Annals of Oncology, this therapeutic strategy, which uses three different drugs, significantly delayed progression and extended survival for breast cancer patients with mutations in the HER2 gene.

Nearly 10% of patients with metastatic breast cancer have cancer promoting HER2 mutations in the absence of HER2 gene amplification or overexpression. Although these tumors initially respond to HER2-inhibiting drugs, they eventually stop responding after new mutations develop. To slow or stop progression of tumors bearing HER2 mutations, Dr. Arteaga and his colleagues, including Nisha Unni, M.D., associate professor of Internal Medicine, and Ariella Hanker, Ph.D., assistant professor of Internal Medicine, tested various combinations of three different drugs among 71 breast cancer patients with HER2 mutations and hormone receptor-positive tumors.

The triple drug combination included neratinib (a HER2 tyrosine kinase inhibitor), fulvestrant (and estrogen receptor inhibitor), and trastuzumab (a HER2 blocking antibody). For 39% of the patients, tumor growth slowed, stopped, or reversed. The partial or complete response continued for an average of 14.4 months, with about 8.3 months free from cancer progression. Those taking only fulvestrant or fulvestrant and trastuzumab showed no response. The researchers are planning a first-in-class multi-institutional neoadjuvant trial of neratinib and letrozole, an aromatase inhibitor, in patients with newly diagnosed invasive lobular breast cancer with HER2 mutations. This research is practice-changing and has led to the inclusion of this three-drug combination in the National Comprehensive Cancer Network's internationally used treatment guidelines.

The University of Texas Southwestern Medical Center recruited Dr. Arteaga from Vanderbilt University School of Medicine with a $6 million Recruitment of Established Investigator grant (RR170061) in 2017.

67. Fecal immunochemical test (FIT) is an effective colorectal cancer screening test. The at-home tests for colorectal cancer (CRC) are often more convenient, less costly, and less inva-

sive than a colonoscopy or other stool-based tests. However, patients have faced challenges with the at-home FIT tests which result in inadequate tests.

Corresponding author Rasmi Nair, MBBS, MPH, Ph.D., assistant professor in the School of Public Health at The University of Texas Southwestern Medical Center, and colleagues looked at in-home FITs submitted between 2010 and 2019 from 56,980 individuals who had a primary care visit through Parkland Health in the year prior to the test. This retrospective cohort study revealed that of the 56,980 individuals completing an index FIT, 10.2% had an unsatisfactory FIT and fewer than half completed a subsequent test after an unsatisfactory FIT.

The data, published in Cancer Epidemiology, Biomarkers, & Prevention on November 15, revealed that the reasons included inadequate specimen (51%), incomplete labeling (27%), old specimen (13%), and broken/leaking container (8%). The study also found higher failure rates among patients who were male, Black, Spanish-speaking, on Medicaid, and patients who received FIT in the mail rather than from a practitioner. The researchers recommend more substantial patient education strategies, better test-tracking procedures, and timely follow-up of problem tests to reduce FIT failure rates and improve patient care through early CRC interventions. “Our findings could impact other at-home tests such as fecal DNA tests for CRC screening and future home testing for human papillomavirus, for instance,” Dr. Nair said. “Understanding the reasons for unsatisfactory home tests, implementing automatic ordering of subsequent tests, and ensuring appropriate completion of tests and follow-up become increasingly important.”

The University of Texas Southwestern Medical Center received a $1.5 million CPRIT Prevention grant (PP160075) in August 2016 to implement a sustainable system-wide infrastructure for colorectal cancer (CRC) screening among a racially diverse and socioeconomically disadvantaged patient population in Dallas County.

68. Acute leukemia is the most common malignancy in children. It accounts for over 25% of all childhood cancers and is the second leading cause of childhood cancer deaths. Survivors of pediatric leukemia often suffer from long-term chronic health conditions such as osteonecrosis, cardiotoxicity, and peripheral neuropathy due to cytotoxic drug-based therapies.

Patient-derived xenograft (PDX) models are a valuable tool for studying tumor evolution and developing novel treatments. PDX models are created by implanting cancer cells or tissues from a patient’s primary tumor into an immunodeficient mouse, simulating human tumor biology. Because children of Hispanic ethnicity have both a higher incidence and poorer outcome for leukemia when compared to non-Hispanic patients, scientists including CPRIT Scholar Siyuan Zheng, Ph.D., assistant professor, Department of Population Health Sciences at The University of Texas Health Science Center at San Antonio, developed new PDX models from Hispanic children with leukemia. Of 117 primary leukemia samples obtained, 82 samples (70%) were successfully grown in mice. This work, published in Science Direct on November 17, also includes the development of a competitive bioinformatics tool, REMOCON, which helps clean up data, which is freely available to researchers, by removing mouse contaminant reads.

This study showed that the PDX models accurately mimic the leukemia seen in the original patients, including specific genetic changes. This makes the models a valuable resource for study-

ing pediatric leukemia and testing potential new treatments.

The University of Texas Health Science Center at San Antonio received four CPRIT Core Facility Support Awards grants (RP160716, RP160732, RP220599, RP220662) totaling $16.5 million; a $1.2 million Academic Research grant (RP180319); and recruited Dr. Zheng in August 2017 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR170055).

69. The use of antipsychotic drugs, including olanzapine and risperidone, is often associated with substantial weight gain and the development of diabetes. The cause of this weight gain is associated with an increased concentration of the hormone, leptin, in fat cells. Researchers, including Philipp Scherer, Ph.D., professor of Internal Medicine and director of the Touchstone Center for Diabetes Research at The University of Texas Southwestern Medical Center, used a mouse model to uncover the underlying mechanisms of unwanted metabolic side effects and to test an antibody that might reduce them.

The results, published in Science Translational Medicine on November 22, show that hyperleptinemia occurs before any increase in body weight. Results also indicated that treating mice with a leptin-neutralizing antibody led to reduced weight gain, inflammation, and mammary gland development as well as improved glucose tolerance in mice with drug-induced side effects. Therefore, leptin neutralization in the context of antipsychotic drug treatment is greatly beneficial to the management of weight gain and metabolic dysfunction.

The University of Texas Health Science Center at Houston received a $6 million CPRIT Core Facility Support Awards grant (RP190561) in August 2019.

70. Cell migration is a major component of metastasis, which accounts for two-thirds of all solid tumor deaths. Many of the genes required for the movement of cancer cells are equally important for normal adult stem cell regeneration and wound healing, that require considerable amounts of energy in the form of adenosine triphosphate (ATP). Thus, understanding the differences between normal and cancer cell migration is critical for the development of targeted therapies. However, few studies have systematically compared normal and cancer cell migration as well as energy requirements side by side.

CPRIT Scholar Jihan Osborne, Ph.D., assistant professor in the Department of Pharmacology and fellow researchers from The University of Texas Southwestern Medical Center, set out to better understand these differences. The team screened human normal and cancer cell lines derived from the lung and breast for migratory potential. The data, reported in Cancers on November 22, revealed that non-malignant cells (of both the lung and mammary) had greater basal ATP levels than the cancer cells at wound induction. Surprisingly, normal human lung epithelial cells migrated faster than the lung cancer cells, representing a paradigm shift in the development of future targeted metastatic therapies.

The University of Texas Southwestern Medical Center recruited Dr. Osborne in November 2020 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members

grant (RR210016). UT Southwestern received a $3.75 million CPRIT Research Training grant (RP210041) in May 2021.

71. Cancer often develops and progresses due to problems caused by excessive DNA damage or problems in DNA repair systems (DDR) leading to genomic instability. Cancer cells often enhance their DDR pathways to cope with the DNA damage from rapid cell division, increased metabolism, and harmful environmental factors. This boosted DDR activity helps cancer cells repair DNA and survive conditions that would harm normal cells.

The realization that such intrinsic changes in the DDR could offer therapeutic opportunities has led a team of researchers to seek ways to improve screening for drug discovery. In an article published in the International Journal of Molecular Sciences on November 23, researchers, including CPRIT Scholar Yang Gao, Ph.D., assistant professor, Department of BioSciences at Rice University, developed a novel drug discovery platform called SaXPy (SAR by X-ray Poses Quickly). This platform allows them to quickly study how potential drugs interact with DNA repair proteins. Using SaXPy, the team successfully mapped out the first-ever X-ray crystal structures of small compounds bound to two key DNA repair proteins, POLH and APE1. The team quickly moved from identifying these initial compounds to developing them into promising early-stage drug candidates. These advances inform chemical tractability and downstream biology and generate novel intellectual property.

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).

72. Childhood cancers, though rare, are the leading cause of disease-related death in children. Survival for patients with metastatic or refractory tumors is still poor and multimodality treatments cause long-term health problems and increase the risk of secondary cancer. Molecularly targeted therapies and immunotherapy can improve overall patient outcomes, but their development requires accurate preclinical models and a better understanding of how the immune system fights cancer.

Subcutaneous patient-derived xenografts (PDXs) are an important tool for childhood cancer research. They involve implanting human tumor samples into mice to study how the tumors respond to drugs and to understand rare cancers, such as pediatric solid tumors. A fundamental question about PDXs is how well they mimic the patient tumors. To answer this question, CPRIT Scholar Siyuan Zheng, Ph.D., assistant professor, Department of Population Health Sciences; Peter J. Houghton, Ph.D., professor in the Departments of Molecular Medicine and Pediatrics at The University of Texas Health Science Center at San Antonio; and Raushan T. Kurmasheva, Ph.D., assistant professor, Department of Molecular Medicine at The University of Texas Health Science Center at San Antonio, and fellow researchers built a resource of subcutaneous xenografts derived from pediatric solid tumors, comprising 68 PDXs established from 65 patients across 16 rare cancer types. This study, published in Nature Communications on November 22, revealed that early-passage PDXs accurately keep the gene expression profiles of the original patient tumors, showing that these gene patterns are specific to the tumors themselves. This powerful new tool is the largest collection of early-passage PDXs from pediatric solid tumors.

The University of Texas Health Science Center at San Antonio received four CPRIT Core Facility Support Awards grants (RP160716, RP160732, RP220599, RP220662) totaling $16.5 million; a $1.2 million Academic Research grant (RP180319); and recruited Dr. Zheng in August 2017 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR170055).

73. The inactivation of tumor suppressor genes and the activation of cancer-causing genes drive the development and progression of cancer. The p53 protein is a crucial tumor suppressor that helps trigger cell death in acute myeloid leukemia (AML) cells after treatment with venetoclax. The MDM2 protein and the XPO1 transporter protein often inactivate the TP53 gene, making treatment less effective.

Michael Andreeff, M.D., Ph.D., Department of Leukemia at The University of Texas MD Anderson Cancer Center, and fellow researchers set out to preclinically and clinically investigate the effects of blocking MDM2 to restore the function of p53. The team combined MDM2 and XPO1 inhibitors in laboratory models of venetoclax-resistant AML. This combination prolonged survival, but it also led to quiescence – in which cells stop replicating and avoid cell death. This prompted the researchers to consider adding venetoclax.

The data, published in Science Advances on November 29, reported that using drugs that block MDM2, XPO1, and BCL2 was more effective against leukemia than in comparison to all single-agent and dual-agent combination treatments. This triple combination significantly improved outcomes in cells from patients with AML that were resistant to standard treatments such as venetoclax. In a mouse model of AML (PDX model), this combination therapy extended survival by 300 to 400% compared to using single drugs alone. This study provides evidence to support further clinical investigations aimed at improving outcomes in patients with venetoclax-resistant AML.

The University of Texas MD Anderson Cancer Center received three CPRIT Academic Research grants (RP121010, RP130397, RP210028) totaling $9.72 million in support of this research.

74. Preferentially Expressed Antigen in Melanoma (PRAME), a protein found in melanoma, plays a role in triggering the immune system response. Typically, PRAME is expressed predominantly in the testis, but in many cancers, including uveal melanoma (UM)— the most common primary malignancy of the eye—it appears where it shouldn't be, and spreads in about one half of patients. About 25% of UM tumors express PRAME, and these cases are strongly associated with an abnormal number of chromosomes (aneuploidy), metastasis, and poor patient outcome.

CPRIT Scholar J. William Harbour, M.D., professor and chair of the Department of Ophthalmology at The University of Texas Southwestern Medical Center, and fellow researchers found that cells expressing PRAME become more sensitive to drugs that block PARP1/2, enzymes that are critical to alternative DNA repair pathways. These findings, published in Oncogene on November 29, reveal how misexpression of PRAME leads to genetic instability and aneuploidy, both hallmarks of cancer. Researchers believe these insights could lead to new ways to treat cancer by targeting these specific features.

The University of Texas Southwestern Medical Center recruited Dr. Harbour in November 2021 from the University of Miami School of Medicine with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR220010).

75. Most microbes are symbiotic (beneficial), providing benefits like aiding digestion. However, if there is a disturbance in that balance, a condition called dysbiosis occurs, stopping these normal interactions. For people who have had or have colorectal cancer (CRC), these changes cause inflammation and can affect survival.

The BE GONE trial, led by a team of researchers from MD Anderson Cancer Center, targeted the gut microbiota of obese surveillance patients with a history of colorectal tumors through a straightforward bean intervention. The team added white navy beans into the diet of CRC survivors test if this addition could positively impact both gut and host health by regulating markers linked to obesity and disease. The findings published on November 30, in eBIOMedicine, revealed that the participants of the BE GONE trial who added a cup of navy beans to their daily meals saw positive changes in their gut microbiome. Changes in the gut microbiome of participants included an increase in beneficial bacteria and a decrease in pathogenic, or opportunistic, bacteria.

“Observing a shift in microbiome diversity with diet intervention alone is rare, and this study underscores the ability of a readily available prebiotic food to bring about such changes,” said corresponding author Carrie Daniel-MacDougall, Ph.D., associate professor, Department of Epidemiology. “Over the course of eight weeks, there was an improvement in participants’ gut health, marked by an increase in beneficial bacteria, which wards off the harmful bacteria.” These findings underscore the prebiotic and potential therapeutic role of beans to enhance the gut microbiome.

Baylor College of Medicine received a $3 million CPRIT Research Training grant (RP160097) to create a postdoctoral training program that crosses traditional boundaries by recruiting and training highly motivated Ph.D. epidemiologists or M.D./DVMs with master’s degree training in epidemiology to become successful cross-trained epidemiologists with a focus on prevention, clinical or translational research in cancers of relevance to our catchment area, and to the entire state.

76. NUT carcinoma (NC) is an aggressive squamous carcinoma caused by the fusion of two proteins, BRD4 and NUT. With a median survival of 6.5 months, NC is the second-most aggressive solid tumor in humans. Despite being four times more prevalent than Ewing sarcoma, NC is vastly under-diagnosed and under-recognized. Routinely effective treatments, including surgery, are inappropriate or unavailable for most NC patients due to the lack of an adequate animal model for research purposes.

In this study, CPRIT Scholar Kyle Eagen, Ph.D., assistant professor, Department of Molecular and Cellular Biology at Baylor College of Medicine, and fellow researchers created a genetically engineered mouse model (GEMM) that closely mimics human NC. They used tamoxifen to create a fusion gene called Brd4::NUTM1 in a mouse model. The model displayed complete disease penetrance, and all mice developed the disease and died shortly afterward. The data was published in

Cancer Research on December 1 and showed that the rapid formation of mNC tumors in 100% of the NC GEMMs is definitive evidence that BRD4–NUT alone potently drives the malignant transformation of squamous progenitor cells into NC. The novel creation and validation provide the global scientific community with a much-needed mouse model that has a working immune system and accurately mimics human NC. This model has the potential to greatly accelerate NC research leading to the development of new treatments.

Baylor College of Medicine recruited Dr. Eagen in August 2021 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR210082).

77. Radiation therapy (RT) is a common cancer treatment used by approximately half of all cancer patients during treatment. RT works by causing damage to the DNA of tumor cells, which can lead to their aging or death. Additionally, RT affects the tumor microenvironment (TME), which is the surrounding tissue and cells near the tumor, through various pathways. This modulation of the TME can also contribute to the treatment's effectiveness against cancer.

To facilitate the design of successful RT and immunotherapy combination trials, researchers from The University of Texas Southwestern Medical Center investigated how RT affects the immune system's initial response, inflammation, and changes in the TME after treatment. They focused on neutrophils, the most abundant immune cell in humans and mice, which exert both pro-tumor and anti-tumor functions. In this study, published in Cancers on December 1, the team used mouse models of prostate and colorectal cancer to investigate whether blocking a specific molecule, CXCR2, could reduce the number of neutrophils entering tumors after RT. They found that RT increased the production of CXCR2 ligands (CXCLs) in the TME at 24 and 48 hours after treatment, suggesting these molecules contribute to neutrophil infiltration caused by RT. By blocking CXCR2, the researchers were able to reduce the neutrophil influx caused by RT, which led to a decrease in tumor growth and improved survival in mice with prostate cancer (RM-9 model). These findings suggest that targeting CXCR2 could enhance the effectiveness of RT in cancer treatment.

The University of Texas Southwestern Medical Center received a $6 million CPRIT Multi-Investigator Research Awards (Version 2) grant (RP180725) in 2018 to fund three research projects to develop innovative therapeutic strategies that could challenge current standard clinical practice to greatly improve treatment outcomes for patients with cancer.

78. Researchers are exploring hemoproteins, proteins associated with iron-containing molecules, as potential catalysts for new-to-nature chemical reactions. However, scientists don't yet fully understand how these proteins balance between productive and unproductive pathways during these reactions. This limits scientists' ability to harness their full potential for creating new and useful compounds.

Researchers, including CPRIT Scholar Rudi Fasan, Ph.D., professor, Departments of Chemistry and Biochemistry at The University of Texas at Dallas, used a combination of tools to investigate how myoglobin, a specific type of hemoprotein, speeds up a chemical reaction called cyclopropanation. By using various investigative tools, they gained important insights into the speed of the reaction, how the protein's structure and light absorption change during the process, and how

crucial intermediate stages form. Importantly, the study, published in Nature Communications on December 2, revealed that when catalyzing reactions, hemoproteins like myoglobin engage in a complex interplay of pathways, some beneficial and others competing. This reveals a much more intricate process than previously thought from earlier studies. These insights are valuable for designing new reactions that use hemoproteins to transfer carbene molecules, which are important in creating various useful chemicals.

The University of Texas at Dallas recruited Dr. Fasan in February 2023 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR230018).

79. Single-cell spatial genomics research is a cutting-edge field that combines the study of individual cells' genetic material with their specific locations within tissues. This approach allows scientists to understand how its spatial context influences the function and behavior of each cell. Various innovative tools and platforms have improved single-cell spatial genomics research. These advancements are crucial for unraveling the complex spatial organization and heterogeneity within tissue cellular patterns.

In this study, researchers from The University of Texas Health Science Center at San Antonio, introduce Spatial-Live, a lightweight and versatile viewer tool designed for flexible single-cell spatial-omics data visualization. Spatial-Live overcomes the fundamental limitations of two-dimensional (2D) orthographic modes. The 3D orbit view in Spatial-Live allows a more intuitive exploration of spatial genomics data, offering dynamic rotation and viewpoint manipulation.

The University of Texas Health Science Center at San Antonio received a $4 million CPRIT Core Facility Support Awards grant (RP220662) in September 2022 to introduce the exciting "third-generation sequencing" technology to the UTHSCA-CGSCC research community.

80. The retromer complex is crucial for sorting proteins within the cell's endosomes, playing an essential role in directing the movement and localization of hundreds of membrane proteins that travel through the endocytic system. This complex sorts and recycles proteins back to their appropriate locations, maintaining the proper function and balance of cellular processes. A retromer-like complex, retriever is a trimeric assembly along with the CCC complex, which plays a key role in managing this recycling process. Despite its importance, the detailed mechanisms of how retriever assembles and interacts with the CCC complex are unclear.

In this study, co-corresponding author Ezra Burstein, M.D., Ph.D., professor, Department of Internal Medicine and chief of the Division of Digestive and Liver Diseases at The University of Texas Southwestern Medical Center, and colleagues used advanced cryogenic electron microscopy to create a detailed, high-resolution structure of the retriever complex in humans. The structure revealed a unique assembly mechanism that sets retriever apart from its related complex, retromer. The team revealed the complete structure of the retriever-CCC complex, providing new insights into how it functions. These findings, published in Nature Structural & Molecular Biology on December 7, show that certain mutations associated with cancer can disrupt the formation of the retriever-CCC complex. This disruption can interfere with the recycling of proteins to the cell surface, potentially contributing to disease.

The University of Texas Southwestern Medical Center received a $4 million CPRIT Core Facility Support Awards grant (RP220582) in 2022 to establish new Cryo-EM Core Services to Drive Cancer Research and Drug Discovery.

81. Endothelial cells (EC), which line the inside of blood vessels, serve essential functions fundamental for normal functioning of every organ. These cells are the first to encounter toxic substances and internal molecules that can cause damage and aging. Cell senescence, where cells permanently stop dividing, is a key factor in aging and age-related diseases. However, the role of EC senescence in aging and disease has been difficult to study, in part because traditional laboratory mice aren't suitable models for this.

Zhongming Zhao, Ph.D., M.S., professor at McWilliams School of Biomedical Informatics and chair for Precision Health, and fellow researchers at the University of Texas Health Science Center at Houston, generated a special type of mouse where they removed the TERT gene, which usually protects cells from aging, specifically from their endothelial cells. TERT is normally active in stem cells and helps maintain cell longevity by preventing telomere erosion, but it is inactive in regular cells, leading to cell aging.

The team analyzed EC from fat tissue and muscle in these mice using advanced RNA sequencing techniques to understand the impact of TERT loss on these cells. Published in Frontiers in Cell and Developmental Biology on December 7, the data from both total RNA sequencing and single-cell RNA sequencing show that the TERT-EC-KO mice are a suitable model for studying EC aging. Researchers can use these mice to explore the effects of EC senescence and to develop models for aging and age-related diseases, especially when subjected to vascular injury. This research could lead to new interventions for metabolic and degenerative diseases associated with aging.

The University of Texas Health Science Center at Houston received a $4.4 million CPRIT Core Facility Support Awards grant (RP180734) in August 2018 to establish the UTHealth Cancer Genomic Core, which will provide state-of-the-art sequencing facilities and timely bioinformatics service and training.

82. TatD proteins are a large family of molecules found in various living things, from bacteria to humans. They play roles in important functions like DNA repair and processing. Humans have three versions of these protiens: TATDN1, TATDN2, and TATDN3. Among these, human TATDN2 is unique in that it has a large, disordered region at the beginning of its structure, which the other members of the family lack.

Alexander Bishop, DPhil, professor, Department of Cell Systems and Anatomy at The University of Texas Health Science Center at San Antonio, and fellow researchers discovered that TATDN2 is essential for survival of BRCA1-deficient cancer cells, but much less so for cancer cells that still have BRCA1. When they reduced TATDN2 levels in cancer cells with normal BRCA1, survival significantly improved. This suggests a potential treatment strategy where targeting TATDN2 could selectively kill BRCA1-deficient tumors while sparing normal tissues. Importantly, this study also

found a potential therapy, miR-4638-5p, that could block TATDN2's activity, offering a new way to target these cancer cells without relying on traditional drugs. These findings, published in Nucleic Acids Research on December 11, demonstrate that targeting TATDN2, perhaps by using miR-4638-5p, could provide a therapeutic window to treat BRCA1-deficient tumors.

The University of Texas at San Antonio received a $3.1 million CPRIT Core Facility Support Award grant (RP210208) in 2021. The University of Texas Health Science Center at San Antonio received a $1.98 million Academic Research Individual Investigator grant (RP150445) in 2015.

83. Cell spatial organization refers to the arrangement, distribution, and interactions of cells within a tissue. Examining the spatial organization of multiple cell types within tumor tissues and their surrounding microenvironments is crucial for understanding how these cells assemble and interact to produce diverse functional outcomes. Recent studies have highlighted the importance of investigating how cell spatial organizations impact cancer biology and tumor progression.

Researchers at The University of Texas Southwestern Medical Center have developed a novel artificial intelligence (AI) model that analyzes the spatial arrangement of cells in tissue samples. This approach, published in Nature Communications on December 11, accurately predicted outcomes for cancer patients, advancing the use of AI for cancer prognosis and personalized treatment strategies while utilizing fewer parameters.

"Cell spatial organization is like a complex jigsaw puzzle where each cell serves as a unique piece, fitting together meticulously to form a cohesive tissue or organ structure. This research showcases the remarkable ability of AI to grasp these intricate spatial relationships among cells within tissues, extracting subtle information previously beyond human comprehension while predicting patient outcomes," said study leader Guanghua Xiao, Ph.D., professor in the Peter O'Donnell Jr. School of Public Health, Biomedical Engineering, and the Lyda Hill Department of Bioinformatics at UT Southwestern. The new AI model, which Dr. Xiao and his colleagues named Ceograph, mimics how pathologists read tissue slides. This model leverages the spatial arrangement of cells in tissue samples to accurately predict outcomes for cancer patients.

The University of Texas Southwestern Medical Center received two CPRIT Academic Research grants (RP180805, RP230330) in 2018 and 2023 totaling $6.7 million.

84. The rapid global dissemination of SARS-CoV-2, the cause of COVID-19, highlights our extreme vulnerability to novel pathogens. Its fast transmission and lack of widespread immunity led to a pandemic that overwhelmed healthcare systems worldwide. The situation worsened due to limited treatment options during variant-dominated waves of the pandemic. Understanding how virus mutations affect antibody interactions is essential for developing broadly protective antibodies and vaccines.

Published in Communications Biology on December 11, this study reported the characterization of a potent neutralizing antibody (N3-1) identified from a COVID-19 patient during the first disease wave. Co-corresponding author Jason McClellan, Ph.D., Department of Molecular Biosciences at The University of Texas at Austin, and team used cryogenic electron microscopy and discovered that N3-1 binds in a unique way to all three receptor-binding domains of the virus's spike protein,

resulting in exceptionally strong binding and the ability to neutralize all major variants of concern until Omicron emerged.

The team then used a structure-based design of N3-1 mutants to improve its binding to all Omicron variants. However, these modifications only partially restored the antibody's ability to neutralize the Omicron BA.1 variant, which has a different conformation. Engineering immunogens with multiple conformational states could enhance vaccine effectiveness by making them less vulnerable to common escape mutations. This approach could result in vaccines that offer broader and more robust protection against various strains of a virus, as it would account for the different structural forms the virus might take. This study sheds light on how SARS-CoV-2 evolves to escape the immune system and emphasizes the need to consider these changes in the design of future vaccines, particularly those that are multivalent and can target multiple spike protein conformations.

The University of Texas at Austin received a $6 million CPRIT Recruitment of Established Investigators grant (RR160023) in 2016 in support of this research.

85. Rotavirus (RV) causes gastroenteritis, a condition characterized by diarrhea, deficient nutrient absorption, and weight loss. Lipid droplets (LDs) are associated with diseases such as diabetes, obesity, and heart disease and are involved in the replication of several intestinal viruses, including RV. However, researchers do not fully understand their specific role in gastrointestinal diseases despite RV causing approximately 128,000 deaths annually in infants and children worldwide.

This study, published in Proceedings of the National Academy of Sciences on December 11, is the first to show that rotavirus infection changes how the intestine processes fats, contributing to the disease's development and symptoms. "We knew that rotavirus triggers the formation of more lipid droplets than normal in the cells it infects, as it turns the lipid droplets into virus factories. While we were studying this process, we discovered that rotavirus binds to and breaks down or degrades DGAT1, an enzyme that contributes to the formation of the lipid droplets," said co-corresponding author Sue E. Crawford, Ph.D., assistant professor, Department of Molecular Virology and Microbiology at Baylor College of Medicine.

Rotavirus infection leads to the degradation of DGAT1 which in turn reduces the production of key nutrient transporters and other proteins required for normal intestinal nutrient absorption, leading to diarrhea. "It was very surprising that a rotavirus protein that until now was only known to be important for the virus to replicate, also plays a role in causing diarrhea, a major component of the disease. The fact that it's not a capsid protein or part of the structure that envelops the genetic material of the virus, as we usually would think, tells us that we should not assume that nonstructural proteins do not play roles in causing disease," said co-corresponding author Mary K. Estes, Ph.D., professor, Department of Molecular Virology and Microbiology at Baylor College of Medicine.

Texas A&M University System Health Science Center received a $5.95 million CPRIT Core Facility Support Awards grant (RP150578) in May 2015 to expand and enhance the capabilities of the Combinatorial Drug Discovery Program (CDDP).

86. Type II topoisomerases (TOP2) are enzymes essential for relieving stress in DNA during processes like transcription, replication, and chromosome separation. Cancer drugs like etoposide (ETO) interfere with TOP2 function by stabilizing TOP2 when it is bound to DNA, preventing it from releasing and repairing the DNA strands it cleaves. This interference helps these drugs effectively kill cancer cells by preventing them from repairing their DNA properly.

To better understand how TOP2 is regulated and how the damage caused by trapped TOP2 is resolved, researchers performed whole-genome CRISPR-Cas9 screening combined with ETO treatment. The study, led by Junjie Chen, Ph.D., professor and chair of the Department of Experimental Radiation Oncology at The University of Texas MD Anderson Cancer Center, revealed that RAD54 like 2 (RAD54L2) is a key factor in a specific pathway that helps cells avoid DNA damage caused by TOP2 inhibitors like ETO. The study, published in Science Advances on December 6, suggests that this conserved TOP2-specific pathway is vital for maintaining cellular function and the preservation of genetic integrity. RAD54L2 and the associated pathway may also represent potential therapeutic targets for enhancing cancer treatments.

The University of Texas MD Anderson Cancer Center received two CPRIT Multi-Investigator Research Awards grants (RP160667, RP180813) totaling $11 million.

87. Breast cancer remains the leading cancer-related cause of death among women and is the most common cancer in 109 countries, excluding melanoma, according to the World Health Organization. Early-stage breast cancer management frequently involves lumpectomy, a breast-conserving surgery (BCS) which aims to remove tumors with clear margins. However, doctors perform a significant number of reoperations due to positive margins, which causes increased patient anxiety, higher morbidity, and increased healthcare costs.

This study explores the integration of Wide Field Optical Coherence Tomography (WF-OCT) with an AI-driven clinical decision support system, with the goal of enhancing productivity and decision making in margin assessment during breast cancer surgery. Co-corresponding author, Mark Nguyen, Ph.D., and team developed an efficient artificial intelligence model using computer technology called convolutional neural networks (CNNs). They trained this model with 585 scans from 151 patients to assess surgical margins in breast cancer surgery. Published in Life on December 14, the study details the journey of formulating an AI model tailored for real-time applications in clinical settings. Clinically, the deep learning model accurately identified 96.8% of pathology-positive margins, which suggests the potential to improve reported re-excision rates due to positive margins from approximately 20% to below 5%. This work is currently part of a randomized and double-armed active prospective, multicenter trial, with the focus centered on examining its impact on positive margin rates during breast-conserving surgery.

Perimeter Medical Imaging AI Inc received a $7.44 million CPRIT Company Relocation grant (DP190087) in August 2019.

88. The aging process heightens multiple diseases, including urinary tract infection (UTI); however, scientists do not fully understand how aging affects the urinary tract's lining and

its connection to diseases. Researchers at Baylor College of Medicine investigated a process called autophagy that allows your body to break down and reuse old cell parts so your cells can operate more efficiently by digesting and recycling them in structures called lysosomes. The results of this study, published in Developmental Cell on December 14, reveal that the aging urinary tract in animal models undergoes changes at the cellular level that disrupt cellular homeostasis (the stable internal conditions essential for proper cell function and survival). These disruptions appear to create conditions that make the urinary tract more susceptible to UTIs, increasing the likelihood of both their occurrence and recurrence. This suggests that the aging process may impair the urinary tract's ability to maintain cellular stability.

"We found that the recycling process naturally slows down as urothelial cells age," said Indira Mysorekar, Ph.D., professor of medicine, Department of Infectious Diseases and chief of Basic and Translational Research at Baylor College of Medicine. "Older cells accumulate larger lysosomes that are less effective at degrading cellular materials, which leads to their toxic accumulation inside the cell." The team also discovered that treating aged mice with D-Mannose, a monosaccharide naturally found in fruits, helped lessen the decline in urinary tract function related to aging. This suggests that mannose supplementation might be beneficial in reducing age-related problems with the urinary system in humans, including reducing the occurrence of UTIs.

Baylor College of Medicine received three CPRIT Core Facilities Support Awards grants (RP170005, RP200504, RP210227) totaling $12.9 million in support of the Proteomics and Metabolomics Core Facility and the Comprehensive Cancer Epigenomics Core Facility.

89. Immune checkpoint inhibitors (ICI) improve survival in patients with certain solid tumors, including colorectal cancer with mismatch repair deficiency/microsatellite instability-high (MSI-H). To date, the U.S. Food and Drug Administration have approved four ICIs for the treatment of advanced MSI-H/dMMR colorectal cancer. Physicians may choose to discontinue patients' immunotherapy after two years when their colorectal tumors shrink or remain stable during ICI treatment. However, scientists have not fully studied the long-term outcomes after stopping immunotherapy following prolonged disease control in large groups of patients.

"Patients very understandably get afraid at the prospect of stopping a therapy which appears to be working and often does not cause many side effects. They've had a diagnosis of stage 4 colorectal cancer, and they wonder about the chance of their cancer coming back if they stop treatment," said Van Morris, M.D., senior author and associate professor in the Department of Gastrointestinal Medical Oncology at the University of Texas MD Anderson Cancer Center. "When we set out to do this study, we didn't know the odds."

The team, including CPRIT Scholar John Paul Shen, Ph.D., assistant professor, Department of Gastrointestinal Medical Oncology at MD Anderson Cancer Center, analyzed data from 64 patients with metastatic colorectal cancer that had high microsatellite instability or mismatch repair deficiency (MSI-H/dMMR). They treated the patients with immune checkpoint inhibitors targeting PD-1 or PD-L1 alone (48 patients) or in combination with another immune checkpoint inhibitor targeting CTLA-4 (16 patients). All patients received ICI therapy for a median of 17.6 months and experienced lasting benefits even after stopping treatment. The data, published in Cancer Research Communications on December 11, reported that at a median of 22.6 months after stopping

immunotherapy, 88% of patients had not experienced a recurrence. The progression-free survival rate after stopping treatment was 98% at one year, 91% at two years, and 84% at three years. The optimistic prognosis for most patients should reassure both patients and providers in making the decision to stop immunotherapy.

The University of Texas MD Anderson Cancer Center received two CPRIT Academic Research grants (RP200356, RP220416) in 2020 and 2022 totaling $3.4 million. MD Anderson recruited Dr. Shen from the University of California, San Diego in 2018 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR180035).

90. Hepatoblastoma is the most common liver tumor diagnosed in children, predominantly in children under the age of 3 years. Treatment typically involves chemotherapy before and/or after surgery, which may include partial removal of the liver or, in some cases, a liver transplant. Doctors use a blood marker called serum Alpha-fetoprotein (AFP) to monitor the disease. Liquid biopsies are becoming more popular because they analyze biomolecules shed into the blood, potentially transforming how doctors diagnose, monitor, and treat cancer. In hepatoblastoma, specific mutations in the CTNNB1 gene are common and can be detected in circulating tumor DNA (ctDNA), making liquid biopsies a promising tool for this cancer type.

Researchers from the Texas Children's Liver Tumor Program at Baylor College of Medicine, along with a team of scientists from Australia, aimed to detect tumor DNA circulating in the blood of children with hepatoblastoma and understand how it relates to traditional markers like AFP. The researchers obtained 38 plasma samples and 17 tumor samples from 20 patients with hepatoblastoma. Using a sequencing technique they developed called QUENCH, the team identified genetic changes in the CTNNB1 gene in the circulating tumor DNA, showing that this approach could potentially be useful for diagnosing and monitoring this type of cancer.

This study, published in Cancers on December 19, demonstrated that combining ctDNA and AFP as complementary markers could improve how doctors diagnose and predict outcomes in cancer. By combining genetic information from ctDNA with protein markers like AFP, researchers might get a more detailed view of how tumors behave. This approach could help tailor treatments more precisely for patients with hepatoblastoma and other cancers where AFP and ctDNA are crucial for understanding the disease.

Baylor College of Medicine received a $6 million CPRIT Multi-Investigator Research Awards grant (RP180674) in 2018.

91. To regulate inflammation, our bodies produce compounds called cannabinoids. Although the process of inflammation can help heal the body, it can also put pressure on nerve endings, which in turn causes pain. However, patients with severe pain can only use highly addictive pain medications, such as opioids, which has led to a public health crises of drug abuse.

CPRIT Scholar Ken Hsu, Ph.D., Department of Chemistry at The University of Texas at Austin, and collaborators are working toward creating a non-addictive painkiller that will shut off inflammation, thereby reducing pain. In this study, the team used an inhibitor, KT109 — which Dr. Hsu

developed in 2012 as a postdoctoral fellow at The Scripps Research Institute — to block the activity of a cannabinoid-producing enzyme in immune cells called DAGLβ.

In this study, the team's new drug candidate effectively tricked the immune system in mice in such a way as to shut off an inflammatory response. The team discovered that disrupting the enzyme DAGLβ activates AMPK, which changes how cells use energy and how proteins inside the cell function. Published in Proceedings of the National Academy of Sciences on December 18, the data revealed that when the researchers blocked this energy pathway, it reversed the pain relief caused by stopping DAGLβ, showing a clear link between the two and offering a novel pathway for developing nonopioid pain relievers.

The University of Texas at Austin recruited Dr. Hsu in 2022 from the University of Virginia with the support of a $4 Million CPRIT Recruitment of Rising Stars grant (RR220063).

92. Gene expression is the process where information encoded in a gene is turned into a function, such as making RNA or proteins. Most RNA produced in cells does not build proteins and is called non-coding RNA (ncRNA), classified as either small (sncRNAs) or long (lncRNAs). LncRNAs play an important part in the development of various organs like the heart, skeletal muscle, and brain, as well as certain diseases. While much is known about the role of ncRNAs in heart diseases, scientists do not know as much about how lncRNAs function in heart development.

Researchers, including Joseph Hill, M.D., Ph.D., professor, Department of Internal Medicine at The University of Texas Southwestern Medical Center, aimed to understand how lncRNAs are expressed in individual cells to uncover new roles and help identify specific functions in different cell types. The team investigated the gene expression patterns using single-cell RNA sequencing data to better understand how certain non-coding RNA molecules are expressed during heart development. The findings, published in Cell Death & Disease on December 18, identified several coding and non-coding transcripts which clinicians can use as early biomarkers for the prognosis for several cardiomyopathies. By using advanced methods to analyze how these RNAs are expressed alongside other genes in specific cell types, researchers were able to identify potential functions of lncRNAs in heart formation. These findings could lead to new therapies for cardiovascular diseases by targeting genes involved in reactivating fetal gene expression.

The University of Texas Southwestern Medical Center received a $1.5 million CPRIT Academic Research Multi-Investigator grant (RP110486-P3) in 2011.

93. Inherited mutations in BRCA genes can lead to defects in DNA damage repair. Targeted therapy with PARP inhibitors – which block a DNA repair protein – is known to extend progression-free survival in patients with BRCA-mutant cancers. However, many patients develop resistance to PARP inhibitors and have poor overall survival, highlighting the need for combination treatment strategies to further improve patient outcomes.

CPRIT Scholar Nidhi Sahni, Ph.D., associate professor, Department of Epigenetics and Molecular Carcinogenesis at The University of Texas MD Anderson Cancer Center, and fellow researchers investigated protein arginine methyltransferases (PRMTs) as potential therapeutic targets. PRMTs

help control gene activity and RNA processing and are involved in many cancer-associated processes. By studying cancer cells treated with PRMT inhibitors, they found that a crucial protein involved in responding to DNA replication stress, called ATR, was also suppressed. The data, published in Cell Reports Medicine on December 19, demonstrates that combining PARP and PRMT5 inhibitors can improve survival in both BRCA-mutant and non-mutant cancer models without causing toxic side effects.

The University of Texas MD Anderson Cancer Center recruited Dr. Sahni from the Dana Farber Cancer Institute in November 2015 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160021). MD Anderson received a $3.7 million CPRIT Core Facility Support Awards grant (RP170628) in August 2017. University of Houston received a $250,000 CPRIT High-Impact/High-Risk grant (RP200520) in August 2020.

94. Histone deacetylase (HDAC) inhibitors are anti-cancer agents that doctors use to treat blood cancers. However, they can also harm healthy cells and may not specifically target the cancer cells. Bocodepsin (OKI-179) is a novel, orally bioavailable, Class I-targeting depsipeptide HDAC inhibitor with promising anti-cancer activity in preclinical solid tumor models.

In this first-in-human phase I clinical study, researchers enrolled 34 patients with advanced or metastatic solid tumors that were refractory or ineligible for standard therapy. The most common tumor types were HR-positive, HER2-negative breast cancer, pancreatic cancer, and ovarian cancer. CPRIT Scholar S. Gail Eckhardt, M.D., FASCO, inaugural director of the LIVESTRONG Cancer Institutes, and chair of the Department of Oncology at The University of Texas at Austin, and team set out to test the safety and tolerability of OKI-179 when administered daily by mouth with intermittent and continuous dosing schedules.

The data published in Cancers on December 23, revealed that OKI-179 displayed manageable side effects, and was generally well-tolerated in patients with advanced solid tumors. The team observed prolonged stable disease in a subset of patients, including platinum-resistant ovarian cancer. Scientists are currently investigating OKI-179 in combination with the MEK inhibitor binimetinib in patients with NRAS-mutated melanoma. This study supports the continued investigation of OKI-179 in combination with other targeted therapies, including MAPK pathway inhibitors, in solid tumors.

The University of Texas at Austin recruited Dr. Eckhardt in 2016 with the support of a $6 million CPRIT Recruitment Established Investigators grant (RR160093).

95. Some patients with acute myeloid leukemia (AML) develop resistance to apoptosis (programmed cell death), which can lead to relapse associated with poor clinical outcomes. Scientists have investigated ferroptosis, an iron-dependent cell death, in therapy-resistant cancers, but little is known of its role in AML.

To explore whether ferroptosis could work in refractory/relapsed AML, researchers led by Hiroki Akiyama, M.D., Ph.D., Michael Andreeff, M.D., Ph.D., and Jo Ishizawa, M.D., Ph.D., from the Department of Leukemia at The University of Texas MD Anderson Cancer Center, examined

how blocking the enzyme GPX4 induces ferroptosis in AML cells. They found that this process is largely controlled by the mitochondria's energy production, possibly involving a specific coenzyme in the mitochondria. The data, published in Leukemia on December 26, reveal that cells that lack this coenzyme were more sensitive to GPX4 inhibition. This suggests that targeting how mitochondria regulate ferroptosis could lead to new treatment strategies for AML.

The University of Texas MD Anderson Cancer Center received a $4 million CPRIT Research Training grant (RP210028) in May 2021 to provide a comprehensive learning environment focused solely on cancer, to position trainees for successful careers in cancer research.

96. Having the ability to regulate how genes behave in our cells is crucial for safe and effective gene therapies. The expression of therapeutic genes needs to be maintained within a therapeutic window because too much of the protein could be toxic, and too little could result in a small or no therapeutic effect. However, the current gene regulation systems have serious limitations.

Scientists at Baylor College of Medicine, including corresponding author Laising Yen, Ph.D., associate professor, Departments of Pathology & Immunology and Molecular and Cellular Biology, developed a technology that effectively regulates gene expression, a solution which might overcome the main obstacles in its clinical use. They modified a section of the RNA near the polyA signal so that it can bind to a small molecule, in this case, FDA-approved tetracycline and engineered a switch on the RNA to turn on the gene at the desired level. The results were published in Nature Biotechnology on January 2, 2024.

"This strategy allows us to be more precise in the control of gene expression of a therapeutic protein. It enables us to adjust its production according to disease's stages or tune to the patients' specific needs, all using the FDA-approved tetracycline dose," Dr. Yen said. "Our approach is not disease-specific, it can theoretically be used for regulating the expression of any protein, and potentially has many therapeutic applications. In addition, this system is more compact and easier to implement than the existing technologies. Therefore, it also can be very useful in the lab to turn a gene of interest on or off to study its function."

Baylor College of Medicine received a $5.2 million CPRIT Core Facility Support Awards grant (RP180672) in August 2018 to purchase high-end equipment that will more than double the current detection capabilities.

97. CD4+ T cells, or helper T cells, are lymphocytes that play a crucial role in coordinating the body's immune response against infection and disease in the body. They interact and activate other cells in the immune system. However, scientists do not fully understand the genetic instructions and processes that control and sustain the activity of these important immune cells.

A team of scientists discovered a stem-like program that controls how CD4+ T cells respond during transplantation, shedding light on the genetic instructions and processes that sustain their activity. The study, published in Nature Immunology on January 2, found that removing the transcription factor IRF4 or the enzyme LDHA from T cells can lead to successful acceptance of

transplants. These findings are significant as they could influence the development of new immunotherapy approaches involving T cells.

Baylor College of Medicine received a $4 million CPRIT Core Facility Support Awards grant (RP200504) in 2020 to support the Comprehensive Cancer Epigenomics Core Facility.

98. Fatty acids are building blocks of cellular membranes as well as important fuels for energy metabolism. However, researchers do not have a complete understanding of how cells coordinate cell cycling with cell survival and death. In this study, corresponding author Boyi Gan, Ph.D., professor, Department of Experimental Radiation Oncology and director, Radiation and Cancer Metabolism Research Program at The University of Texas MD Anderson Cancer Center, and researchers studied how halting the cell cycle, the process by which cells divide, affects ferroptosis, a type of controlled cell death caused by excessive damage to the fatty molecules (lipids) in cell membranes.

The team discovered that when cancer cells slow down or stop dividing, they build up lipid droplets, allowing them to store fats that protect the cells against death. Cancer cells that were resistant to treatments such as palbociclib (treatment for advanced breast cancer), 5-FU (a chemotherapy agent), or radiation had higher levels of these lipid droplets and were more resistant to ferroptosis. The results, published in Nature Communications on January 2, suggest a novel approach to overcoming resistance to cancer treatments that target cell division. By finding ways to trigger ferroptosis, researchers might be able to target cancer cells that are resistant to traditional therapies because they aren't actively dividing.

The University of Texas MD Anderson Cancer Center received a $1 million CPRIT Individual Investigator grant (RP230072) in February 2023 to provide novel therapeutic strategies to overcome PARPi resistance in BRCA1-deficient cancers.

99. Spatial transcriptomics (ST) is a technique that allows scientists to measure and map gene activity within a tissue sample. To better understand how cancer starts, progresses, and resists treatment, Linghua Wang, M.D., Ph.D., associate professor in the Department of Genomic Medicine at The University of Texas MD Anderson Cancer Center, and colleagues harnessed the potential of big data to fight cancer and to advance understanding of the cellular and molecular cues.

The team developed iStar, a new method that combines data from ST and high-resolution histology (detailed microscopic tissue) images to predict spatial gene activity with super-resolution. This method, which appeared in Nature Biotechnology on January 2, enhances gene expression detail to near-single-cell levels in ST and enables gene expression prediction in tissue sections where only histology images are available. This breakthrough could help scientists develop more effective therapies.

The University of Texas MD Anderson Cancer Center received a $900,000 CPRIT Individual Investigator grant (RP200385) in 2020 to improve efficacy in CAR T-cell therapy in relapsed/refractory diffuse large B-cell lymphoma (DLBCL) patients.

100. Prostate cancer (PCa) is the most common cancer in men, excluding skin cancer, and is the second leading cause of cancer-related mortality. Hormonal therapy targeting the androgen receptor is the typical treatment for advanced and metastatic PCa, but it causes significant side effects.

Heat Shock factor 1 (HSF1) is a stress response transcription factor that scientists have identified as a proto-oncogene (a healthy gene) in many solid tumors but is able to mutate and become an oncogene. An international team of researchers, including CPRIT Scholar Xia Gao, Ph.D., assistant professor, Department of Pediatrics-Nutrition at Baylor College of Medicine, previously identified a HSF1 small molecule inhibitor, SISU-102, that inhibits the growth of both hormone sensitive and hormone-resistant PCa lines and mouse models of advanced PCa, and this compound is now under commercial development for clinical trials.

In this study, published in Communications Biology on January 3, the team combined this inhibitor with other approaches to understand how HSF1 works and to find additional weaknesses in advanced PCa. They discovered that HSF1 activates a metabolic enzyme CBS by directly binding to the CBS gene, and that blocking CBS is more effective than blocking HSF1 in inducing PCa cell death. The team found that the combination treatment targeting HSF1 and CBS is an effective therapeutic strategy for advanced PCa. The findings offer new insights into HSF1's role and suggest an effective treatment strategy for advanced PCa.

Baylor College of Medicine recruited Dr. Gao in 2021 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR210056).

101. Current third-line and later treatment options for RAS-mutant metastatic colorectal cancer have limited effectiveness. In a Phase Ib trial of 48 patients, researchers led by David S. Hong, M.D., deputy chair, Department of Investigational Cancer Therapeutics at The University of Texas MD Anderson Cancer Center, found that combining two drugs, sotorasib, a $KRAS^{G12C}$ inhibitor, and panitumumab, an EGFR inhibitor, showed promising results in a subset of patients with colorectal cancer whose cancer did not respond to chemotherapy. In the dose expansion cohort of 40 patients, the disease control rate was 93% and the tumor shrinkage rate was 88%, with a median progression-free survival and overall survival of 5.7 months and 15.2 months, respectively. None of the patients experienced dose-limiting toxicities, and grade three treatment-related adverse events were mostly dermatologic, occurring in 27% of patients. These results, published in Nature Medicine on January 4, suggest sotorasib–panitumumab demonstrated acceptable safety with promising efficacy.

The University of Texas MD Anderson Cancer Center received a $6 million CPRIT Core Facility Support Awards grant (RP150535) in 2015 for the Precision Oncology Decision Support Core.

102. Hydroponics, a method of growing plants without soil, was developed to reduce soilborne diseases. While hydroponics provides plants with balanced nutrients, it can also lead to contamination of the nutrient solution. Researchers, including CPRIT Scholar Vanderlei Bagnato, Ph.D., professor, Department of Biomedical Engineering at Texas A&M Engineering Experiment Station, set out to assess the effectiveness of a decontamination system using UV-C light to clean

the solution during nutrient recirculation in hydroponics.

The team evaluated lettuce samples exposed to UV-C in the hydroponic fluid, with control groups not exposed to UV-C. They found that using UV-C light to clean the nutrient solution sped up plant growth and maintained or improved nutritional values compared to lettuce grown without UV-C treatment. This method also reduced production time, enhanced nutrient absorption, and increased the content of some compounds and minerals. The data, published in Scientific Reports on January 5, reveals that the use of the UV-C decontamination system in hydroponic systems significantly improved microbial control and vegetable development in hydroponics.

The Texas A&M Engineering Experiment Station recruited Dr. Bagnato in 2022 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR220054).

103. Multiple factors contribute to the development of nervous system tumors. However, researchers don't know what proportion of the risk of these tumors are attributable to genetic and environmental factors. Researchers, including Maral Adel Fahmideh, Ph.D., Center for Epidemiology and Population Health at Baylor College of Medicine, conducted the largest and most comprehensive family-based quantitative genetic study of nervous system tumors to date. The team used a sibling design, and cases of nervous system tumors were identified through linkage of the selected siblings with the Cancer Register.

This study, published in Frontiers in Oncology on January 8, estimated that 29% of the risk for nervous system tumors can be attributed to inherited genetics, while 71% is influenced by unique environmental factors. These findings emphasize the role of environmental influences and genetic predispositions in the development of these tumors, providing insights that aid in developing risk prediction models to prevent nervous system tumors.

Baylor College of Medicine received a $3 million CPRIT Research Training grant (RP160097) in 2016 for a post-graduate training program in Integrative Epidemiology.

104. Ovarian cancer is the leading cause of gynecologic cancer death in developed countries. When ovarian cancer is detected in stage I, the five-year survival rate is greater than 90%, but when the cancer has spread, leading to stages III and IV, the cure rate falls to less than 20%. Advances in surgery and combination chemotherapy have improved 5-year survival in patients with epithelial ovarian cancer. However, the cure rate has changed little over the last two decades, due in part to late-stage diagnosis (III-IV) in 70–75% of cases. The detection of a larger fraction of women at an early stage could significantly impact survival.

In this study, co-corresponding author Robert Bast, M.D., professor of Medicine, Department of Experimental Therapeutics at The University of Texas MD Anderson Cancer Center, and fellow researchers compared multiple antigens, autoantibodies (AAb), and antigen-autoantibody (Ag-AAb) complexes to CA125 for early detection of ovarian cancer. The data, published in the British Journal of Cancer on January 9, identified a panel of four biomarkers that, when combined, improve sensitivity while maintaining high specificity compared to CA125 alone, especially for detecting early-stage (I-II) disease. The team also discovered three promising autoantibodies in patients

with early-stage disease that may detect the disease earlier than CA125 alone.

The University of Texas MD Anderson Cancer Center received a $1.5 million CPRIT Individual Investigator Research Awards for Prevention and Early Detection grant (RP160145) in November 2015 for early detection of ovarian cancer with tumor associated proteins and autoantibodies.

105. The role of the immune system in keeping metastatic cancer cells dormant is not well understood. In this study, CPRIT Scholar Filippo Giancotti, MD., Ph.D., professor, Department of Cancer Biology at The University of Texas MD Anderson Cancer Center, and fellow researchers discovered that a molecule, long noncoding RNA Malat1, plays a key role in how cancer cells evade the immune system and restart growth after spreading to other parts of the body (metastasis). In mouse models of breast cancer and other cancers, Malat1 was essential for both tumor growth and the reactivation of dormant metastatic cells.

Malat1 works by helping cancer cells regulate gene activity and produce proteins that allow them to survive and self-renew. One of these proteins, SERPINB6B, helps cancer cells avoid a form of immune-triggered cell death (called pyroptosis), allowing them to escape detection and destruction by the immune system. By blocking Malat1 with specialized drugs, researchers were able to reduce metastasis in a way SERPINB6B-dependent manner. This discovery, published in Nature Cancer on January 9, highlights that Malat1 is at the nexus of tumors initiation, reactivation, and evasion. This suggests that targeting Malat1 could be a promising strategy for cancer treatment.

The University of Texas MD Anderson Cancer Center recruited Dr. Giancotti in 2016 from Memorial Sloan Kettering Institute of Cancer Research with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR160031). MD Anderson Cancer Center received a $4.9 million CPRIT Core Facilities Support Awards grant (RP180684) in August 2018 to establish an Integrated Single Cell Genomics (SCG) Core Facility.

106. Lung cancer is the deadliest form of cancer with less than a 15% five-year survival rate, accounting for nearly 1.6 million cases around the world annually. Conventional treatment strategies frequently lead to relapse and severe side effects such as hair loss, nausea, fatigue, and nerve damage.

Researchers led by Kytai Nguyen, Ph.D., professor of bioengineering at The University of Texas at Arlington, designed a cell-specific drug delivery system which targets lung tumors while reducing toxicity. The researchers developed a biomimetic drug carrier based on chimeric antigen receptor (CAR) transduced T-cell membranes. This novel technique involves isolating the cell membrane from these modified T-cells, loading the membranes with chemotherapy medications, and then coating them onto tiny drug-delivery granules. When these nanoparticles, which are roughly 1/100 the size of a strand of hair, are injected back into the patient, the cell membrane acts as a guide, directing the nanoparticles to the tumor cells with precision. This approach, described in Bioactive Materials on January 11, 2024, is designed to deceive the patient's immune system, as the nanoparticles mimic the properties of immune cells, avoiding detection by the body's immune system. This innovative approach aims to deliver drugs directly to tumors, minimizing harm to other organs. "Our method uses the patient's own cellular material as a Trojan horse to transport

a targeted drug payload directly to the lung cancer cells," said Dr. Nguyen.

The University of Texas at Arlington received a $250,000 CPRIT High Impact/High Risk grant (RP210206) in August 2021 to develop and test a cell-based nanoparticle system, to ensure a tumor site/cancer cell specific approach rather than a systemic one, enhancing the efficacy of cancer therapy.

107. The key to developing new anti-cancer drugs depends on the ability to understand and predict how cancer genes interact with anti-cancer treatments. Deep learning, an advanced computational method, has demonstrated significant potential in identifying and predicting these intricate interactions. For example, the innovative deep learning model, DeepDR, integrates drug screens of cell lines and genomics of tumors, enabling accurate predictions of real-world therapy responses in cancer patients. However, not all researchers have the resources and programming expertise to leverage this potential.

To make deep learning methods more accessible, co-corresponding author Yidong Chen, Ph.D., Department of Population Health Sciences at The University of Texas Health Science Center at San Antonio, and colleagues developed shinyDeepDR, an intuitive and user-friendly web platform designed for the computational screening of 265 potential anti-cancer drugs, to access their innovative DeepDR model. In this descriptor, the team showcased the potential application of shinyDeepDR by studying a prevalent "undruggable" gene mutation in CTNNB1 and its frequently co-occurring activation in hepatocellular carcinoma (HCC). The study, published in Patterns on January 12, demonstrated that shinyDeepDR produces accurate predictions and identifies promising drug targets for an undruggable gene mutation in HCC, which aligns with findings from in vivo models.

The University of Texas Health Science Center at San Antonio received two CPRIT Core Facility Support Awards grants (RP160732, RP220662) totaling $7.68 million; and an $892,157 CPRIT Individual Investigator Research grant (RP190346) in August 2019 to predict drug response from genomic data using deep learning methods.

108. Acute hemolytic anemia is a condition where red blood cells are destroyed faster than they can be produced, which often occurs alongside cancer, infections, or certain medications. This negatively impacts patient quality of life and response to treatment. Hematopoietic stem cells (HSCs) can regenerate the blood system, but how they are directed to replace lost red blood cells during anemia is not well understood.

Corresponding author Daisuke Nakada, Ph.D., professor, Department of Molecular and Human Genetics at Baylor College of Medicine, and collaborating researchers, investigated the effects of anemic stress on HSCs. The team reported that during anemia, HSCs increasingly absorb iron, which activates genes involved in red blood cell production, helping them regenerate these cells in a process dependent on a protein called Tet2. The data, published in Nature Communications on January 15, show that suppressing iron uptake or reducing TET2 protein expression hinders red blood cell growth. Conversely, when more iron is added to the system, it helps HSCs develop into mature red blood cells. These findings demonstrate that HSCs play an active role in red blood

cell regeneration during anemia, regulated by iron and Tet2.

Baylor College of Medicine received a $5.2 million CPRIT Core Facility Support Awards grant (RP180672) in August 2018 to purchase high-end equipment that will more than double the current detection capabilities.

109. Protein kinases are key regulators of cell function and drive a wide range of cancer-relevant biological functions. Alterations in kinase activity can lead to cancer, including some types of breast cancers. One important protein is ERBB2, which helps guide treatment choices. The current method used in clinics, immunohistochemistry (IHC), provides only rough estimates, making it less precise. A newer technique, mass spectrometry-based proteomics, offers more accurate measurements and can analyze hundreds of proteins at once.

To improve sensitivity and accuracy, researchers including CPRIT Scholar Matthew Ellis, MB BChir, Ph.D., professor and director, Lester and Sue Smith Breast Center at Baylor College of Medicine, developed a method called kinase inhibitor pulldown (KiP), which uses drugs that bind to specific kinases to isolate and measure them. This method was tested in breast cancer models and identified many important kinases. The team then created a more precise technique, called parallel reaction monitoring (PRM), to measure proteins even in small samples, like those from needle biopsies.

The data, published in Clinical Proteomics on January 16, reported the accurate classification of different types of breast cancer. The team created a potential tool for more precise cancer diagnostics which could lead to better-targeted treatments based on a more detailed understanding of the proteins involved in cancer.

“This paper emphasizes that new methods in protein mass spectrometry hold great promise for better definition of the individual druggable landscape present in each cancer and should be more widely used for research and, ultimately, clinical care,” said Dr. Ellis.

Baylor College of Medicine recruited Dr. Ellis in 2014 from Washington University with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR140033). BCM received two CPRIT Core Facility Support Awards (RP170005, RP210227) totaling $9 million in support of the Proteomics and Metabolomics Core Facility.

110. For years, scientists have debated over how much diet and non-genetic environmental factors contribute to cancer formation. A team of researchers, including CPRIT Scholar Xia Goa, Ph.D., assistant professor, Departments of Pediatrics-Nutrition and Molecular and Cellular Biology at Baylor College of Medicine, discovered that a diet high in folate, a type of vitamin B, increases the risk of colon cancer in an animal model.

The study, published in Cancer Research Communications on January 19, 2024, found that animals on a folate-supplemented diet had a significantly shortened overall survival with more and larger tumors compared to the animals in a non-supplemented diet. The tumors also showed the presence of immune cells called tumor-associated macrophages, which is associated with immunosuppression and poor prognosis in colorectal cancer patients.

"We investigated whether this pathway involved epigenetics, a system of bookmarking DNA that determines which genes will or will not be expressed in a cell. Epigenetics is one way cells can control the activities of their genes without altering the DNA sequence and is closely linked to the environment," said corresponding author Lanlan Shen, M.D., Ph.D., professor, Department of Pediatrics-Nutrition at Baylor College of Medicine. "Importantly, we observed substantially increased epigenetic methylation of gene p16 – a gene involved in colon cancer development – in animals on the supplemented diet compared to controls." These findings reveal a direct link between dietary folate and accelerated tumor development in the colon and highlight the need for monitoring the long-term safety of folate fortification in high-risk individuals.

Baylor College of Medicine recruited Dr. Goa in August 2021 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR210056).

111. Cancer stem cells (CSC) play a critical role in self-renewal, relapse, and therapy resistance in colorectal cancer, driving disease development and progression. While many colorectal cancer CSC marker genes have been identified, the ability to identify these cells at the single-cell level is limited.

CPRIT Scholar John Paul Shen, M.D., Department of Gastrointestinal Medical Oncology at The University of Texas MD Anderson Cancer Center, and fellow researchers performed single-cell RNA sequencing on samples of 6 primary colon tumors, 9 liver metastatic tumors, and 11 normal (nontumor) controls to identify colorectal CSCs at the single-cell level. The team extracted a single-cell stemness signature (SCS_sig) that accurately identified "gold-standard" colorectal CSCs that expressed all marker genes. The data, published in Molecular Cancer Research on January 23, 2024, revealed that patients with higher SCS_sig scores had significantly shorter disease-free survival time after surgery. This suggests that high stemness, the ability of cancer cells to self-renew, is associated with a higher risk of relapse and highlights the importance of this trait as a prognostic indicator.

The University of Texas MD Anderson Cancer Center recruited Dr. Shen from the University of California, San Diego in 2018 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR180035).

112. Acinar-to-ductal metaplasia (ADM) is a precursor to the development of pancreatic ductal adenocarcinoma (PDAC). While the role of ADM in PDAC progression is understood, the mechanisms underlying human ADM remain elusive.

For the first time, researchers including CPRIT Scholar Pei Wang, Ph.D., associate professor, Department of Cell Systems and Anatomy at The University of Texas Health Science Center at San Antonio, have been able to examine these changes in human pancreatic tissues during ADM. This study, published in Cells on January 18, reveals how two molecular pathways, Hippo and TGF-β, interact. The team revealed how these two pathways control acinar cells to undergo ADM and drive PDAC initiation, which could lead to new clinical applications. While this study was conducted in a lab setting, it represents the closest approximation to human physiology that has been

achieved to date.

The University of Texas Health Science Center at San Antonio recruited Dr. Wang from Stanford University School of Medicine in August 2012 with the support of a $1.9 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (R1219). UTHSC at San Antonio received two CPRIT Core Facility Support Awards grants (RP210126, RP220662) totaling $7.64 million, and two Research Training grants (RP140105, RP170345) totaling $5.57 million.

113. Hepatoblastoma (HB) is the most common liver cancer in children. HB has seen the most rapid increase among all pediatric solid tumors in the last decade. Since histone deacetylase (HDAC) inhibition has been proposed for HB, researchers at Baylor College of Medicine and colleagues hypothesized that they could create an effective combination treatment strategy using HDAC inhibition with chemotherapy.

Utilizing a preclinical HB pipeline, the team found that using panobinostat with vincristine and irinotecan (VIP) effectively reduced tumor size in preclinical models developed from patients with high-risk, relapsed, and treatment-refractory HB. Published in the Journal of Hepatology on January 16, the data demonstrates that combination therapy with VIP reduces the size of high-risk, relapsed, and treatment-refractory tumors and provides preclinical evidence to support using this combination therapy in future clinical trials.

“After just one week of therapy, the tumors that were treated with VIP had a significant decrease in volume and alpha fetoprotein levels, the tumor marker,” said corresponding author Sanjeev A. Vasudevan, M.D., associate professor of surgery at Baylor College of Medicine. “These findings are very encouraging as they suggest that VIP therapy may be a promising and effective option for patients with currently untreatable high-risk, relapsed or refractory HB.”

Baylor College of Medicine received a $6 million CPRIT Multi-Investigator Research Awards grant (RP180674) in 2018 and a $4 million CPRIT Core Facility Support Awards grant (RP220646) in September 2022.

114. Amyloidoses are a variable group of fatal disorders that are caused by the buildup of amyloid fibrils in affected organs. Amyloid transthyretin (ATTR) amyloidosis is caused by the deposition of transthyretin in the form of amyloid fibrils in virtually every organ in the body.

In this study, corresponding author Lorena Saelices, Ph.D., assistant professor, Department of Biophysics at The University of Texas Southwestern Medical Center, and fellow researchers studied the structure of cardiac ATTR fibrils in the heart of patients with the genetic mutation ATTRv-I84S. Using cryo-electron microscopy, the researchers examined the structures of these abnormal protein deposits which were extracted from three patients with ATTR amyloidosis who carried this genetic mutation.

The data, published in Nature Communications on January 17, demonstrates that even among patients with the same mutation, there were variations in the fibril structures. In contrast, the structures of fibrils from patients suffering from brain amyloidosis are disease specific. These findings suggest that different amyloid diseases might have multiple fibril structures, calling for further

studies.

The University of Texas Southwestern Medical Center received a $5.5 million CPRIT Core Facility Support Awards grant (RP170644) in August 2017 to establish a new Cryo-Electron Microscopy Core Facility and Service for Structure Determination at UT Southwestern Medical Center.

115. For postmenopausal patients with early-stage estrogen receptor (ER)–positive/ERBB2–negative breast cancer, aromatase inhibitors (AI) are the standard treatment. However, approximately 20% of patients experience disease recurrence. Selective ER degraders (SERDs) have the potential to further improve outcomes. Adding fulvestrant to anastrozole (A+F) to this treatment improved survival in postmenopausal women with advanced estrogen receptor (ER)–positive/ERBB2–negative breast cancer. However, this combination has not been tested in early-stage disease.

CPRIT Scholar Matthew Ellis, MB BChir, Ph.D., professor and director, Lester and Sue Smith Breast Center at Baylor College of Medicine, and fellow researchers aimed to determine whether fulvestrant, alone or in combination with the AI anastrozole, is superior to anastrozole alone in this population, in terms of endocrine-sensitive disease rate (ESDR). In this phase 3 randomized clinical trial of 1,362 patients, the ESDR following 6 months of neoadjuvant fulvestrant or anastrozole plus fulvestrant did not demonstrate superiority over anastrozole alone in improving ESDR. The results were published in JAMA Oncology on January 18 and warrant further study.

Baylor College of Medicine recruited Dr. Ellis in 2014 from Washington University with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR140033).

116. Endometrial cancer is the most common gynecologic cancer, and patients with advanced disease have poor survival rates. The receptor tyrosine kinase ephrin type-A receptor 2 (EphA2) is highly expressed in many types of human cancer but found at very low levels in most normal tissues. In preclinical models of ovarian, breast, and pancreatic cancer, the inhibition of EphA2 decreased tumor growth and increased survival.

Robiya Joseph, Ph.D., Department of Gynecologic Oncology and Reproductive Medicine at The University of Texas MD Anderson Cancer Center, and fellow researchers hypothesized that combining EphA2 and HDAC inhibitors could enhance its therapeutic benefit. The team used mouse models of endometrial cancer to examine the antitumor effects of an EphA2 inhibitor and panobinostat, as individual agents and in combination. The results, published in the International Journal of Molecular Sciences on January 20, 2024, showed that the combination triggered DNA damage and reduced cancer cell survival more effectively than either treatment alone.

Texas A&M University System Health Science Center received two CPRIT Core Facility Support Awards grants (RP200668, RP150578) totaling $9.9 million to support the Combinatorial Drug Discovery Program.

117. Small cell lung cancer (SCLC) accounts for 13% of lung cancers and is one of the

leading causes of cancer-related mortality in the United States. Although SCLC tumors may initially respond to treatment, they're highly metastatic and tend to develop resistance to treatment. SCLC cells rely heavily on telomerase, an enzyme that keeps them alive and allows them to spread by maintaining their telomeres. Normal cells die or senesce as their telomeres shorten over time. In cancer cells, however, the telomerase enzyme helps cancer cells maintain their telomeres, live longer, and metastasize. SCLCs are nearly all telomerase positive, making it a promising treatment target.

CPRIT Scholar Esra Akbay, Ph.D., assistant professor, Department of Pathology at The University of Texas Southwestern Medical Center, and team focused on exploiting telomerase. Using preclinical mouse and human derived models, the researchers tested a compound called 6-Thio-2'-deoxyguanosine (6TdG) in mouse and human models and found that low intermittent doses effectively inhibited tumor growth and reduced metastasis.

"It's difficult to devise treatments that affect cancer cell DNA because most of the time they're also toxic to bone marrow cells, which produce immune and blood cells," Dr. Akbay said. "But 6-thio-dG is nontoxic to healthy cells in therapeutic doses." The study, published in Nature Communications on January 22, emphasizes the immune-enhancing and metastasis-reducing effects of 6TdG and provides a potential therapeutic approach to SCLC.

The University of Texas Southwestern Medical Center recruited Dr. Akbay in September 2016 from the Dana-Farber Cancer Institute/ Harvard Medical School with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160080). UTSW Medical Center received a $3.7 million CPRIT Core Facility Support Awards grant (RP180770) in August 2018 to support the Preclinical Radiation Core Facility.

118. Every year, approximately 80,000 breast cancer patients in the United States will experience metastatic breast cancer (MBC), where cancer cells spread from the breast to other parts of the body. Checkpoint inhibitors, a type of immunotherapy, have shown great progress in the treatment of MBC. However, they have been ineffective in treating patients with bone metastases.

CPRIT Scholar Han Xiao, Ph.D., associate professor of chemistry, biosciences, and bioengineering at Rice University, and his team sought to find a more effective way to treat these bone metastases. The team hypothesized that there must be another novel checkpoint axis they could target for the breast cancer cells in bone. Published in PNAS on January 22, the results of their study uncovered a unique glyco-immune checkpoint axis in bone metastases that involves a protein called sialic acid-binding Ig-like lectin (Siglec)-15. The data revealed that elevated levels of Siglec-15 in the bone metastatic niche can promote tumor-induced osteoclastogenesis, a process crucial for bone remodeling and repair, as well as suppress antigen-specific T cell responses.

"Current FDA-approved checkpoint inhibitors are mediated by protein-protein interactions that suppress immune cells," Dr. Xiao explained. "Siglec-15, however, is a glyco-immune checkpoint inhibitor. Instead of binding to a protein, Siglec-15 binds to the sugars you find on the cell surfaces and that's how it can suppress the immune system. This is an entirely new type of immune checkpoint that offers great promise for future treatment for bone cancers."

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).

119. The HPV vaccination is the safest and most effective way to prevent six kinds of HPV-related cancers. The U.S. Advisory Committee on Immunization Practices currently recommends a two-dose series among individuals 9 to 14 years of age and a three-dose series among individuals 15 to 26 years of age. Because data comparing two versus three doses of 9vHPV vaccine in individuals aged 15 to 26 years of age are limited, Abbey Berenson, M.D., Ph.D., professor, Departments of Obstetrics & Gynecology and Pediatrics, and director, Center for Interdisciplinary Research in Women's Health at The University of Texas Medical Branch at Galveston, and colleagues set out to uncover the differences.

The preliminary findings of this ongoing, single-blinded, randomized trial of the 9vHPV vaccine among individuals 15 to 26 years of age in the United States were published in NEJM Evidence on January 23. The team enrolled and randomly assigned 438 participants to the two-dose (n=217) or three-dose (n=221) group. At one month after the final vaccine dose, the seroconversion rate for each of the nine HPV genotypes in the vaccine was 100% among participants in the two-dose group and 99% in the three-dose group. These results suggest that two doses of the 9vHPV vaccine may be sufficient to fully vaccinate adolescents and young adults.

"Because of the current discourse within the medical community about how many HPV vaccine doses are sufficient, it was important to publish the preliminary findings of our study sooner, rather than later," Dr. Berenson said. "No study has previously examined the non-inferiority of the 9vHPV vaccine among 15- to 26-year-olds. Thus, our findings are beginning to fill an important gap of knowledge within the medical field."

The University of Texas Medical Branch at Galveston received a $1.5 million CPRIT Academic Research grant (RP190022) in 2019 for a randomized, controlled trial comparing the immunogenicity of 2 doses vs. 3 doses of the 9-valent HPV vaccine in females and males 15 to 26 years of age.

120. Chronic inflammation, also known as inflammaging, is a hallmark of tissue aging and can contribute to cancer development and progression. Cellular senescence, a process by which a cell ages and permanently stops dividing but does not die, also contributes to cancer development and tissue aging. One of the key features of senescent cells is the secretion of proinflammatory factors collectively known as the senescence-associated secretory phenotype (SASP).

Researchers have found that an enzyme called TXNRD1, is important for both promoting tumors and aiding the immune system in recognizing aging cells. CPRIT Scholar Rugang Zhang, Ph.D., professor and chair, Department of Experimental Therapeutics at The University of Texas MD Anderson Cancer Center, and colleagues reported that in mouse studies, TXNRD1 was shown to drive inflammation and aging through the cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) innate immune response pathway, separate from its usual enzyme activity. The results, published in Nature Aging on January 24, suggest that this interaction is a potential

therapeutic target for both tissue aging and cancer.

The University of Texas MD Anderson Cancer Center recruited Dr. Zhang in November 2022 with a $6 million CPRIT Recruitment of Established Investigators grant (RR230005).

121. Small cell lung cancer (SCLC) is a highly aggressive form of lung cancer with limited treatment options and generally poor prognosis. Although SCLC has historically been treated as a single disease entity, recent studies have revealed that there are biologically distinct subgroups of SCLC and that these subgroups have different therapeutic vulnerabilities and hence could be used for tailoring treatment regimens. Unfortunately, the development of biomarkers in SCLC is hindered by the lack of access to tissue as diagnostic specimens are often limited to fine needle aspirations and surgery is rarely performed.

Researchers led by John Heymach, M.D., Ph.D., and CPRIT Scholar Peter Van Loo, Ph.D., at The University of Texas MD Anderson Cancer Center, recently reported on four distinct SCLC subgroups based on mRNA profiling. In this study the team investigated the potential use of DNA methylation from both tumor and ctDNA in a cohort of 179 SCLC patients whose subtypes are assigned based on their recently established classification system. They developed machine learning approaches to allow the classification of SCLC subtypes using DNA methylation from both tissue and liquid biopsy samples to identify SCLC subgroups and enable precision medicine in SCLC.

These approaches, published in Cancer Cell on January 25, using gene expression data as well as DNA methylation in SCLC highlight that reliable subtyping in transcriptionally defined cancer is feasible from tumor specimen as well as by using a methylation-based liquid biopsy assay. The findings indicate that DNA biomarkers using tumor or blood samples can help identify different SCLC subtypes, a critical step toward bringing precision, biomarker-directed therapy into the clinic for SCLC and potentially other tumor types.

The University of Texas MD Anderson Cancer Center received two CPRIT Core Facility Support Awards grants (RP120348, RP170002), a CPRIT Early Clinical Investigator grant (RP210159), and a CPRIT Research Training grant (RP210028). MD Anderson recruited Dr. Van Loo in November 2020 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR210006).

122. Most breast cancer deaths are linked to its metastatic spread to distant organs, such as bones and lungs. Treatment options remain limited for aggressive breast cancers, including triple-negative breast cancer (TNBC) and basal-like breast cancer.

Researchers led by CPRIT Scholar Pawel Mazur, Ph.D., Department of Experimental Radiation Oncology at The University of Texas MD Anderson Cancer Center, utilized high-resolution single-cell RNA-seq (scRNA-seq) from a cohort of breast cancer patients to study single cells and discovered that the enzyme, SMYD2, plays a key role in the spread of cancer. In preclinical models, the team revealed that blocking SMYD2 improved survival rates by blocking the primary tumor cell's ability to metastasize. These findings, reported in Cell Discovery on January 31, re-

vealed that targeting SMYD2 could be a promising new way to treat and prevent metastatic breast cancer.

The University of Texas MD Anderson Cancer Center recruited Dr. Mazur in August 2016 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160078), and received two CPRIT Academic Research grants (RP210028, RP220391) totaling $5 million.

123. Circadian rhythm is the body's 24-hour internal clock that regulates cycles of alertness and sleepiness by responding to light changes in our environment. When this rhythm is disrupted for a long time, it can increase the risk of developing non-alcoholic fatty liver disease (NAFLD)-related hepatocellular carcinoma (HCC). However, the underlying mechanisms and direct relevance to HCC have not been established.

In this study, co-corresponding author Loning Fu, Ph.D., associate professor, Department of Medicine/MCB at Baylor College of Medicine, and fellow researchers aimed to determine whether chronic circadian dysregulation, commonly known as jetlag, can increase liver cancer risk. Using blood analyses and microscopy studies of the livers, the team revealed that mice with human-like liver conditions and patients with liver cancer, showed signs of multiple commonalities, including glucose intolerance, abnormal fat accumulation in the liver, inflammation, and liver scarring.

"We found that, compared to mice kept in normal light/dark cycles, mice in the jet-lagged group had a shorter lifespan as well as increased cirrhosis, jaundice (when skin or the white of the eyes turns yellow) and also developed cancer in both mouse and human liver cells," Dr. Fu said. "Importantly, chronic jet lag also induced metastasis from humanized livers." This study, published in the Journal of Hepatology in February 2024, is the first to experimentally demonstrate that chronic circadian dysfunction is indeed a human carcinogen.

Baylor College of Medicine received a $9.77 million CPRIT Multi-Investigator Research Awards grant (RP150587) in 2015. BCM received two CPRIT Core Facility Support Awards grants (RP210227, RP200504) totaling $8 million to support the Comprehensive Cancer Epigenomics Core Facility and the Proteomics and Metabolomics Core Facility.

124. Hepatocellular carcinoma (HCC) was the fourth leading cause of cancer deaths worldwide in 2018, and new HCC cases are projected to increase by 35% by the year 2030. The MYC oncogene is a master transcription factor that can regulate the expression of thousands of genes in the genome, and is often dysregulated in human cancer, including HCC. Drugs that target the MYC pathway could be effective in treating HCC, however, identifying small molecules that directly target MYC function has been challenging.

Co-corresponding author Yulin Li, M.D., Ph.D., assistant professor of Immunotherapy in Medicine at Houston Methodist Research Institute, and fellow researchers used a CRISPR-based genome-wide library screen to identify gene targets that, when inactivated, are lethal to cancer cells only with high, and not low, MYC expression. The data, published in Nature Communications on February 1, revealed that the team's genome wide CRISPR-screen served as a powerful approach to determine specific MYC-SL genes and pathways, offering new targets for HCC treat-

ment.

The Methodist Hospital Research Institute received a $900,000 CPRIT Individual Investigator grant (RP200472) in August 2020.

125. Chimeric antigen receptor (CAR) T cell therapy is effective in the treatment of blood cancers such as lymphomas and leukemias, leading to long-term remission. However, limitations exist such as treatment resistance and difficulty in targeting solid tumors. Led by Navin Varadarajan, Ph.D., Department of Chemical and Biomolecular Engineering at the University of Houston, researchers set out to overcome these limitations.

The team studied how CAR T cells kill cancer cells, using cells from healthy donors and patients. They discovered that multiple pathways are involved in CAR T cell-mediated killing. The results, published in Cell Death & Disease on February 2, 2024, highlight how these T cells can be engineered for optimal anti-tumor efficacy. By understanding these mechanisms, the team aims to engineer more effective CAR T cells for treating a wider range of cancers, including solid tumors.

University of Houston received a $1.2 million CPRIT Individual Investigator Research Awards grant (RP180466) in February 2018 to study immune cells directly from patients undergoing treatment within Texas to identify biomarkers of responses.

126. Cutaneous melanoma is the deadliest form of skin cancer, despite recent advances in targeted and immune therapies. Melanoma cells can change their behavior and adapt to treatments during the early treatment phases, making them hard to eradicate. Cell stiffness plays a crucial role in various cellular functions and processes. Changes in cell stiffness can also indicate underlying physiological or pathological conditions. For example, cancer cells often exhibit increased stiffness compared to normal cells, which can contribute to their invasive properties and ability to spread throughout the body.

In this study, researchers including Manfred Schartl, Dr. rer. nat., visiting professor, Texas A&M University, used atomic force microscopy (AFM) to explore cell stiffness in melanoma. They found that as melanoma progresses and becomes more invasive, the cells become less stiff. The data, published in Cancers on February 6, revealed that this reduction in stiffness could serve as a biomarker for tracking melanoma progression and potentially in patients harboring cutaneous melanoma.

Texas State University received a $248,458 High Impact/High Risk CPRIT grant (RP200657) in August 2020 to identify previously unknown genes involved in melanoma progression that are potentially important for personalized therapies.

127. Pancreatic ductal adenocarcinoma (PDAC) is projected to be the second leading cause of cancer death in the U.S. by 2040. With limited available treatment options for metastatic PDAC, the 5-year survival rate is less than 5%. Most PDAC cases (about 90%) involve mutations in the KRAS gene, which are changes in the DNA that drive cancer growth. However, the impact

of different KRAS mutations and additional mutations on treatment resistance and patient outcomes is not well understood in pancreatic cancer.

In this study, CPRIT Scholar John Paul Shen, Ph.D., assistant professor, Department of Gastrointestinal Medical Oncology at The University of Texas MD Anderson Cancer Center, and fellow researchers studied 803 patients who had been tested for somatic tumor mutations at MD Anderson and an external cohort (n = 408) of patients with pancreatic cancer from the PanCAN KYT® dataset, to see how different KRAS mutations and additional genetic changes affected survival. Published in NPJ Precision Oncology on February 3, the data revealed that patients without KRAS mutations or with a specific KRAS mutation (G12R) lived longer than those with other KRAS mutations (G12D or Q61). Co-mutations also influenced patient outcomes. These results suggest that personalized treatment strategies based on specific KRAS mutations and co-mutations could improve therapy for pancreatic cancer patients.

The University of Texas MD Anderson Cancer Center recruited Dr. Shen from the University of California, San Diego in 2018 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR180035).

128. Ewing sarcoma is a cancer of the bone or soft tissue that usually affects children and young adults. This malignancy is caused by a specific genetic change called the EWS-ETS fusion transcription factor, most commonly EWS-FLI1. Researchers at The University of Texas Health Science Center at San Antonio previously found two types of cells in Ewing sarcoma: one type ($CD133^{high}$) grows quickly, while the other type ($CD133^{low}$) grows slowly and is more resistant to chemotherapy.

In this study, Yuzuru Shiio, M.D., Ph.D., associate professor, Department of Biochemistry & Structural Biology, and team discovered that an enzyme called ubiquitin-specific protease 1 (USP1) plays a key role in how sensitive these cancer cells are to chemotherapy and in promoting the growth of Ewing sarcoma. These results, published in Genes & Cancer on February 5, 2024, highlight the importance of USP1 in the development and treatment of Ewing sarcoma.

The University of Texas Health Science Center at San Antonio received three CPRIT Academic Research grants (RP160487, RP160841, RP190385) totaling $2.6 million.

129. Recent developments in additive manufacturing (AM), also known as 3D printing, and selective laser melting (SLM) have enabled the creation of medical implants using a biocompatible material called Ti-6Al-4V (Ti64) powder. These patient-specific implants can be customized to match an individual's bone anatomy precisely due to the high customizability of the AM process. Implants with functionally graded latqesdqQawtices (FGLs) can be tailored to match the properties of bone, such as strength and density, while maintaining their biocompatibility.

In this study, researchers from Rice University, including CPRIT Scholar B. J. Fregly, Ph.D., professor, Department of Mechanical Engineering and Bioengineering, investigated and compared the mechanical properties and manufacturing defects of different FGL samples using compression testing, digital image correlation (DIC), and micro-CT imaging. They found that the sharpness of

the grading pattern did not significantly impact important mechanical properties like stiffness, yield strength, and energy absorption in graded lattice structures. The results, published in Materials on February 8, revealed that the primary factors influencing these properties were manufacturing defects rather than stress concentrations typically associated with aggressive grading patterns. This suggests that improving the manufacturing process to reduce defects could enhance the performance of these custom medical implants.

Rice University recruited Dr. Fregly from the University of Florida in May 2017 with the support of a $5.1 million CPRIT Recruitment of Established Investigators grant (RR170026).

130. Apical periodontitis (AP) is a painful disease that develops quickly following dental infections. It involves inflammation around the tissues near an infected tooth, leading to bone loss and disruption of bone health. This disease shows different symptoms and responses to treatment between men and women, highlighting the need to understand sex-specific mechanisms of AP.

Researchers in the Department of Endodontics at The University of Texas Health Science Center at San Antonio, used RNA sequencing in a mouse model to study gene activity in the tissue around infected teeth, focusing on sensory nerve fibers called nociceptors. The team found that men and women show different patterns of gene activity within the tissue surrounding infected teeth. The data, reported in Frontiers in Molecular Biology on February 9, revealed these differences suggest that specific genes in the infected area are influenced by nociceptors, potentially affecting how the infection develops and responds to treatment in men and women. These differences could potentially influence how these infections develop and how they respond to treatment in males and females.

The University of Texas Health Science Center at San Antonio received a $4 million CPRIT Core Facility Support Awards grant (RP220662) in September 2022 to introduce the third-generation sequencing technology to the UTHSCA-CGSCC research community.

131. Acute myeloid leukemia (AML) is an aggressive cancer responsible for approximately 11,000 deaths annually in United States. AML occurs mostly in adults over 65, a population who often responds poorly to aggressive treatments and thus has limited options.

Researchers led by Xiaolu Cambronne, Ph.D., assistant professor, Department of Molecular Biosciences at The University of Texas at Austin, discovered that AML patients with poorer outcomes had elevated levels of SLC25A51, a cellular transporter. In AML cells, these levels are too high, driving rapid cell growth. When the researchers lowered SLC25A51 levels, cancer cell growth slowed down, and in animal studies, survival improved. By lowering the transporter levels, the cancer cells died off, the disease progressed much more slowly, and the animal models survived longer.

The data, published in Cell Metabolism on February 14 could lead to more effective chemotherapy against AML in the future. “It appears that we can take these transporter levels back to a normal baseline, or even a little below that, and healthy cells are not negatively impacted,” Dr. Cambronne said. “That makes it a more targeted therapy.”

The University of Texas at Austin received a $250,000 CPRIT High Impact/High Risk grant (RP210079) in August 2021 to determine whether the block of SLC25A51 stops the expansion of the cancer.

132. Bladder cancer (BLCA) is a common malignancy that causes more than 150,000 deaths per year worldwide. The challenge of managing BLCA is its variability in how it spreads and forms new or recurring tumors in the bladder. In patients with BLCA, researchers have discovered that many patients have inactivated SMARCB1 leading to increased activation of the STAT3 inflammation pathway known for its role in promoting aggressive kidney cancer.

In this study, co-corresponding author Nagireddy Putluri, Ph.D., professor, Department of Molecular and Cellular Biology at Baylor College of Medicine, and team used lab models of bladder cancer without SMARCB1. SMARCB1 deficiency led to increased STAT3 activation which accelerated tumor growth and spread to other parts of the body. The researchers showed that treatment with a STAT3 inhibitor reduced tumor growth and metastasis in vivo. The team also developed a novel genetic test to help identify SMARCB1-deficient patients most likely to benefit from STAT3 inhibitors. These findings, published in Nature Communications on February 14, support the clinical evaluation of STAT3 inhibitors for the treatment of SMARCB1-deficient bladder cancer.

Baylor College of Medicine received two CPRIT Core Facility Support Awards grants (RP210227, RP170691) totaling $8.7 million. The University of Texas Health Science Center at Houston received a $5.8 million CPRIT Core Facility Support Awards grant (RP170668) in August 2017.

133. Early-stage lung adenocarcinoma (LUAD) patients face a 20–50% risk of recurrence or disease-related death, highlighting an unmet need in early-stage LUAD patients who would likely benefit from post-surgery chemotherapy. Researchers, including co-corresponding author Samir M. Hanash, M.D., Ph.D., Department of Clinical Cancer Prevention, and director, Department of Red and Charline McCombs Institute for the Early Detection and Treatment of Cancer at The University of Texas MD Anderson Cancer Center, began researching blood-based biomarkers, such as circulating tumor DNA (ctDNA), proteins, and autoantibodies. However, none of these molecular biomarkers had yet been translated into clinical practice.

In this study, researchers focused on circulating miRNAs in blood samples taken before treatment from stage I LUAD patients. The team compared samples from patients who subsequently developed recurrence after surgery or remained recurrence-free for up to six years. Using a microarray technique, they identified potential miRNA biomarkers for predicting recurrence in early-stage LUAD. The data, published in International Journal of Molecular Sciences on February 16, identified and validated circulating miR-23a-3p and miR-320c as novel biomarkers for predicting recurrence in patients with early-stage LUAD. These findings could help identify patients who might benefit from additional treatment after surgery.

The University of Texas MD Anderson Cancer Center received two CPRIT Academic Research grants (RP160668, RP180505) in 2016 and 2018 totaling $5.4 million.

134. High-risk human papillomaviruses (HPVs) are the underlying cause for over 5% of all cancers. The incidence of HPV+ head and neck squamous cell cancers is fast increasing in the United States and worldwide and is now considered an epidemic. It is essential for scientists to identify the antitumor host immune mediators to create effective treatment strategies.

Researchers from The University of Texas MD Anderson Cancer Center, including Jagannadha Sastry, Ph.D., professor in the Department of Immunology at The University of Texas MD Anderson Cancer Center, previously reported that a vaccine (TVAC) using a specific combination of immune-boosting agents helped clear HPV vaginal tumors in mice but was less effective for HPV oral tumors. In this study, published in Vaccines on February 17, the team substituted one of the agents in the vaccine with TVQC and found that this triggered a strong immune response, particularly through CD8 T cells and natural killer dendritic cells (NKDCs), a novel type of natural killer cells that express a marker usually seen in dendritic cells, called CD11c. This new combination resulted in complete regression of over 70% of oral and 80% of vaginal HPV tumors. The results highlight the importance of NK-mediated innate immune effector responses in total antitumor immunity to treat HPV+ cancers.

The University of Texas MD Anderson Cancer Center received an $883,146 CPRIT Individual Investigator Award (RP180472) in February 2018 for mucosal vaccine formulations for targeted therapy of HPV cancers.

135. The TP53 tumor suppressor gene is deleted or mutated in 84% of triple-negative breast cancers (TNBC) and 75% of HER2-amplified breast cancers, suggesting that changes in TP53 drives breast cancer. However, the exact role of p53 in tumor maintenance is not well understood. To provide further insight, researchers from The University of Texas MD Anderson Cancer Center generated TNBC models with mutations at two specific hotspots in the TP53 gene.

Led by Guillermina “Gigi” Lozano, Ph.D., Department of Genetics, the team engineered these models so that mutant TP53 expression could be turned on or off specifically in tumor cells, while maintaining wild-type p53 in the surrounding tissue. Using single-cell transcriptomics, the researchers found that TNBCs depend on mutant p53 for survival and that mutant p53 (two different mutants) protects cells from ferroptosis (cell death). The data, published in Science Advances on February 14, highlights specific potential targets meriting further evaluation for these patients, as blocking the mutant p53 function could make the cancer cells more vulnerable to treatment.

The University of Texas MD Anderson Cancer Center received a $4.9 million CPRIT Core Facilities Support Awards grant (RP180684) in August 2018 to establish an Integrated Single Cell Genomics (SCG) Core Facility.

136. The stimulator of interferon genes (STING) protein is crucial for the immune system, as it detects the presence of foreign DNA inside our cells and triggers an immune response against infections and cancer. STING responds to a molecular signal called cGAMP, which is produced when cells sense an infection or cancer, signaling immune cells to prepare for defense. Although activating STING to fight cancer isn’t a new concept, molecules developed to target STING have largely been ineffective.

In this study, co-led by Jinming Gao, Ph.D., Elaine Dewey Sammons Distinguished Chair in Cancer Research at The University of Texas Southwestern Medical Center, researchers created a new experimental therapy that embedded cGAMP in PC7A nanoparticles. The data, published in Science Immunology on February 16, revealed that the combination initially activates STING with cGAMP and then maintained this strong activation for an extended period. This polymeric STING-activating nanoparticle, PolySTING, uses a shock-and-lock dual activation mechanism. The researchers found that a type of immune cell, conventional type 1 dendritic cells (cDC1s), is crucial for STING-mediated rejection of various established and metastatic tumors in mice.

This subset of myeloid cells is essential for STING-mediated antitumor immunity and associated biomarkers could be used for prognosis. “The gold standard of current cancer immunotherapies releases the brakes on the immune defense against tumors. Our strategy steps on the gas to drive immune activation,” said Dr. Gao.

The University of Texas Southwestern Medical Center received two CPRIT Individual Investigator grants (RP220150, RP220242) totaling $2.1 million.

137. Small cell lung cancer (SCLC) initially responds well to chemotherapy, but it often becomes resistant after relapse. In this study, CPRIT Scholar Benjamin Drapkin, M.D., Ph.D., assistant professor in the Department of Internal Medicine, and CPRIT Scholar Sihan Wu, Ph.D., assistant professor, Children’s Medical Center Research Institute at The University of Texas Southwestern Medical Center, and team created a pre-clinical system to study this resistance using models created from samples taken from 51 patients with SCLC.

To better understand why patients often develop resistance after early relapse, the team used models which replicated key clinical features of SCLC in vivo against three chemotherapy regimens: cisplatin plus etoposide, olaparib plus temozolomide, and topotecan. For one patient, serial PDX models revealed that cross-resistance was acquired through MYC amplification on extrachromosomal DNA (ecDNA). MYC paralogs play a pivotal role in cancer growth and survival through regulation of a variety of cellular processes. Genomic and transcriptional profiles of the full panel revealed that MYC paralog amplifications on ecDNA were recurrent in relapsed cross-resistant SCLC, and this was corroborated in tumor biopsies from relapsed patients. The results, published in Cancer Discovery on February 22, revealed that ecDNAs with MYC paralogs are recurrent drivers of cross-resistance in SCLC, offering new targets for future treatment.

The University of Texas Southwestern Medical Center recruited Dr. Wu in 2021 with a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR210034). UT Southwestern recruited Dr. Drapkin in 2019 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR200007).

138. Renal cell carcinoma (RCC) is the most common malignant kidney cancer with an aggressive subtype called Translocation Renal Cell Carcinoma (tRCC) prevalent in children/adolescents. Patients with tRCC have a poor prognosis and the disease is incurable when it spreads. tRCC is linked to chromosomal translocations involving the TFE3 gene, and the most common gene fusion is ASPSCR1-TFE3. However, the molecular mechanisms behind this fusion and the development of tRCC have been poorly understood, partially due to a lack of animal models.

In this study, James Brugarolas, M.D., Ph.D., professor, Department of Internal Medicine, Hematology-Oncology Division at The University of Texas Southwestern Medical Center, and researchers conducted genomic analyses on a cohort of human tRCC patients and compared the findings to their new mouse model of tRCC. They engineered the mice to express a human ASPSCR1-TFE3 fusion protein, which is commonly associated with tRCC, using a Pax8-CRE driver. This driver is known to trigger various kidney cancer-related genes in clear cell RCC. he results showed that this genetic alteration disrupted kidney development (nephrogenesis) and glomerular formation in the mice, leading to neonatal death. This study, published in The Journal of Clinical Investigation on February 22, helps to further explain the role of the ASPSCR1-TFE3 fusion in tRCC development and significantly expands the available tumor models for research and the development of new treatments for tRCC.

The University of Texas Southwestern Medical Center received a $1.15 million CPRIT Individual Investigator Research Awards for Cancer in Children and Adolescents grant (RP180191) in February 2018.

139. Point-of-care sensors, which are low-cost and user-friendly, play a crucial role in precision medicine by providing quick results for individuals. Since frequent monitoring and rapid testing are critical in preventing drug resistance or cancer recurrence, CPRIT Scholar Caroline Ajo-Franklin, Ph.D., professor, Department of BioSciences, and director of the Rice Synthetic Biology Institute at Rice University, and fellow researchers aimed to develop a glucometer-based allosteric sensor (GBAS) to electrochemically sense specific biomarkers in blood and meet the miniaturization and signal amplification requirements for point-of-care (POC) use.

This study, published in Nature Communications on February 24, describes two parallel innovations that transform the conventional glucometer into a POC sensor capable of detecting therapeutic drugs. Instead of making complex changes to protein structures to generate an on/off signal, the researchers engineered a protein that slightly adjusts the rate of glucose oxidation in response to 4-hydroxytamoxifen (4-HT), a metabolite of the drug tamoxifen and carried in the blood. They developed an algorithm to decode the 4-HT signal, effectively mitigating interference caused by varying glucose levels within the sample. In addition, they harnessed glucose to power the sensor itself, eliminating the need for bulky batteries. By combining an organic electrochemical transistor (OECT) with this self-powered sensor, the team achieved stronger signal detection. The team anticipates that these engineering strategies and analysis methods will stimulate a variety of GBAS capable of detecting steroid therapeutics. These sensors hold broad applications, ranging from doping controls in sports medicine to monitoring medication compliance.

“The dream is to have technology similar to what’s available today for monitoring and treating variations in blood glucose, and have that be true for basically any drug,” said Dr. Ajo-Franklin.

Rice University recruited Dr. Ajo-Franklin from the Ernest Orlando Lawrence Berkeley National Laboratory in November 2019 with support from a $6 million CPRIT Recruitment of Established Investigators grant (RR190063).

140. Appendiceal adenocarcinoma is a rare and understudied disease. Serum tumor markers (TMs) – specifically CEA, CA19-9 and CA125 – have been useful with diagnosis, prognosis, and treatment response in gastrointestinal and gynecological cancers; however, there is limited information regarding their use in patients with appendiceal adenocarcinoma.

To examine if TMs would also be useful for appendiceal adenocarcinoma, researchers led by CPRIT Scholar John Paul Shen, M.D., and Abdelrahman Yousef, M.D., both from the Department of Gastrointestinal Medical Oncology at the University of Texas MD Anderson Cancer Center, conducted a cohort study of 1,338 patients – the largest ever cohort of this kind – to reveal associations between TM levels, tumor characteristics, and patient outcomes. They found that elevated levels of any of the three TMs were associated with significantly worse 5-year survival, and patients with elevated levels of all three TMs were at the highest risk of death. Interestingly, patients with low-grade tumors and normal CEA levels had a particularly good prognosis. The results, published in JAMA Network Open on February 28, 2024, suggest elevated levels of CEA, CA19-9, and CA125 are associated with overall survival in appendiceal adenocarcinoma, highlighting the importance of including all 3 biomarkers in the initial workup of patients with this disease.

The University of Texas MD Anderson Cancer Center recruited Dr. Shen from the University of California, San Diego in 2018 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR180035).

141. Lung adenocarcinoma (LUAD), the most common form of lung cancer, is being detected at earlier pathological stages because of enhanced screening. However, patient prognosis remains moderate to poor, which warrants the need to devise improved treatment strategies.

Researchers at The University of Texas MD Anderson Cancer Center, including corresponding author Humam Kadara, Ph.D., professor, Department of Translational Molecular Pathology, studied 246,102 single epithelial cells from 16 early-stage LUADs and 47 matched normal lung samples using single-cell sequencing. The team created a new atlas of epithelial and malignant lung cells, uncovering new cellular pathways and precursors in the development of lung adenocarcinoma.

“The large number of epithelial cells we studied, coupled with new technologies, enabled us to identify two distinct fates for type II cells,” Dr. Kadara said. “They share a common intermediate state, but one path leads to type I cells and the other progresses to tumors. Interestingly, we even found these intermediate cells in normal lung tissue and in normal regions surrounding lung cancers, and they’re stuck there. If they were transient, or quickly transitioning, we wouldn’t find as many of them, but they’re there.” This study provides evidence that tumor cells arise from these intermediate cells and suggests that KRAS inhibitors could be clinically beneficial for treatment or even interception of primitive stages of lung adenocarcinoma. These discoveries, published in Nature on February 28, may lead to the derivation of targets to prevent the initiation and development of LUAD.

The University of Texas MD Anderson Cancer Center received two CPRIT Individual Investigator grants (RP150079, RP220101) totaling $1.7 million.

142. Bladder cancer (BCa) is the second most common malignancy of the urinary system, and is a heterogeneous disease with significant diagnostic, therapeutic, and prognostic problems. There is a need for minimally invasive ways to detect it early and predict its progression. Molecular markers can provide the opportunity to diagnose a bladder tumor early, identify patients who are at risk of recurrence, and/or predict how tumors will respond to therapeutic approaches. Recently, researchers have been exploring circular RNAs (CircRNAs), special non-coding RNAs with a stable structure found throughout the body, as potential biomarkers for cancer.

In this study, CPRIT Scholar Jeremy Wilusz, Ph.D., associate professor, Department of Biochemistry and Molecular Pharmacology at Baylor College of Medicine, and colleagues focused on a circRNA synthesized from the human STAG2 gene, which plays a role in BCa biology. The team detected and validated several circSTAG2 isoforms in BCa cells, tumors, and in the patients' urine. The team found that the levels of circSTAG2(16–25) were higher in urine samples derived from patients with recurrent BCa. The data, published in Cancers on February 28, suggest that circSTAG2(16–25) could serve as a potential diagnostic or prognostic biomarker, offering a promising tool for improving patient outcomes.

Baylor College of Medicine recruited Dr. Wilusz in 2021 with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR210031).

143. One of the most active research fields in chemistry is the synthesis of colloidal metal and metal oxide nanocrystals. Their potential applications as nanomedicine and artificial enzymes (nanozymes) have fueled enthusiasm.

In this study, researchers including Yaowu Hao, Ph.D., in the Department of Materials Science and Engineering at The University of Texas at Arlington, and Xiankai Sun, Ph.D., in the Department of Radiology at The University of Texas Southwestern Medical Center, developed a simple and effective process using aqueous solution at room temperature to produce a variety of ultrasmall metal and metal oxide nanocrystals. Using only a beaker and a piece of dialysis membrane, the team successfully created ultrasmall nanocrystals of metals like cobalt (Co), nickel (Ni), copper (Cu), silver (Ag), gold (Au), palladium (Pd), as well as metal oxides such as Cu2O, FeO, and CeO2. This is the first time that dialysis tubes have been used in nanocrystal synthesis.

The results of this study, published in Crystals on February 29, 2024, found that the gradual change in pH caused by the diffusion of OH^- ions through the dialysis membrane played an essential role in the formation of these nanocrystals. This method can be readily adapted for almost all transition metal elements, providing researchers in the fields of catalysis and nanomedicine an easy access to a wide range of ultrasmall metal and oxide nanocrystals.

The University of Texas Southwestern Medical Center received a CPRIT Core Facility Support Awards grant and a Shared Instrumentation Award grant (RP170638, RP110771) totaling $9.85 million. The University of Texas at Arlington received a $198,039 CPRIT High Impact/High Risk grant (RP190678) in 2019.

144. Prostate cancer is the second most common type of cancer and the fifth leading cause of cancer death among men worldwide. When diagnosed early, instead of treating early-stage patients with radiation and surgery, clinicians monitor these patients through a process called Active Surveillance (AS), using MRI data to track tumor progression. However, current methods rely on general population statistics, which may impact detection of patient-specific tumor progression, leading to a delay in life-saving treatment.

In this pilot study, led by Guillermo Lorenzo, Ph.D., at the Oden Institute of Computational Engineering and Sciences at The University of Texas at Austin, researchers are pioneering a personalized approach to predict prostate cancer progression. The team developed a computational model that uses MRI data from routine screenings during AS that can be used to predict how tumors develop prior to the treatment stage of prostate cancer. This model, which is not yet available in clinical practice, can predict changes in tumor size and cellular characteristics, offering better personalized tumor forecasting.

Published in Cancer Research Communications on March 1, the findings could improve early detection of dangerous prostate tumor growth and provide clinicians with the ability to classify prostate cancer risk based on biomarker availability. According to CPRIT Scholar Thomas Yankeelov, Ph.D., Oden Institute core faculty and director of the Center for Computational Oncology, this work “underscores the next generation of tools for guiding the treatment of prostate cancer.”

The University of Texas at Austin recruited Dr. Yankeelov in 2015 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR160005).

145. Cancer cells interact with the immune system in three ways: they can hide, fight back, or build a physical barrier. It is a well-known fact that tumors are only slightly more acidic than healthy tissue, but the acidity is not uniform throughout the cancer cells. In tumors, dysregulated cancer cell metabolism and poor blood flow through the blood vessels cause the tumor microenvironment to become acidic.

Study leader Jinming Gao, Ph.D., professor, Departments of Biomedical Engineering, Cell Biology, Otolaryngology – Head and Neck Surgery, and Pharmacology at The University of Texas Southwestern Medical Center, and colleagues designed a set of nanoparticles that light up at specific levels of acidity years ago. They found that one nanoparticle, pegsitacianine, fluoresced brightly in tumors. However, the team was not certain why pegsitacianine fluoresced since researchers believed that a tumor’s acidity was too mild to trigger its activation.

Using pegsitacianine probes, the researchers imaged cells sampled from a variety of human and mouse cancer types. The results, published in Nature Biomedical Engineering on March 4, revealed that the cells were significantly more acidic on one side compared to the other. Samples from human tumors showed that this acid wall was practically devoid of an immune cell type known to fight cancer, CD8+ T cells, within the tumors. The team then grew cancer cells and CD8+ T cells together in an acidic environment (5.3 pH). The cancer cells remained while the CD8+ T cells died within three hours. The team found that the cancer cells pumped the acid into the surrounding environment, creating a wall of increased acidity around the tumor’s edge. This data suggests that severe acidity might obstruct immune cell attack without harming the cancer

cells. “This study revealed a previously unrecognized polarized extracellular acidity that is prevalent around cancer cells,” said Dr. Gao. Pegsitacianine has now passed phase two clinical trials in patients as a tool for image-guided cancer surgery.

The University of Texas Southwestern Medical Center received an $885,684 CPRIT Individual Investigator grant (RP180343) in February 2018.

146. The genetic makeup of tumors changes over time in response to treatments or attacks from the immune system, making it harder to destroy cancer cells. This evolution allows cancer cells to adapt and survive and is a common reason for secondary resistance that occurs for almost all new therapies despite initial outstanding responses. Understanding how tumors evolve genetically is important for developing more targeted and effective therapies against cancer. Because of recent technological advancements, such as next-generation sequencing and liquid biopsy, researchers can detect timely changes in the molecular profile of cancer induced by a treatment.

Researchers from The University of Texas MD Anderson Cancer Center and colleagues presented a patient with metastatic medullary thyroid carcinoma (MTC) harboring a previously uncharacterized RET activation loop deletion mutation. The patient initially responded well to selpercatinib but the tumor adapted through multiple genetic alterations, leading to resistance after 24 months. By identifying these mutations, researchers were able to adjust the treatment with a combination of targeted therapies, including larotrectinib and entrectinib, which addressed the newly developed resistance mechanisms. This practical approach, published in NPJ Precision Oncology on March 4, based on a cancer’s evolving genetic profile represents a shift towards more dynamic and personalized oncology care.

The University of Texas MD Anderson Cancer Center received a $6 million CPRIT Core Facility Support Awards grant (RP150535) in May 2015 for the Precision Oncology Decision Support Core.

147. Multiple myeloma (MM) is the second most common hematological malignancy in the United States. MM is a complex disease with variations among patients, and current methods for predicting outcomes have some limitations.

CPRIT Scholar Chao Cheng, Ph.D., associate professor, Department of Medicine at Baylor College of Medicine, and colleagues developed a novel gene signature specific to normal plasma cells using single-cell RNA-sequencing data to help predict how MM progresses in patients. They developed and validated the associations of the resulting plasma cell malignancy (PBM) score with disease state, progression, and clinical outcomes using data from five independent myeloma studies consisting of 2,115 samples.

The data, published in Blood Cancer Journal on March 6, reveals the PBM score links to key genes that drive MM, and shed light on how the disease progresses at the molecular level. These results represent an advance in precision medicine for MM by introducing and validating the PBM score as a predictive tool. The independent information provided by the PBM score, beyond the

established clinical scoring systems, provides an opportunity for refining risk stratification and guiding decisions on therapeutic approaches to MM.

Baylor College of Medicine recruited Dr. Cheng in August 2018 from the Geisel School of Medicine at Dartmouth with a $4 million CPRIT Recruitment of Rising Stars grant (RR180061).

148. SMARCA4 is a protein that helps regulate the activity of gene expression in B cells (a type of immune cell). However, SMARCA4 is one of the most commonly mutated genes in human cancers, including roughly 30% of germinal center derived Burkitt lymphomas, a highly aggressive form of B-cell lymphoma. Germinal center (GC) reactions are essential for refining immune responses and establishing long-term immunity by producing memory B cells, which can quickly recognize and respond to future encounters with the same antigen. However, the role of SMARCA4 in promoting lymphoma development is unclear.

To provide further insight, researchers led by Michael Green, Ph.D., associate professor, Department of Lymphoma/Myeloma at The University of Texas MD Anderson Cancer Center, examined the normal role of SMARCA4 in GC B cells. When a mutation disrupts the SMARCA4 process, B cells tend to “recycle” themselves into the highly proliferative GC dark zone. This dark zone recycling is a key step in normal immune responses but, when dysregulated, it can lead to uncontrolled growth, especially when combined with the influence of MYC - a gene that make proteins involved in cell growth, cell maturation, and cell death. This bias toward dark zone recycling promotes Burkitt lymphoma development. These findings, published in Cancer Cell on March 7, provide valuable insights into how alterations in SMARCA4 contribute to lymphoma formation, highlighting the gene’s role in malignant transformation. Targeting the molecular mechanisms behind SMARCA4 dysfunction and MYC-driven proliferation may offer new strategies for treating Burkitt lymphoma and possibly other cancers with similar genetic profiles.

The University of Texas MD Anderson Cancer Center received a $1.4 million CPRIT Individual Investigator Research Awards for Cancer in Children and Adolescents grant (RP220208) in February 2022.

149. Medulloblastoma (MB) is the most common malignant brain cancer in children. Doctors typically treat MB patients with surgical resection, radiotherapy, and chemotherapy. However, researchers have not yet determined the best therapeutic targets for high-risk groups.

Researchers, including CPRIT Scholar Michael Taylor, M.D., Ph.D., director, Neuro-oncology Research Program, and professor, Department of Pediatrics, Section of Hematology-Oncology at Baylor College of Medicine, targeted long, noncoding genetic material called lnc-RNAs that drive the expression of cancer-causing genes. The team treated a mouse model of group 3 medulloblastoma with their experimental intravenous therapy, lnc-HLX-2-7, and it showed reduced tumor growth by 40%–50%. Next, they added cisplatin, a chemotherapy drug currently used to treat medulloblastomas, alongside the new therapy, which caused the tumors to shrink even more and prolonged the animals’ survival.

The results, published in Cell Reports on March 8, reveal an innovative approach that shrinks

group 3 medulloblastoma tumors. This combination therapy extended the animals' lives by about 84 days compared with a 44-day increase in survival on lnc-HLX-2-7 alone. The results provide a strong rationale for targeting lnc-HLX-2-7 as a specific and potent therapeutic approach in children with G3 MB.

Researchers Baylor College of Medicine recruited Dr. Taylor in May 2022 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR220051).

150. Heart failure affects close to 30 million people worldwide. An underlying cause is the inability of the adult myocardium to regenerate after injury, such as a heart attack. Researchers including corresponding author Hesham Sadek, M.D., Ph.D., professor, Department of Biophysics and Molecular Biology at The University of Texas Southwestern Medical Center, targeted the transcriptional activity of two genes, Meis1 and Hoxb13, as a viable approach for heart regeneration.

In this study, researchers performed an in-silico screening to identify FDA-approved drugs that can inhibit Meis1 and Hoxb13 transcriptional activity. The team found that two FDA-approved drugs, paromomycin (Paro) and neomycin (Neo), improved left ventricular systolic function and decreased scar formation in both small and large animal models after a cardiac injury. The medications, when given in combination, target two proteins that regulate the heart muscle's regeneration capabilities. Published in Nature Cardiovascular Research on March 11, the data revealed that the effectiveness of these two drugs in inducing regeneration in large animals holds promise for their potential use in human clinical trials.

"The fact that these are FDA-approved drugs with established safety profiles makes it much easier to start testing this in humans in the near future," said Dr. Sadek. "Further studies can help us better understand the efficacy of pro-regenerative therapeutics and accelerate their delivery to the clinical setting."

The University of Texas Southwestern Medical Center received a $897,570 CPRIT Individual Investigator Research Awards for Prevention and Early Detection grant (RP160520) in November 2015 to study the effect of radiotherapy on the growth and renewal of the heart muscle and to investigate how preventing DNA damage in the heart can protect against the deleterious effects of radiotherapy.

151. Hepatocellular carcinoma (HCC) is the most common liver cancer and the fourth most frequent cause of cancer-related deaths worldwide. There is a high recurrence rate among patients who undergo resection and a high frequency of advanced stage disease at the time of diagnosis. Some studies have shown the clinical benefit of combination immunotherapy in a subset of patients with HCC, but an increased risk of specific toxicities associated with these regimens limit their use.

CPRIT Scholar Yujin Hoshida, M.D., Ph.D., director of the Liver Tumor Translational Research Program at The University of Texas Southwestern Medical Center, and fellow researchers sought a treatment regimen with similar efficacy but with an improved safety profile. The team investigated whether bavituximab may enhance the efficacy of pembrolizumab in HCC in a multicenter

single-arm two-stage phase 2 trial for patients who had not received prior systemic therapies. Although previous clinical trials had shown that only about 16% of HCC patients responded to pembrolizumab alone, nine patients, or 32%, responded to the combined therapy, and two patients had no evidence of disease at the end of the trial.

The results, published in Nature Communications on March 11, revealed that adding bavituximab did not appear to increase side effects over those taking pembrolizumab alone based on data from prior trials. Notably, this trial enrolled patients at clinical sites targeting disparate demographics with a high proportion of non-White patients analyzed which highlights the feasibility of enrolling diverse demographics in HCC trials.

The University of Texas Southwestern Medical Center recruited Dr. Hoshida in 2018 from the Icahn School of Medicine at Mount Sinai with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR180016).

152. Fanconi Anemia (FA) is an autosomal recessive disorder characterized by an increased susceptibility to cancer due to mutations in any of the 23 known FANC genes. FANC genes help protect cells from damage that can lead to cancer, but when these genes mutate, it is harder for the cells to repair properly.

Researchers, co-led by CPRIT Scholar Katharina Schlacher, Ph.D., Department of Cancer Biology at The University of Texas MD Anderson Cancer Center, found that FA patients frequently display FANC co-mutations, which increases the disease's severity. The team developed a mouse model by combining Brca2/Fancd1 and Rad51c/Fanco genes, both of which are critical in DNA repair. These mice exhibited disease characteristics closely mirroring those seen in human FA patients, such as bone marrow failure, rapid progression to cancer, increased sensitivity to cancer treatments, and significant issues with maintaining DNA replication stability. The mouse model, presented in Nature Communications on March 11, offers a comprehensive pre-clinical model to investigate diverse FA disease manifestations, especially how multiple genetic mutations can influence the severity of the disease and response to treatment. By understanding these interactions, scientists can better predict how genetic interactions affect the progression of FA and cancer in patients. It also provides an important platform for developing new treatment strategies for those affected by FA and cancer.

The University of Texas MD Anderson Cancer Center recruited Dr. Schlacher in 2014 from the Memorial Sloan-Kettering Cancer Center with the support of a $2 million Recruitment of First-Time, Tenure-Track Faculty Members grant (R1312). MD Anderson received a CPRIT Individual Investigator Research Awards grant (RP180463), a MIRA grant (RP180813), and a Research Training grant (RP210028) totaling $10.5 million.

153. The KCNQ2 gene provides instructions for making a protein that plays a crucial role in nerve cell function, particularly in the brain. Variants in KCNQ2 can disrupt the protein's function, potentially leading to a range of neurological and developmental issues in affected individuals. Among these, KCNQ2-related epileptic encephalopathies are common findings in genetic tests for epilepsy in young children, though understanding the pathogenic mechanisms behind

these variants can be challenging due to their heterogeneity.

Senior author Edward C. Cooper, M.D., Ph.D., associate professor, Department of Neurology, Neuroscience, and Molecular & Human Genetics at Baylor College of Medicine, and team analyzed KCNQ2 G256W variant via a multilevel experimental approach that included molecular, cellular, and in vivo analyses to address its pathogenicity. They modelled the structural consequences based on reported cryo-electron microscopy structures of the KCNQ2 channel and related channel proteins. This led to insights into how the variant disrupts the normal function of the KCNQ2 protein.

Their findings, published on March 12, as a Reviewed Preprint in eLife Neuroscience, revealed that the G256W variant impacts multiple aspects of KCNQ2 channel function, including its ion-conducting ability, as well as the protein's expression and localization within cells. This research helps to advance understanding of why and how variants in KCNQ2 cause this neurodevelopmental disorder.

Baylor College of Medicine received a $5.4 million CPRIT Core Facility Support Awards grant (RP190602) in August 2019 to add new technologies to the two CryoEM Cores in the Texas Medical Center.

154. APOBEC3A (A3A) and APOBEC3B (A3B) are proteins mainly responsible for the APOBEC signatures detected in tumors. A3A and A3B act as defense mechanisms against DNA or RNA viruses and transposons by inducing mutations in tumors. However, they can generate mutations which are particularly prevalent in breast, lung, cervical, and head & neck cancer genomes. However, it has been unclear whether A3A and A3B cause the same types of mutations in cancer cells or if they cause distinct genetic changes.

A team of researchers, including CPRIT Scholar Reuben Harris, Ph.D., professor and chairman, Department of Biochemistry & Structural Biology at The University of Texas Health Science Center at San Antonio, found that specific DNA sequences surrounding their target sites highly influence the activity of A3A and A3B. Based on this observation, the team developed an innovative approach called Oligo-seq, an in vitro sequencing-based method, which allowed them to classify cancer patients based on the mutations they had accumulated from each enzyme. This method enabled the differentiation between A3A- and A3B-induced mutations in cancer genomes, providing a clearer understanding of the distinct roles each enzyme plays in cancer development.

The data, published in Nature Communications on March 18, represent a significant advance in the field. Researchers can develop novel therapies to suppress mutation formation by selectively targeting each enzyme.

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). UT Health at San Antonio received a $4 million Research Training grant (RP170345) in November 2016 to train individuals committed to cancer research and prevention in the basic science, translational and clinical areas of research.

155. Pancreatic ductal adenocarcinoma (PDAC) has a desmoplastic (dense tissue) tumor stroma, which creates a physical barrier to treatment and suppresses the immune system. A protein, Galectin-3 (GAL3), is found in high amounts in PDAC and can contribute to cancer progression, making it a potential target for future treatments. However, its role in the pancreatic tumor microenvironment remains unclear.

To provide further insights, researchers including Zhongming Zhao, Ph.D., professor at McWilliams School of Biomedical Informatics, and chair for Precision Health at The University of Texas Health Science Center at Houston, created in vivo models of pancreatic cancer and genetically deleted GAL3 in both cancer cells and myeloid (immune) cells.

In this study, published in Gastroenterology on March 9, data revealed that when GAL3 levels decreased, levels of CXCL12 - a chemokine involved in immune cell signaling - increased. This suggests that CXCL12 could potentially act as a compensating mechanism when GAL3 is deficient, potentially contributing to cancer progression and immune suppression. These results show that GAL3 promotes PDAC progression and immunosuppression via both direct effects on cancer cells and by influencing the immune environment. Combined treatment targeting GAL3, CXCL12-CXCR4 axis, and PD-1 represents a novel therapeutic strategy for PDAC. This multifaceted approach could potentially overcome the challenges posed by the tumor's dense stroma and its immunosuppressive microenvironment.

The University of Texas Health Science Center at Houston received a $4.4 million CPRIT Core Facility Support Awards grant (RP180734) in August 2018 to establish the UTHealth Cancer Genomic Core.

156. As cancer cells replicate and evolve, subclones - distinct cellular lineages - compete for dominance and drive tumor progression. Despite extensive research, a comprehensive picture of how these subclones interact and evolve during cancer dissemination is still developing. To address this, researchers co-led by Andrea Viale, M.D., Department of Genomic Medicine at The University of Texas MD Anderson Cancer Center, developed a new model for pancreatic cancer that enables detailed study of subclone evolution within tumors and metastases.

Using patient-derived pancreatic cancer cells, the team created clonal replica tumors to trace the dynamics of subclonal lineages without interference from external factors. They found that subclones undergo continuous fluctuations during tumor growth, with dominant subclones suddenly collapsing and being replaced by others. The data, published in Science Advances on March 13, revealed that a large fraction (30 to 90%) of the subclones that sustain primary tumor growth appear at a secondary site at some point during tumor progression as well as in tumors that do not metastasize. This suggests tumor dissemination is a nonspecific, widespread behavior of tumor cells. The researchers linked the ability of a subclone to disseminate and form metastases at a second site to its fitness within the primary tumor. This implies that subclones that thrive in the primary tumor are more likely to successfully colonize new areas and drive metastasis.

This new orthotopic clonal replica tracing (CRT) approach represents a technological advancement in modeling human disease and revealed a new level of subclonal complexity intrinsic within tumors. This study emphasized the extent of functional diversity that occurs naturally during tumor expansion and demonstrated that tumor evolution is far more dynamic and complex than previously understood. These findings could guide more precise therapeutic strategies for managing metastatic disease.

The University of Texas MD Anderson Cancer Center received a $1 million CPRIT Individual Investigator grant (RP230373) in February 2023, and a $4 million CPRIT Research Training grant (RP210028) in May 2021.

157. Hematopoietic stem and progenitor cells (HSPCs) produce red and white blood cells and platelets. Proper regulation of HSPCs is crucial to prevent uncontrolled dysfunction. However, STAT3 function in HSPCs has been difficult to dissect as Stat3-deficiency in bone marrow induces systemic inflammation, which can impact HSPC activity.

To address this, researchers led by Stephanie Watowich, Ph.D., Department of Immunology, Program for Innovative Microbiome and Translational Research (PRIME-TR) at The University of Texas MD Anderson Cancer Center, developed mixed bone marrow chimeric models with inducible Stat3 deletion in 20% of the bone marrow, avoiding the confounding effects of systemic inflammation. The results showed that Stat3-deficient HSPCs were significantly impaired in their ability to rebuild the blood system following primary or secondary bone marrow transplantation. This impairment caused increased and uncontrolled activation of interferon (IFN) signaling pathways in the absence of STAT3.

Further investigation revealed that blocking the type I IFN receptor suppressed excessive HSPC proliferation, DNA damage, autocrine immune signaling, and p53 pathway - a critical regulator of cell cycle and apoptosis. The study, published in Leukemia on March 11, reveals the importance of targeting therapeutic STAT3 inhibitors specifically to diseased cells to avoid off-target loss of healthy HSPCs. The findings provide a foundation for developing more refined approaches to STAT3 inhibition, ensuring that healthy HSPCs remain unaffected while targeting defective or diseased cells, potentially improving treatment outcomes for cancer patients.

The University of Texas MD Anderson Cancer Center received two CPRIT Research Training grants (RP170067, RP210028) totaling $8 million to support the Training Program for Basic and Translational Scientists.

158. Estrogen receptor-positive (ER+) breast cancer is the most common breast cancer subtype. Although CDK4/6 inhibitors (CDK4/6i) have improved survival of patients with ER+ breast cancer, patients treated with CDK4/6i eventually develop drug resistance and progress, leaving patients with limited therapeutic options. Previous studies have shown that an increasing number of tumors resistant to CDK4/6i have lost the function of a gene called RB1.

In this study, corresponding author, CPRIT Scholar Carlos L. Arteaga, M.D., professor of Internal Medicine, director of the Harold C. Simmons Comprehensive Cancer Center, and associate dean of Oncology Programs at The University of Texas Southwestern Medical Center, and fellow researchers performed a genome-wide CRISPR screen on cells from two ER+ breast cancer lines to delete RB1 – making them resistant to all three CDK4/6 inhibitors approved by the U.S. Food and Drug Administration. Next, they screened over 19,000 genes and focused on PRMT5, a gene already implicated in the progression of various cancer types, including breast, and for which pharmaceutical inhibitors are in development.

The team reported that when they administered treatment with PRMT5 along with a drug that degrades ERs in mice bearing human ER+ tumors with RB1 deletion, it blocked the tumors from growing much better than either treatment alone and put the animal models in partial remission. These findings, published in Nature Communications on March 13, suggest a promising therapeutic strategy of dual blockade targeting both ER and PRMT5 for the treatment of ER+/RB-deficient

breast cancer.

The University of Texas Southwestern Medical Center received a $1.05 million CPRIT Individual Investigator grant (RP220309) in February 2022 to investigate chemical modification of ribosomal RNA. The University of Texas Southwestern Medical Center recruited Dr. Arteaga from Vanderbilt University School of Medicine with a $6 million Recruitment of Established Investigator grant (RR170061) in 2017.

159. The tumor immune microenvironment (TIME) plays a significant role in tumor initiation, progression, metastasis, and response to therapy. Tissue-resident memory T cells (T_{RM}) are a unique type of immune cell that reside in peripheral tissues and many kinds of cancer types, but the presence and potential impact of T_{RM} in TIME are unknown.

Researchers including CPRIT Scholar Chao Cheng, Ph.D., associate professor, Department of Medicine at Baylor College of Medicine, and team used data from single-cell RNA sequencing (scRNA-seq), to establish whether the presence and abundance of T_{RM} cells in patients correlate with better melanoma prognosis. From this profile, they can generate gene signatures which can possibly be correlated with the presence of disease.

The team extracted 11 distinct gene signatures that were highly correlated with T_{RM} abundance in the patients. The data revealed that T_{RM} infiltration is associated with longer overall survival and abundance of T cells, NK cells, M1 macrophages, and memory B cells in the TIME. Next, they developed a 22-gene T_{RM}–derived risk score to effectively classify patients into low- and high-risk categories, particularly in T cell-mediated responses. The analysis, published in iScience on March 15, suggests that T_{RM} abundance is associated with melanoma TIME activation and patient survival. The T_{RM}-based machine learning model could guide the development of more effective and personalized anti-tumor immunotherapeutic treatment regimens.

Baylor College of Medicine recruited Dr. Cheng in August 2018 from the Geisel School of Medicine at Dartmouth with a $4 million CPRIT Recruitment of Rising Stars grant (RR180061).

160. Immunotherapy has gained widespread acceptance as an effective treatment for cancers due to its potential to induce complete response and durable immune memory. However, despite the success of checkpoint blockade therapies, such as CTLA-4 inhibitors, the overall response rates and survival benefit indicate untapped potential. In their previous studies, Naveen Sharma, Ph.D., and CPRIT Scholar James Allison, Ph.D., and fellow researchers at The University of Texas MD Anderson Cancer Center, showed that, while ICOS (inducible T cell costimulator) pathway activation in combination with CTLA-4 blockade relies on a T cell-mediated response, CD8+ T cells only partially contribute to tumor rejection.

In a new study, the team hypothesized that tumor-associated macrophages (TAMs) may play a role in enhancing the efficacy of combination therapy. TAMs are immune cells that infiltrate the tumor microenvironment (TME) and can either promote or inhibit tumor growth, depending on their activation state. The team focused on understanding the interaction between TAMs and T cells within the TME, particularly when combining an ICOS agonist with CTLA-4 blockade (such as ipilimumab).

The ICOS is a T cell–specific protein shown to enhance the efficacy of CTLA-4 immune checkpoint blockade therapy. Using high-dimensional profiling, the researchers analyzed changes in immune cells that infiltrate tumors and found that TAMs play a crucial role in remodeling the tumor microenvironment. The results, published in the Journal of Experimental Medicine on March 22, revealed that the TAMs' phenotype and their contribution to antitumor immunity depend on the specific TME, suggesting that it is possible to reprogram TAMs to support antitumor responses when appropriately targeted. Combining an ICOS agonist with a therapeutic combination employing CTLA-4 blockade might enhance antitumor immune responses by leveraging the dual roles of T cells and TAMs, potentially leading to more effective cancer therapies.

The University of Texas MD Anderson Cancer Center recruited Dr. Allison in 2012 with the support of a $10 million CPRIT Recruitment of Established Investigators grant (R1203).

161. Dry eye syndrome causes inflammation, corneal damage, and sensorineural changes. In this study, researchers evaluated the hypothesis that dry eye alters the types and activity levels of immune cells in the cornea.

The team, led by Stephen Pflugfelder, M.D., professor and chair in the Department of Ophthalmology at Baylor College of Medicine, used single cell RNA seq to compare the immune cells in the corneas of healthy mice with those that had experimentally induced short-term dry eye. They found that the cornea contained 12 immune cell populations, that include several types of monocytes, macrophages, neutrophils, dendritic cells, innate and conventional lymphocytes, and mast cells.

Published in Frontiers in Medicine on March 23, the data revealed that monocytes are attracted to the affected area in conditions that lead to dryness or dehydration. Once there, these monocytes transform into macrophages, and they begin producing more genes associated with inflammation. The study suggests that these macrophages, found near cornea nerves, might play a role in the nerve changes and discomfort associated with dry eye syndrome. This provides evidence for additional studies to investigate the pathogenic role of macrophages in dry eye associated corneal disease and eye discomfort.

Baylor College of Medicine received a $5.2 million CPRIT Core Facility Support Awards grant (RP180672) in August 2018 to purchase high-end equipment that will more than double the current detection capabilities.

162. Non-Hodgkin lymphoma (NHL) is the seventh most common cancer and the ninth leading cause of cancer death for both men and women in the United States. Previous studies have suggested that clinical trials often underrepresent certain groups, such as older patients, racial/ethnic minorities, and women. To investigate the association between trial participation, race/ethnicity, travel distance and 13 neighborhood socioeconomic status (nSES) on NHL trial participation, CPRIT Scholar Christopher Flowers, M.D., M.S., Department of Lymphoma/Myeloma at The University of Texas MD Anderson Cancer Center, and colleagues, performed a retrospective analysis of adult patients treated at MD Anderson.

The team examined 3,146 consecutive adult patients with NHL seen between January 2017 and

December 2020. The study cohort was predominantly male and non-Hispanic white (NHW). The most common insurance types were private insurance and Medicare; only 1.1% of patients had Medicaid. The researchers found that trial participation decreased with age, and specific NHL diagnoses were associated with different participation levels. In addition, there were noticeably lower participation rates among patients with lower socioeconomic status at an individual level.

This evaluation of clinical enrollment provides insights into participation barriers to overcome in certain patient populations. The findings, published in Blood Advances on March 23, revealed that in this large academic cohort, age was the predominant factor associated with decreased participation, as was diagnosis. Patient race, gender, insurance type, and nSES were not associated with trial participation.

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 Recruitment of Established Investigators grant (RR190079).

163. Ultrasound imaging and ultrasound-mediated gene and drug delivery are rapidly advancing diagnostic and therapeutic methods. However, the need for microbubbles, which are too large to cross many biological barriers effectively, often limits the use of this technology.

Researchers, including CPRIT Scholar George Lu, Ph.D., assistant professor, Department of Bioengineering, CPRIT Scholar Han Xiao, Ph.D., associate professor, Department of bioengineering and biosciences at Rice University, and Richard Bouchard, Department of Imaging Physics at The University of Texas MD Anderson Cancer Center, have developed ultrasmall, stable, gas-filled protein nanostructures. Researchers believe that the novel diamond-shaped 50-nanometer gas vesicles (50-NM GVs), comparable to the size of viruses, are the smallest stable, free-floating structures for medical imaging ever created. Unlike larger microbubbles (1-10 micrometers), researchers use these new 50-NM GVs as contrast agents which can penetrate tissues and reach important immune cell populations in lymph nodes. The team used electron microscopy images of lymphatic tissue and revealed that these nanostructures cluster inside cells that activate the innate immune response. This ability suggests their potential use in immunotherapies, cancer prevention and early diagnosis, and infectious disease treatment.

This work, published in Advanced Materials on March 24, outlines future research directions, including evaluating the nanobubbles' biosafety and ability to produce an immune response and determining the optimal ultrasound settings for use in living organisms.

"More broadly, this represents a significant advancement in material design, potentially leading to innovative applications across various scientific fields," Dr. Lu said. "Because these nanostructures are composed entirely of proteins and are produced within living bacteria, they exemplify how biogenic materials can surpass the performance of synthetic materials."

Rice University recruited Dr. Lu in 2019 with a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR190081), and 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). The University of Texas MD Anderson Cancer Center received a $895,907 CPRIT Individual Investigator grant (RP190131) in 2019.

164. Immune checkpoint inhibitors (ICIs) have expanded the treatment landscape against cancers since the U.S. Food and Drug Administration approved the first drug in this category in 2011. ICIs work by blocking protein checkpoints that prevent the immune system from attacking cancer cells. Clinical trials have shown that ICIs work in only a small number of patients and it is presumed that the number of tumor mutations present in cancer cells is a reliable predictor of ICI success. David Hsieh, M.D., assistant professor, Department of Internal Medicine in the Division of Hematology and Oncology at The University of Texas Southwestern Medical Center, and fellow researchers set out to determine if the tumor mutation burden (TMB), the number of mutations present in a tumor, is a consistent marker of how well ICIs will work.

Because the previous studies were relatively small and had a limited number of cancer types, the team used a database which included de-identified genetic information on hundreds of thousands of malignant tumors derived from patients with many different cancer types, to analyze TMB in 70,698 tumors of 27 different types of cancer. The data involved 14,736 patients treated with ICIs that target an immune checkpoint protein known as PD-1/L1 and 55,962 who never received an ICI. The researchers then compared TMB with patient outcomes in both groups.

The data, published in Nature Cancer on March 25, 2024, showed that TMB predicted ICI benefit in only 12 of the 27 cancer types. These findings revealed that TMB is not a reliable indicator of whether ICIs will improve outcome – a potential paradigm shift for the field. “Our study challenges the paradigm that tumor mutational burden is a universal marker of how immunogenic a cancer will be. Current standards that rely on this assumption could lead to both undertreatment and overtreatment of patients,” said Dr. Hsieh.

The University of Texas Southwestern Medical Center received a $1.5 million CPRIT Early Clinical Investigator grant (RP200549) in August 2020.

165. The human FACT (facilitates chromatin transcription) complex is a chromatin remodeler that regulates gene expression by controlling which genes that cells are actively using. This process influences a wide range of cellular functions, including immune responses.

Researchers, including CPRIT Scholar Dustin Hancks, Ph.D., assistant professor, Department of Immunology at The University of Texas Southwestern Medical Center, began by searching for proteins in mammalian cells that bind to A51R. They hypothesized that poxvirus A51R proteins were likely inhibiting an antiviral defense that is common between insect and mammalian hosts. However, the precise nature of this defense and how A51R proteins blocked it was previously unknown.

The team identified a FACT-mediated, interferon-independent, antiviral pathway, which the researchers named the FACT-ETS-1 Antiviral Response (FEAR) pathway. This pathway restricted poxvirus replication, acting as a defense mechanism against viral infection. The study revealed that the interaction between the A51R viral protein and the FACT complex in cells enhances poxvirus replication in human cells and virulence in mice. This represents a mechanism by which viruses can manipulate host cellular processes to benefit their replication and survival during infection.

The data show that FACT also restricts replication of other viruses, including rhabdoviruses, flaviviruses, and orthomyxoviruses, suggesting broad roles for FACT in antiviral immunity beyond poxviruses. This study, published in Nature Microbiology on March 27, revealed that the FEAR pathway is critical for protection against viral threats and describes a unique mechanism used by viruses to evade immune defenses. A better understanding of FEAR may lead to better vaccines, new treatments to fight viral infection, or new ways to treat autoimmune diseases.

The University of Texas Southwestern Medical Center recruited Dr. Hancks in 2017 from the University of Utah, School of Medicine with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR170047).

166. Pharyngeal pumping and its reduction following injury are a well-documented behavior in C. elegans that is commonly used as a model for studying basic biological processes, including those relevant to human health. CPRIT Scholar Piya Ghose, Ph.D., assistant professor of biology at The University of Texas at Arlington, and fellow researchers explored the use of the C. elegans pharyngeal pumping behavior in the study of neurodegenerative disease and possible links with psychiatric disease.

The team examined five genes implicated in two forms of neurodegeneration, Hereditary Spastic Paraplegia (HSPs) and Alzheimer's Disease (AD). They measured both the baseline pharyngeal pumping rate and the depressive response (a decrease in pumping rate) after a touch stimulus. All five mutants showed a reduced baseline pumping rate, suggesting that the C. elegans pharyngeal pumping assay could be useful for studying neurodegenerative conditions on a broad scale.

The data, published in microPublication Biology on March 27, highlights two pharyngeal pumping behaviors as genetically distinct. This means they could offer different insights into the functions of genes associated with neurodegeneration. The findings point to the potential of baseline pharyngeal pumping behavior as a tool to further investigate AD and the spasticity observed in HSP. Additionally, researchers could expand this model to study other neurodegenerative and psychiatric pathologies.

The University of Texas at Arlington recruited Dr. Ghose in August 2019 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR190091).

167. Lung cancer is the leading cause of cancer death globally. Environmental factors, including exposure to carcinogenic polycyclic aromatic hydrocarbons (PAHs) from cigarette smoke or air pollution, cause most lung cancers. Research has shown that omega-3 fatty acids are beneficial against a variety of medical conditions including cancer.

In this study, Bhagavatula Moorthy, Ph.D., professor, Department of Pediatrics at Baylor College of Medicine and Texas Children's Hospital, and fellow researchers investigated whether omega-3 fatty acids, such as eicosapentaenoic acid and docosahexaenoic acid, could protect against lung cancer. The data, published in Molecular Sciences on March 28, revealed that omega-3 fatty acids can significantly reduce the harmful DNA damage caused by carcinogenic PAHs in the lungs and the formation of tumors in mice exposed PAHs. These results suggest that omega-3 fatty acids may be a promising chemo-preventive agent for lung cancer, especially in people at high risk

due to environmental exposure.

Baylor College of Medicine received an $899,151 CPRIT Individual Investigator Research Awards for Prevention and Early Detection grant (RP190279) in May 2019.

168. Rhabdomyosarcoma (RMS), the most common childhood soft tissue sarcoma, can sometimes be linked to genetic risk factors known as cancer-predisposition variants (CPVs). However, there has been little research regarding CPV risk association in children with RMS.

Corresponding author Philip Lupo, Ph.D., Department of Pediatrics, Section of Hematology-Oncology and the Dan L. Duncan Comprehensive Cancer Center at Baylor College of Medicine, and fellow researchers set out to determine the association of CPVs with outcomes among children with rhabdomyosarcoma in a cohort of 580 children enrolled in Children's Oncology Group studies. In this study, published in JAMA Network Open on March 28, the presence of CPVs in rhabdomyosarcoma-associated genes was associated with more adverse outcomes, suggesting that the incorporation of CPV status could inform novel risk-stratification strategies. Researchers also found that children with fusion-negative rhabdomyosarcoma and CPVs had comparable outcomes to children with no CPVs and fusion-positive rhabdomyosarcoma, an aggressive subtype known to have poor outcomes. "The results of our study support germline testing for cancer-predisposition variants among children with rhabdomyosarcoma, which could aid in early clinical surveillance strategies for patients and cascade testing of family members," Dr. Lupo said.

Baylor College of Medicine received a $1.49 million CPRIT Individual Investigator Research Awards for Prevention and Early Detection grant (RP170071) in November 2016 to create the first family-based study of rhabdomyosarcoma (RMS) for genomic analyses to fully explain the role of cancer predisposition genes on the risk of RMS.

169. Gas vesicles (GVs) are microbial protein organelles which help the cells float by trapping gas inside. GV engineering has multiple applications including reporter gene imaging (an indirect method to detect the process of gene expression), acoustic control, and payload delivery. These vesicles appear naturally in five phyla of bacteria and two groups of the archaea (single-cell organisms), but until now, scientists haven't fully understood how GVs group together inside cells.

"Inside cells, gas vesicles are packed in a beautiful honeycomb pattern. How this pattern is formed has never been thoroughly understood. We are presenting the first identification of a protein that can regulate this patterning, and we believe this will be a milestone in molecular microbiology," said CPRIT Scholar George Lu, Ph.D., assistant professor of bioengineering at Rice University.

The team, using genetic, biochemical, and imaging approaches, discovered a protein called GvpU, which has a role in controlling the clustering of GVs. When they added the GvpU protein in vitro or expressed it in Escherichia coli, it influenced how these gas vesicles clump together. The data, published in Nature Microbiology on March 29, revealed possibilities for creating GVs with adjustable clustering, which could lead to advanced biosensors—biological tools that detect specific molecules and generate measurable signals. This finding is a significant step forward in

molecular microbiology.

Rice University recruited Dr. Lu in 2019 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR190081).

170. Loss of protein function is a driving force of ageing. Haematopoietic stem cells (HSCs) create rapidly dividing progenitor cells, which then go on to produce hundreds of billions of red blood cells, white blood cells, and platelets every day. Given their longevity and the absence of frequent cell division to dispose of protein aggregates, maintaining protein homeostasis (proteostasis) is important.

“A driving force of cellular aging is the accumulation of proteins that have reached the end of their useful life…With age, proteins tend to misfold, aggregate, and accumulate inside the cell, which leads to toxic stress that can disrupt cell function,” said CPRIT Scholar Andre Catic, M.D., Ph.D., assistant professor, Huffington Center on Aging at Baylor College of Medicine. Previous studies revealed that mammalian cells express several hundreds of molecular chaperones, proteins that preserve or change the three-dimensional conformation of existing proteins. Scientists have implicated cyclophilins, one of the most abundant chaperones, in the aging process, but they have not yet studied how these proteins affect other cellular proteins.

In this study, researchers worked with mice to characterize the protein content of HSCs. The team discovered that cyclophilin A, also called PPIA, is a prevalent chaperone. Further experiments revealed that aged HSCs significantly decreased cyclophilin A expression, and genetically eliminating cyclophilin A accelerated natural aging in the stem cell compartment. In contrast, reintroducing cyclophilin A into aged HSCs enhanced their function. The data, published in Nature Cell Biology on March 29, supports cyclophilin A as a key factor in the longevity of HSCs.

The data also suggest that cyclophilin A interacts with intrinsically disordered proteins from the moment of their synthesis. “As these proteins are being made, cyclophilin A makes sure they keep the appropriate conformations and are maintained at sufficient levels,” Dr. Catic said. “Genetic depletion of cyclophilin A results in stem cells distinctively lacking intrinsically disordered proteins.”

The University of Texas Health Science Center at Houston received a $4.4 million CPRIT Core Facility Support Awards grant (RP180734) in August 2018. Baylor College of Medicine recruited Dr. Catic in 2014 with the support of a $2 million Recruitment of First-Time, Tenure-Track Faculty Members grant (RR140038). Baylor College of Medicine received two CPRIT Core Facility Support Award (RP170005, RP180672) totaling $10.17 million.

171. Photodynamic therapy (PDT) uses light to trigger chemical reactions that kill cancer cells. While effective for various cancers, PDT has been less successful in treating pigmented melanoma because melanin absorbs too much light. Finding effective treatments for cancers of the eye is crucial since approximately 50% of ocular melanoma patients die from metastasis even after local treatment, including eye removal.

Researchers, including CPRIT Scholar Vanderlei Bagnato, Ph.D., professor, Department of Biomedical Engineering at Texas A&M University, proposed a new method called melanin-mediated multi-photon PDT to treat ocular melanoma. They compared the effectiveness of 1- versus 2-photon PDT on pigmented and nonpigmented melanoma cells using different photosensitizers. They

found that under a special pulsed laser, melanin can absorb multiple photons and transfer the energy to the photosensitizer, enhancing the treatment's effectiveness. In experiments with mice, this method completely eradicated conjunctival melanoma tumors, showing promise as a minimally invasive treatment option. Published in Biophysics and Computational Biology on March 29, these results demonstrate the potential of multi-photon PDT for treating melanoma both in lab-grown cells and in live mice.

Texas A&M Engineering Experiment Station recruited Dr. Bagnato in 2022 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR220054).

172. The overexpression of two proteins, BCL-xL and BCL-2, play key roles in the development of cancer and cancer drug resistance. These proteins help cancer cells survive and grow, making them harder to treat. Researchers in this study focused on how a molecule called 753b, which can degrade both BCL-xL and BCL-2, works at the molecular level.

Previously they had identified 753b as the only PROteolysis TArgeting Chimera (PROTAC) molecule that can degrade both BCL-xL and BCL-2 in cells. However, how it interacted with VHL, a protein that helps tag BCL-xL/BCL-2 for destruction, remained unknown.

To overcome the severe side effects of Venetoclax, the only FDA-approved antitumor drug targeting a BCL-2 family member, co-corresponding author, Shaun Olsen, Ph.D., associate professor, Department of Biochemistry & Structural Biology at The University of Texas Health Science Center at San Antonio, and team developed PROTAC DT2216 by linking ABT263 with a VHL (E3 ligase) binding ligand. The study, published in Nature Communications on March 29, reported that the team designed a degrader, WH244, which is more potent than earlier versions and specifically targets BCL-xL/BCL-2. This work presents a streamlined approach that combines rational design and structure-based insights backed with cell-based studies to develop effective PROTAC-based cancer therapies with fewer side effects than current treatments including Venetoclax.

The University of Texas at San Antonio received a $3.1 million CPRIT Core Facility Award grant (RP210208) for the core facility renewal for the Center for Innovative Drug Discovery.

173. Alzheimer's Disease (AD) is a progressive neurodegenerative disease that causes brain atrophy and is the primary cause of dementia. Although AD has become easier to diagnose than before, there is still a limited understanding of how the disease occurs and how it progresses. Therefore, early detection and prevention are challenging, making it imperative to prioritize the understanding of the underlying causes of AD in individuals 65 and older.

Due to the complexity of AD, Zhongming Zhao, Ph.D., Department of Epidemiology at the School of Public Health and director, Center for Precision Health, and team aimed to integrate genetic risk factors identified from large-scale genome-wide association studies data and epigenetic signals from DNA methylation through a network module approach. The researchers used their in-house tool, the dense module search of genome-wide association studies (dmGWAS), to identify gene networks associated with AD. dmGWAS is a robust network-based method designed to identify the complex interplay between disease-associated genes by integrating GWAS data with a reference network. This study incorporated DNA methylation data from the AD post-mortem brain as the epigenetic element within this framework. The results, published in Epigenomes on April 1, revealed that by combining genetic and epigenetic data, this integrative network approach improved the understanding of AD's causes and origins. This data supports additional avenues for targeted therapeutic interventions and more effective treatment strategies.

The University of Texas Health Science Center at Houston received a $4.4 million CPRIT Core

Facility Support Awards grant (RP180734) in August 2018 for the UTHealth Cancer Genomics Core.

174. Epithelial ovarian cancer (EOC) is the most lethal gynecologic cancer in the United States. High-grade serous ovarian cancer (HGSOC) accounts for >70% of EOC cases and is responsible for most EOC-associated deaths. HGSOCs exhibit defects in the DNA repair process called homologous recombination (HR) often due to mutations in genes such as BRCA1 and BRCA2.

Abnormal changes in the process of attaching sugar molecules (glycans) to proteins or lipids on the surface of cells is a crucial strategy used by cancer cells to evade the body's immune system.

CPRIT Scholar Rugang Zhang, Ph.D., professor and chair, Department of Experimental Therapeutics at The University of Texas MD Anderson Cancer Center, and fellow researchers explored how this glycosylation helps these cells evade the immune system. The data, published in Nature Communications on April 2, revealed that, regardless of their HR status, EOC cells grown in mice with strong immune systems, exhibited higher levels of fucosylated glycans on ovarian cancers compared to cells grown in mice with weakened immune systems. By using a compound called 2-fluoro-L-fucose (2FF) to block this glycosylation, they observed improved immune responses against the cancer, both in the presence and absence of immunotherapy. The treatments were well-tolerated and did not affect the weight of the mice. These discoveries may guide the development of therapeutic strategies aimed at boosting anti-tumor immunity with precision by targeting HR-proficient EOCs, a critical unmet need in this cancer.

The University of Texas MD Anderson Cancer Center recruited Dr. Zhang in November 2022 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR230005).

175. Nucleic acids, such as microRNAs (miRNAs) or small interfering RNAs (siRNAs), are useful tools for cancer therapy. However, there are limitations of RNAs for therapy including difficulty in targeting the tumor microenvironment (TME), high clearance rates from the bloodstream, and low biocompatibility. Cells secrete small particles called extracellular vesicles (EVs), and researchers have considered mammalian-derived EVs as a potential drug delivery system. However, concerns related to their potential immunogenicity, low loading efficiency, low yield, and high-cost pose challenges to their use.

To overcome these limitations, researchers from The University of Texas MD Anderson Cancer Center considered plant-derived vesicles (PDVs) for efficient delivery of small RNAs to the TME. The team developed an alternative delivery system, called HEXPO, which combines plant-derived vesicles from watermelon with a synthetic molecule (polyamidoamine) to deliver small RNAs to tumors. They performed several in vivo experiments to demonstrate the therapeutic efficacy of this compound and explored in vitro biological mechanisms underlying the anti-tumor effects of miRNA146. The data, published in npj Precision Oncology on April 6, demonstrated that the HEXPO system is highly effective for the delivery of miR146a-5p to the TME and resulted in significant inhibition of tumor growth in three in vivo cancer models. In addition, they reported a previously undiscovered role for miR146a in ovarian cancer biology, revealing a reduction in production of new blood vessels of miR146. These findings suggest that researchers should conduct additional studies which use a combination approach with immune-targeted drugs.

The University of Texas Medical Branch at Galveston received a $4 million CPRIT Research Training grant (RP170593) in November 2016 for the Computational Cancer Biology Training Program.

176. Nearly one out of every eight men will get prostate cancer during their lifetime, making it the most common cancer among men other than skin cancer. Advanced prostate cancer, including metastatic castration-resistant prostate cancer (mCRPC), is difficult to treat because of its capacity to develop resistance to conventional therapies, including androgen receptor (AR) inhibitors. One such cause of resistance is due to lineage plasticity, where cancer cells transform from one cell type to another driven by AR signaling, enabling them to evade targeted treatments.

In this study, CPRIT Scholar Ping Mu, Ph.D., assistant professor, Department of Molecular Biology at The University of Texas Southwestern Medical Center, and fellow researchers identified a deficiency of Zinc Finger Protein 397 (ZNF397) as a critical trigger for this transformation in prostate cancer cells. This deficiency leads to a change from a reliance on AR signaling for cell growth to increased dependence on activity involving the gene Ten Eleven Translocation 2 (TET2). The transition renders cancer cells more adaptable, allowing them to become resistant to therapies targeting AR signaling.

This study, published in Cancer Discovery on April 8, also reveals that by inactivating TET2, the researchers effectively reversed resistance to AR-targeted therapies in ZNF397-deficient tumors. The findings provide a potential target for the development of novel prostate cancer therapies.

The University of Texas Southwestern Medical Center recruited Dr. Mu in August 2017 from Memorial Sloan-Kettering Cancer Center with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR170050). UT Southwestern received two CPRIT Individual Investigator grants (RP220473, RP230363) totaling $2.25 million.

177. Results for treating non-small cell lung cancer (NSCLC) remain dismal despite advancements; between 30% and 55% of patients with early-stage or locally advanced NSCLC will experience disease recurrence and eventually die. Researchers urgently need non-invasive markers to predict disease relapse, stratify patients, and guide treatment options in the perioperative setting.

Habitat Imaging is a modern approach used in cancer imaging that identify tumor subregions, or 'habitats,' sharing traits characterized by imaging biomarkers. Researchers from The University of Texas MD Anderson Cancer Center used habitat imaging patterns to group tumors based on their appearance on CT and FDG-PET. The team further tested their clinical relevance by stratifying patients' risk of recurrence after curative surgery or radiotherapy using multi-institutional, multi-modality (imaging and genomics) cohorts of resected NSCLC. In this study of 394 NSCLC patients, the team developed and validated a preoperative CT and ^{18}F-FDG PET–based signature that serves as a prognostic biomarker for patients with NSCLC.

The study revealed a proof-of-concept imaging framework to stratify patients into three clinically meaningful subtypes with distinct prognoses, which add to the prognostic information obtained from clinicopathological risk factors and ctDNA alone. The study, published in Nature Communications on April 11, revealed that if prospectively validated, the proposed imaging signature could potentially serve as an earlier indicator of recurrence.

The University of Texas MD Anderson Cancer Center received a $4 million CPRIT Research Training grant (RP210028) in May 2021 to provide a comprehensive learning environment focused solely on cancer, to position trainees for successful careers in cancer research.

178. Li-Fraumeni syndrome (LFS) is a hereditary disorder characterized by germline mutations in the TP53 tumor suppressor gene. Patients with LFS are at increased risk for various cancer types with a lifetime risk of 93% in women and 73% in men. Unfortunately, genetic counselors have only been able to provide the general risks associated with LFS. Although scientists have developed risk prediction models for other hereditary cancer syndromes, such as the hereditary breast and ovarian cancer syndrome and its associated genes BRCA1/2, LFS has remained an untouched area until recently.

Researchers at The University of Texas MD Anderson Cancer Center, including Banu Arun, M.D., Departments of Clinical Cancer Genetics and Breast Medical Oncology, developed two models for families with Li-Fraumeni syndrome: a competing-risk model that predicts cancer-specific risks for the first primary and a recurrent event model that extends the prediction to multiple primary cancer. The team applied their software suite LFSPRO to make risk predictions and assessed performance by using clinical data from 3,297 patients across 124 families. The data, published in Journal of Clinical Oncology on April 3, 2024, revealed that the models performed well in predicting TP53 mutations in patients with either primary or multiple primary cancers who underwent genetic counseling sessions. These models reveal the significance of using clinical data and improving data collection during clinic visits to potentially improve risk prediction for patients with hereditary cancers.

The University of Texas MD Anderson Cancer Center received an $896,896 CPRIT Individual Investigator Research Awards for Prevention and Early Detection grant (RP200383) in August 2020 to create an advanced clinical risk assessment tool that will more accurately quantify an individual's future cancer risk over his/her lifetime.

179. Pancreatic ductal adenocarcinoma (PDAC) is aggressive and difficult to treat, underscoring the need for more effective therapeutic targets. In a previous study, led by Jie Fu, Ph.D., Jianhua Ling, Ph.D., and Paul Chiao, Ph.D., at The University of Texas MD Anderson Cancer Center, results showed that when the researchers deleted the Plk3 tumor suppressor, it accelerated cell death resistance in KRAS G12D-mutant pancreatic cancer. However, how Plk3 works remained unknown.

In this study, the team, including John Tainer, Ph.D., explored how Plk3 helps control cancer in genetically engineered mice with KRAS G12D mutations. They found that the nardilysin (NRDC) enzyme cuts a Plk3 precursor, resulting in Plk3 activation that promotes cell death and suppresses cancer progression and metastasis. The data, published in Nature Communications on April 11, highlights NRDC and Plk3 as potential biomarkers for prognosis and as a potential therapeutic strategy for patients with KRAS G12D-mutant pancreatic cancer.

The University of Texas MD Anderson Cancer Center received a $5.9 million CPRIT Multi-Investigator Research Awards grant (RP180813) in August 2018 to support the BACIS Program with a focus on BRCA mechanisms underlying PARPi sensitivity and those with a significant probability of causing therapeutic resistance.

180. Drug repurposing involves using approved or investigational drugs beyond the scope of the original medical application. Although there is a large amount of data regarding cancer drug sensitivity in cancer cell lines, there is little drug response data from patients.

In this study, corresponding author Yidong Chen, Ph.D., Department of Population Health Sciences at The University of Texas Health Science Center at San Antonio, and fellow researchers developed a new method using advanced deep learning models to predict how tumors might respond to different drugs. The team trained a deep learning model, Scaden-CA, to break down a tumor into its different cancer cell types and then used that information to predict how the tumor would respond to drugs.

The data, published in Science Direct on April 12, offers insights into both drug repurposing and the underlying mechanisms. The model and algorithm effectively bridge the gap for translating cell line drug sensitivity data into tumor drug response. This study could enable more precise prediction of responses to drug treatment, consequently paving the way to personalized medicine.

The University of Texas Health Science Center at San Antonio received a $4 million CPRIT Core Facility Support Awards grant (RP220662) in September 2022 to introduce the exciting “third-generation sequencing” technology to the UTHSCA-CGSCC research community and received an $892,157 CPRIT Individual Investigator Research grant (RP190346) in August 2019 to predict drug response from genomic data using deep learning methods.

181. The loss of the von Hippel-Lindau (VHL) tumor suppressor gene is linked to clear cell renal cell carcinoma (ccRCC), which comprises approximately 85% of primary renal cancers. N6-Methyladenosine (m6A) is the most abundant mRNA posttranscriptional modification and participates in the pathogenesis and progression of various cancers. However, it is unclear whether VHL has some functional connection with m6A signaling.

CPRIT Scholar Qing Zhang, Ph.D., associate professor, Department of Pathology at The University of Texas Southwestern Medical Center, and colleagues set out to establish how VHL affects m6A, particularly in how it controls a gene called PIK3R3, which is involved in a key cancer-related pathway (PI3K/AKT). Through detailed genetic analysis, the researchers found that VHL-m6A signaling may regulate a selection of genes. The results revealed that depleting VHL caused m6A levels to drop, while the presence of VHL increased m6A levels in kidney cells. The findings, published in the Journal of Clinical Investigation on April 15, suggest that VHL influences m6A in a way that may contribute to kidney cancer growth, potentially opening new doors for understanding and treating ccRCC progression.

The University of Texas Southwestern Medical Center recruited Dr. Zhang in May 2019 with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR190058).

182. DEAD-box ATPases constitute a very large protein family present in all cells, often in great abundance. They play critical roles in building ribosomes, which are essential for protein production, during the biogenesis of large (60S) ribosomal subunits, but their precise molecular functions are currently unknown. One crucial rRNA element of the 60S is the universally conserved peptidyl transferase center (PTC), which is responsible for peptide bond formation during protein synthesis.

Researchers from The University of Texas Southwestern Medical Center, including CPRIT Scholar Jan Erzberger, Ph.D., assistant professor, Department of Biophysics, investigated the possible role of Dbp10 in PTC formation during nucleolar pre-60S assembly. They used a mutant version

of the protein that breaks down energy more slowly than usual. By using this mutant, researchers were able to study the activity of Dbp10 during the formation of the large 60S ribosomal subunit in greater detail. The findings, published in Nature Communications on April 17, showed that Dbp10 activity is essential for the formation of the ribosome active site and revealed how this function integrates with subsequent assembly steps to drive ribosome formation.

The University of Texas Southwestern Medical Center recruited Dr. Erzberger from ETH Zurich in August 2015 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR150074). The University of Texas Southwestern Medical Center received a $5.5 million CPRIT Core Facility Support Awards grant (RP170644) in August 2017 to establish a new Cryo-Electron Microscopy Core Facility and Service for Structure Determination at UT Southwestern Medical Center.

183. Esophageal adenocarcinoma (EAC), the most common subtype of esophageal cancer in Western countries, shows poor prognosis with rapid growth. EAC is predominant in males and is up to fivefold more common among Whites than Blacks. However, Black patients with EAC have poorer survival rates and the racial disparity remains largely unknown.

To investigate this disparity, researchers from Baylor College of Medicine, including co-corresponding author Aaron Thrift, Ph.D., associate professor, Department of Epidemiology and Population Sciences, used whole-exome sequencing to show somatic mutation profiles derived from tumor samples from 18 EAC male patients, 10 of EAC tumor tissues in Black patients and 8 in White patients. Somatic mutation profiles refer to the pattern of genetic alterations in the tumor cells that occur due to various factors such as environmental exposures, DNA replication errors, and exposure to mutagens.

The team identified three molecular EAC subgroups based on pre-defined esophageal cancer-specific mutation patterns. They also identified differentially mutated genes and compared the mutation load between Black and White patients. The findings, published in Scientific Reports on April 18, underscore the possibility that EAC may have different genetic mutation patterns among different races. Further comprehensive studies are necessary to validate these findings in larger sample sizes and to better understand the genetic mechanisms driving these differences.

Baylor College of Medicine received a $3.6 million CPRIT Research Training grant (RP210037) to support the Systems Epidemiology for Cancer Training Program (SECT Program).

184. CAR T cell therapy has been successful for recurrent or high-risk leukemias and lymphomas. However, it has not shown promise in treating solid tumors. In the HEROS 2.0 trial, a prospective, interventional phase 1 study for people with advanced sarcoma, a team of international researchers sought to advance their findings from their previous clinical trial, the HEROS study, where they found that CAR T cells directed at HER2+ tumor cells had a favorable safety profile, but poor CAR T expansion and persistence limited clinical benefit.

In HEROS 2.0, researchers tested HER2-CAR T cell infusions, a therapy that uses CAR T cells engineered to target the HER2 protein, which is overexpressed on the surface of sarcoma cells. Patients first received chemotherapy to reduce their own immune cells, allowing the infused CAR T cells to expand. The primary goal was assessment of safety of one dose of HER2 CAR T cells

after lymphodepletion and the secondary outcome was determination of antitumor responses. The team tested thirteen patients in 14 enrollments, and 7 received multiple infusions. The results, published in Nature Cancer on April 24, showed antitumor activity with clinical benefit in 50% of individuals treated. This data revealed that this therapeutic approach is safe and is associated with clinical benefit in sarcoma patients.

“We are now studying the tumors and the way we engineer the CAR T cells to better facilitate the safe delivery of higher doses, thereby enhancing antitumor activity by increasing the magnitude of CAR T cell expansion and persistence,” said Meenakshi Hedge, M.D., associate professor of pediatrics – hematology/oncology at Baylor College of Medicine.

Baylor College of Medicine received a $4 million CPRIT Research Training grant (RP160283) in November 2015, and a $5.3 million Core Facility Support Awards grant (RP180785) in August 2018. The University of Texas MD Anderson Cancer Center received a $1.22 million CPRIT Shared Instrumentation Awards grant (RP121010) in March 2012.

185. Researchers need to be able to readily search and retrieve digital histopathology slides, but currently pathologists must manually search and retrieve these images. Developing automated search and retrieval systems for the digitized cancer images could help researchers find the information they need more quickly, leading to better understanding and treatment of diseases.

In this case study, CPRIT Scholar Jacob Luber, Ph.D., assistant professor in the Department of Computer Science and Engineering at The University of Texas at Arlington, and colleagues investigated the clinical readiness of four state-of-the-art histopathology slide search engines (Yottixel, SISH, RetCCL, HSHR) for automating search and retrieval of digital histopathology slides using both unseen datasets and several patient cases. The data, published in the NEJM AI on April 25, provides a qualitative and quantitative assessment of each model’s performance in providing retrieval results that are reliable and useful to pathologists. Dr. Luber’s team found inconsistent results across all four algorithms, and upon testing the models on real patient cases, they found that the results were not yet ideal for clinical use. The researchers are now devising new guidelines to standardize the clinical validation of AI tools. They are also developing new algorithms to develop more reliable and accurate predictions for successful clinical adoption.

The University of Texas at Arlington recruited Dr. Luber in November 2021 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR220015).

186. Metastasis, the spread of cancer cells to other parts of the body, is the leading cause of cancer-related deaths despite medical advances. Researchers face challenges in gathering adequate data used to study metastatic cancer with the current methods.

To tackle this issue, Yidong Chen, Ph.D., professor, Department of Population Health Science, The University of Texas Health Science Center at San Antonio, and colleagues developed a metastatic cancer expression generator (MetGen), a deep learning model that generates metastatic gene expression files using cancer and tissue samples. MetGen was able to generate comparable samples to actual metastatic cancer samples, and excellent cancer and tissue classification yields performance rates. Additionally, they demonstrated MetGen’s interpretability using meta-

static prostate cancer and metastatic breast cancer. MetGen has learned highly relevant signatures in cancer, tissue, and tumor microenvironments, such as immune responses and the metastasis process, which can potentially foster a more comprehensive understanding of metastatic cancer biology. The development of MetGen, as described in MDPI Cancers on April 25, represents a significant step toward the study of metastatic cancer biology by providing a generative model that could help researchers better understand cancer metastasis and lead to the discovery of new treatments.

The University of Texas Health Science Center at San Antonio received an $892,157 CPRIT Individual Investigator Research grant (RP190346) in August 2019 to predict drug response from genomic data using deep learning methods, and a $3.68 million Core Facility Support Awards grant (RP160732).

187. Current research methods have limitations when it comes to fully understanding and treating diseases of the human brain. A central question for regenerative neuroscience is whether synthetic neural circuits, such as those built from two species, can function in an intact brain. How neurons connect with one another, and fire, makes integrating cells from two species complicated.

CPRIT Scholar Jun Wu, Ph.D., assistant professor, Department of Molecular Biology at The University of Texas Southwestern Medical Center, and colleagues explored this by mixing rat and mouse neuronal cells early in the development of mouse embryos. Using a genetic-editing tool, C-CRISPR, the team deleted every trace of a gene called Hesx1, which controls the development of a large region in the brain that coordinates much of an animal's behavior, in a group of mouse blastocysts. As published in Cell on April 25, the researchers demonstrated that adding rat neurons to mouse brains, whose brains were missing crucial cells, could help the organs to recover function. By demonstrating that a mouse can sense the world using neurons from another species, the team established a technique called neural blastocyst complementation as a powerful tool to study brain development, plasticity, and repair.

A potential challenge with developing chimeras (organisms with cells from different species) for human organ transplants is the risk of the human body rejecting the organs. However, because the team added the rat cells long before the embryos had formed an immune system, the animals' bodies never learned to recognize the cells as foreign and thus never attacked them. The experiments could help scientists to better understand how different species' brains develop, and aid efforts to grow 'chimeric' pigs with human organs that they could use for transplantation in people.

The University of Texas Southwestern Medical Center recruited Dr. Wu in August 2017 from Salk Institute for Biological Studies with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR170076).

188. Creating the proteins that cells use to perform their activities begins with transcription, the process when an RNA polymerase protein latches onto a DNA strand and copies – or transcribes – the encoded information into an RNA molecule. The promoter is the region where RNA polymerase attaches to begin transcription and typically consists of hundreds of base pairs, the building blocks of DNA. Although promoters are crucial for initiating transcription in every gene, their nature in the human genome remains unclear.

CPRIT Scholar Jian Zhou, Ph.D., assistant professor in the Lyda Hill Department of Bioinformatics at The University of Texas Southwestern Medical Center, and fellow researchers developed a machine learning model called Puffin. After analyzing data from tens of thousands of recognized human promoters, Puffin identified three types of sequence patterns: motifs, initiators, and trinucleotides. Puffin showed that depending on the arrangement of these elements, they can activate or repress transcription of a gene. This allowed the researchers to predict whether and how transcription would occur if they mutated promoters. These findings, published in Science on April 26, present a unified model for transcription initiation in most human promoters and shed new light on fundamental questions related to promoter sequence and function.

This program is available on a free web server (tss.zhoulab.io) so that other researchers can test any promoter sequence of interest. “Although promoters are essential for the function of every gene, our understanding of how these genetic elements operate is incomplete despite decades of study that have defined many of their features. Our research sheds new light on how these sequences work in humans and other mammals,” said Dr. Zhou.

The University of Texas Southwestern Medical Center recruited Dr. Zhou in August 2019 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR190071).

189. Drug discovery relies on efficient identification of small molecules that can bind to proteins and influence their behavior. However, scientists often overlook how drug binding impacts protein structure over time. Researchers led by Chris Brosey, Ph.D., and John Tainer, Ph.D., Department of Molecular and Cellular Oncology at The University of Texas MD Anderson Cancer Center, developed a novel drug discovery method called time-resolved, high throughput small-angle X-ray scattering (TR-HT-SAXS), which allows them to screen small molecules while mapping changes in a protein’s structure.

Using TR-HT-SAXS screening, the team tested this method on the mitochondrial protein AIF. The team monitored how a library of small molecules alters AIF structural states over time. Published in Nature Chemical Biology on April 26, the follow-up biochemical and structural experiments validated these findings, suggesting that TR-HT-SAXS can identify small molecules that bind to and modify proteins in desired ways. The team anticipates that continued creation and analysis of HT multidimensional SAXS datasets will provide further opportunities to link chemistry, kinetics, and macromolecular conformation.

The University of Texas MD Anderson Cancer Center received a $5.9 million CPRIT Multi-Investigator Research Awards grant (RP180813) in August 2018 to support the BACIS Program with a focus on BRCA mechanisms underlying PARPi sensitivity and those with a significant probability of causing therapeutic resistance.

190. CRISPR screens, which directly edit the DNA in human cells, help scientists find potential biomarkers and mechanisms of treatment sensitivity or resistance. DepMap teams have screened over a thousand cancer cell lines with CRISPR knockout libraries. However, studying genetic interactions (GIs) has been challenging and costly. One class of GIs that has received special attention is the synthetic lethal relationship between paralogs - gene pairs or families that arise through duplication of a single ancestral gene.

In this study, CPRIT Scholar Traver Hart, Ph.D., associate professor, Department of Bioinformatics and Computational Biology at The University of Texas MD Anderson Cancer Center, and colleagues identified background-independent paralog synthetic lethals from previous CRISPR genetic interaction screens and found that the Cas12a platform provides superior sensitivity and assay replicability. As reported in Nature Communications on April 27, the team developed a new CRISPR/Cas12a platform called in4mer, a highly customizable platform, offering a significant advance in the study of genetic interactions. Compared to the five-paralog synthetic lethal studies, in4mer requires fivefold fewer reagents for the same assay. This improvement has major implications for the cost effectiveness in genetic interaction assays in mammalian cells. With the in4mer system, a wider range of the research community will be able to add targeted genetic interaction surveys to their experimental toolkits.

The University of Texas MD Anderson Cancer Center recruited Dr. Hart in February 2016 from the University of Toronto with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160032). MD Anderson also received two CPRIT High Impact/High Risk grants (RP210173, RP210073) in 2021 totaling $500,000.

191. Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related death worldwide. Patients with early-stage HCC have five-year survival rates approaching 70% with curative treatments, compared with a median survival of one to two years after palliative therapies for those with more-advanced tumor burden. However, the efficacy of HCC screening in patients with cirrhosis is controversial because of the lack of randomized data and the inherent biases of cohort studies.

Delayed evaluation of the risk-to-benefit ratio has led to controversies in other cancer screening programs, including prostate cancer, colorectal cancer in older individuals, and breast cancer in younger women. In this study, researchers including Amit Singal, M.D., professor, Department of Internal Medicine at The University of Texas Southwestern Medical Center, characterized the benefits of HCC screening after considering lead-time and length-time biases in a diverse, contemporary cohort of at-risk patients. The team performed a retrospective study of patients with a new diagnosis of HCC between January 2008 and December 2022. Out of 1,313 patients, screening detected HCC in 42.3% patients. Detection by screening was associated with improved early-stage detection and survival, which persisted after adjusting for lead-time and length-time biases. These findings, published in JAMA Network on April 29, suggest that HCC screening remains an important target for interventions by facilitating early tumor detection.

The University of Texas Southwestern Medical Center received a $3.75 million CPRIT Research Training grant (RP210041) in May 2021 to support the Cancer Intervention and Prevention Discoveries Program, and a $2.5 million Academic Research grant (RP200554) in August 2020. Baylor College of Medicine received a $9.77 million CPRIT Multi-Investigator Research Awards grant (RP150587) in 2015.

192. Researchers at The University of Texas MD Anderson Cancer Center set out to determine what to do when smokers fail after their initial attempt to quit. Paul Cinciripini, Ph.D., professor and Margaret & Ben Love Chair in Clinical Cancer Care, and colleagues set out to determine the best subsequent strategy for non-abstinence following initial treatment with varenicline (a smoking cessation aid) or combined nicotine replacement therapy (CNRT).

Using a double-blind, placebo-controlled, sequential multiple assignment randomized trial, researchers chose 490 volunteers to receive six weeks of varenicline or CNRT. After six weeks, they randomized non-abstainers to continue, switch, or increase medication dosage for six additional weeks. The team conducted the study from June 2015 through October 2019 in a Texas tobacco treatment clinic. The data, published in JAMA Network on May 2, revealed smokers who failed to quit with varenicline in the trial's first phase were seven times more likely to quit by the end of the second phase if they increased the dosage of varenicline. There was also a nearly two-fold increase in those who successfully quit if they switched from a CNRT regimen to varenicline. These results are favorable compared to the near zero chance of abstinence seen in patients who switched from varenicline to CRNT or left on the same treatment plans.

The University of Texas MD Anderson Cancer Center received a $1.5 million CPRIT Individual Investigator Research Awards for Prevention and Early Detection grant (RP150228) in February 2015.

193. The healthcare industry uses Large Language Models (LLMs), such as Generative Pre-trained Transformer (GPT) models represented by ChatGPT, to facilitate patient-clinician communication. To date, few studies have examined the potential of LLMs in reading and interpreting clinical notes, turning unstructured texts into structured, analyzable data.

Researchers from The University of Texas Southwestern Medical Center, led by Yang Xie, Ph.D., chair in Cancer Research, the School of Public Health, aimed to evaluate ChatGPT's capacity to extract information from free-text medical notes efficiently and comprehensively. The team selected a dataset of more than 1,000 lung cancer pathology reports as the corpus for extracting detailed diagnosis information. Then they developed and improved a prompt engineering process which involves crafting a high-quality prompt and compared the ChatGPT output with expert-curated structured data. They used case studies to provide insights into how ChatGPT read and interpreted notes and why it made mistakes in some cases.

The results, published in npj Digital Medicine on May 1, revealed that providing clear guidance on the output format emphasizing evidence-based inference, providing chain of thought prompting by asking for tumor size information, and providing specific examples are critical in improving the efficiency and accuracy of extracting structured data from the free-text pathology reports. The application of ChatGPT in interpreting clinical notes holds promise in transforming how healthcare professionals and patients utilize these documents and could ultimately lead to more efficient clinical research and improved patient care.

The University of Texas Southwestern Medical Center received a $5.4 million CPRIT Core Facility Support Awards grants (RP180805) in 2018 and received a $1.3 million CPRIT Individual Investigator Research Awards for Cancer in Children and Adolescents grant (RP230330) in 2023.

194. Human skin, the largest organ in the body, protects the body from external physical, chemical, and biological contaminants. Researchers have conducted many studies to develop an accurate representative model for human skin to study skin diseases, wound inflammation, and the development of regenerative therapies for skin wounds. One of the primary barriers to generating full thickness skin has been the lack of functional blood vessels in these skin models, which are necessary for mimicking real skin structure and function.

In this current study, corresponding author Kameel Zuniga, Ph.D., Department of Biomedical Engineering at The University of Texas at Austin, and colleagues created a unique vascularized HSE (VHSE) model using collagen/keratin hydrogels to better mimic the skin's natural environment and the incorporation of functional vasculature with a physiological flow. As reported in the International Journal of Molecular Sciences on May 3, the team successfully developed multiple skin models from the frequently used organotypic skin model (AHSE) to complex, multilayered vascularized VHSE. The VHSE model improved skin barrier function, vessel development, and skin structure compared to a static AHSE model. In future studies, researchers could use this vascularized skin model for more realistic studies of immune responses by introducing immune cells into the vessel or for wound healing research, where blood vessel permeability is an important factor.

The University of Texas at Austin recruited Dr. Yankeelov in 2015 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR160005).

195. Immune checkpoint inhibitors (ICI) have greatly advanced cancer therapy over the last decade, improving overall survival for patients. However, ICI can cause immune-related adverse events including myocarditis. To diagnose ICI myocarditis, doctors often rely on a combination of tests, with endomyocardial biopsy (EMB) remaining the gold standard despite its invasive nature. Typically, EMB samples show a predominantly CD8+ T cellChr infiltration into the heart tissue. However, researchers have not suitably studied the impact of peripheral cytokine levels (proteins involved in immune responses) on the prognosis and treatment of ICI myocarditis.

In this study, CPRIT Scholar Nicolas Palaskas, M.D., associate professor of medicine in the Department of Cardiology at The University of Texas MD Anderson Cancer Center, and fellow researchers sought to identify cytokines that could predict and direct the treatment of ICI myocarditis. The team performed a single-center, retrospective cohort study of patients with ICI myocarditis who had available peripheral cytokine levels between January 2011 and May 2022. The study found that Interleukin (IL)-6 and tumor necrosis factor-α (TNF-α) were the most elevated cytokines in these patients.

However, elevated levels of these cytokines did not significantly predict major adverse cardiovascular events or 90-day mortality. The results, published in Diseases on May 3, cast doubt on the prognostic value of peripheral cytokine levels, particularly TNF-α, in predicting outcomes for ICI myocarditis. Additionally, the use of the TNF-α inhibitor infliximab did not lead to different survival outcomes, suggesting the immune response in ICI myocarditis is more complex than previously thought. This highlights the need for more research into the role of cytokines within heart tissue itself, rather than just in the blood, to develop better treatments for this condition.

The University of Texas MD Anderson Cancer Center recruited Dr. Palaskas in August 2020 with the support of a $1.5 million CPRIT Early Clinical Investigator grant (RP200670).

196. Fusicoccanes are a group of natural compounds found in various living organisms which exhibit diverse biological activities. These molecules can act as modulators of 14-3-3 protein–protein interactions which play a crucial role in regulating cell growth, survival, and signaling. However, their innate structural complexity presents significant challenges for chemical synthesis.

Rice researchers led by CPRIT Scholar Hans Renata, Ph.D., associate professor of chemistry, investigated the biological activities of the fusicoccanes by using a novel strategy to synthesize 10

distinct fusicoccanes. Through experimentation and enzyme engineering, the team identified improved enzyme variants tailored to the synthetic process. The study marks a significant advancement in chemical synthesis techniques, leveraging modern organic chemistry and engineered enzymes.

“This work demonstrates the importance of enzyme engineering in enabling the synthesis of biologically relevant compounds,” Dr. Renata said. “By harnessing the power of engineered enzymes, we’ve achieved the synthesis of these complex molecules and also paved the way for further chemical modifications.” This work, published in Nature Chemistry on May 6, may facilitate similar innovations in the synthesis of other valuable molecules, prompting advancements in a variety of fields.

Rice University recruited Dr. Renata in May 2022 with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR220087).

197. Imaging genetics is a research field focused on understanding how genetic variations influence observable traits or diseases using medical imaging. However, imaging genetics has mostly relied on traits identified by human experts. In this study, corresponding author Rui Chen, Ph.D., professor, Molecular and Human Genetics at Baylor College of Medicine, and colleagues proposed a new approach, image-based genome-wide association study (iGWAS), to explore genetic factors associated with phenotypes using paired images of the inner wall of the eye and genetic data from the UK Biobank.

The team used an algorithm that automatically identifies features in images of the inner wall of the eye that are unique to each individual yet consistent between their left and right eyes. These features are represented as a set of 128 numbers that can quantitatively describe the characteristics of these images without the bias of human labeling. The findings, published in PLOS Genetics on May 10, indicate that this method was able to extract endophenotypes and identify genes relevant to the retina, including retina colors, retinal vessel development, and eye diseases such as glaucoma, diabetic retinopathy, and age-related macular degeneration. The benefit of self-supervised-learning-derived phenotypes is that they do not require external training labels. Researchers can leverage big datasets to improve understanding of diseases, using self-supervised methods to efficiently extract meaningful information from medical images.

The University of Texas Health Science Center at Houston received a $5.8 million CPRIT Core Facility Support Awards grant (RP170668) in August 2017.

198. Chimeric antigen receptor (CAR) T cells, a therapy used to treat B cell malignancies, can identify T cell subsets which are particularly effective at fighting cancer. In this study, corresponding author Navin Varadarajan, Ph.D., professor, Department of Chemical and Biomolecular Engineering at the University of Houston, and colleagues used infusion products of individuals with large B cell lymphoma to integrate functional profiling using advanced techniques.

The team identified a specific group of CD8+ T cells called CD8-fit T cells, which are capable of migration and serial killing and maintain balanced mitochondrial and lysosomal volumes. When cells have the right balance of mitochondria and lysosomes, it helps them stay healthy and operate efficiently. As published in Nature Cancer on May 15, the results revealed that this combined

approach is powerful for discovering and applying the optimal CD8-fit T cells, which could lead to better treatment for B cell malignancies. Additionally, the data revealed that the CD8-fit signature is present in pre-manufactured T cells, longitudinally persists in patients post-infusion, and most importantly, is associated with long-term positive clinical responses.

Baylor College of Medicine received a $4 million CPRIT Core Facility Support Awards grant (RP200504) in 2020 to support the Comprehensive Cancer Epigenomics Core Facility. University of Houston received a $1.2 million CPRIT Individual Investigator Research Awards grant (RP180466) in February 2018 to study immune cells directly from patients undergoing treatment within Texas to identify biomarkers of responses.

199. Ferroptosis is a type of programmed cell death that occurs when iron and lipid peroxides accumulate in cells. Cellular sensitivity to ferroptosis is controlled primarily by how well the cell can manage and neutralize harmful molecules called lipid hydroperoxides. Albert C. Koong, M.D., Ph.D., division head and professor, Division of Radiation Oncology at The University of Texas MD Anderson Cancer Center, and fellow researchers set out to define the elusive role of the unfolded protein response (UPR) in regulating ferroptosis.

In this study, the team showed that the protein, inositol-requiring enzyme 1 (IRE1α), also determines cellular sensitivity to ferroptosis. Cancer and normal cells depleted of IRE1α gain resistance to ferroptosis, while enhanced IRE1α expression promotes sensitivity to ferroptosis. The results, published in Nature Communications on May 15, revealed a previously unidentified function of IRE1α in determining cellular sensitivity to ferroptosis, a finding that may lead to the development of treatment strategies for ferroptosis-associated normal tissue damage and improvement in the efficacy of existing cancer therapies.

The University of Texas MD Anderson Cancer Center received two CPRIT Individual Investigator grants (RP190192, RP230072) totaling $1.9 million in February 2023 to facilitate the translation of the most promising XBP1 inhibitors into potentially curative treatment strategies for TNBCs.

200. Transient Receptor Potential Vanilloid Type 2 (TRPV2) is a protein found in cells that acts like a sensor which helps cells detect and respond to changes in their environment. TRPV2 plays an important role in cancer progression, immune response, and neuronal development. Despite TRPV2's physiological impact, scientists still don't fully understand how TRPV2 works or which endogenous proteins help it carry out its functions.

CPRIT Scholar Marian Kolacsay, Ph.D., assistant professor, Department of Experimental Radiation Oncology at The University of Texas MD Anderson Cancer Center, and colleagues leveraged APEX2-MS proximity labeling proteomics to identify and quantify which proteins are near TRPV2 when it's active. They found many proteins that could play a role in how TRPV2 influences cell behavior. The results, published in Science Direct on May 9, revealed valuable insights into the intricate interplay between TRPV2, calcium signaling proteins, and cell adhesion molecules. The functional connections they established spotlight the significance of TRPV2 in orchestrating cellular response.

The University of Texas MD Anderson Cancer Center recruited Dr. Kalocsay in February 2022 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR220032).

201. The Ataxia-Telangiectasia Mutated (ATM) gene is a tumor suppressor involved in mediating pathways affecting cancer cell survival and proliferation. Aberrations resulting in ATM LOF (loss of function) can lead to multiple cancers, but clinical studies of therapies targeting ATM-aberrant cancers have yielded mixed results. Scientists including Funda Meric-Bernstam, M.D., chair of the Department of Investigational Cancer Therapeutics and the medical director of the Institute for Personalized Cancer Therapy at The University of Texas MD Anderson Cancer Center, are working to identify the optimal biomarker of ATM LOF in cancer to direct targeted therapy selection, interpret clinical results, and improve patient outcomes.

In this study, the team presented the first disclosure and preclinical development of a novel drug, ART0380, a selective ATR inhibitor, and tested its antitumor activity in multiple preclinical cancer models. Next, the researchers assessed a novel ATM LOF biomarker approach in retrospective clinical data sets of patients treated with platinum-based chemotherapy or ATR inhibition. The findings, reported in Clinical Cancer Research on May 15, confirmed that their method of identifying ATM LOF could help predict who might benefit most from treatments like ART0380 or certain chemotherapy drugs. Thus, ATM LOF is a promising therapeutic target in certain patient populations.

The University of Texas MD Anderson Cancer Center received a $6 million CPRIT Core Facility Support Awards grant (RP150535) in May 2015 for the Precision Oncology Decision Support Core.

202. Limb-sparing internal hemipelvectomy surgery, which removes part of the pelvis and replaces it with a custom prosthesis, offers a promising option for pelvic cancer patients. However, little is known about how well custom prosthesis reconstruction with a total hip replacement helps restore pre-surgery walking function and neural control. CPRIT Scholar B. J. Fregly, Ph.D., professor of mechanical engineering and bioengineering at Rice University, and fellow researchers aimed to develop a computational methodology that can predict a patient's post-surgery walking function from his pre-surgery walking data and the planned surgical decisions.

The team conducted a case study which combined comprehensive walking data with personalized neuromusculoskeletal computer models to analyze changes in walking function and neural control for a single pelvic sarcoma patient after internal hemipelvectomy surgery with custom prosthesis reconstruction. The data, published in Frontiers in Bioengineering and Biotechnology on May 17, revealed that although the patient's post-surgery walking looked mostly normal, the participant exhibited substantial changes in his walking function when quantified using experimental data. This study provides important insights that could enhance post-surgery walking function by improving custom prostheses design and modifying surgical decisions. It also lays the groundwork for developing computer tools that could predict a patient's walking function after surgery based on their pre-surgery data, helping doctors personalize treatments and rehabilitation plans.

Rice University recruited Dr. Fregly from the University of Florida in May 2017 with the support of a $5.1 million CPRIT Recruitment of Established Investigators grant (RR170026).

203. Hepatocellular carcinoma (HCC) is the third-leading cause of cancer-related mortality worldwide, according to 2020 data from the World Health Organization, with limited treatment options and a five-year survival rate of about 30%. Cancer cells process nutrients and energy differently than normal cells and because of these differences, understanding their specific nutritional needs could reveal vulnerabilities that scientists could target for treatment.

Researchers, led by Maralice Conacci-Sorrell, Ph.D., associate professor of cell biology at The University of Texas Southwestern Medical Center, discovered that liver cancer cells, particularly those driven by the MYC gene, rely heavily on the amino acid tryptophan compared to normal cells. These cancer cells take in more tryptophan but do not use it as efficiently as normal cells. By removing tryptophan from the diet of mice, the team stopped the growth of MYC-driven liver tumors and restored normal gene function in liver cells. Notably, this tryptophan deprivation did not harm normal cells, which suggests a potential treatment strategy that targets cancer cells without affecting healthy tissue. Additionally, this study, published in Nature Communications on May 20, identified a specific tryptophan-derived substance, indole 3-pyruvate (I3P), which helps these liver cancer cells grow, pointing to I3P as a potential target for future HCC treatments.

The University of Texas Southwestern Medical Center received a $3.4 million Research Training grant (RP210041) in 2021 and a $1.05 million CPRIT Individual Investigator grant (RP220046) in 2022.

204. A ketogenic diet (KD), which is high in fat and low in carbohydrates, is known for its potential health benefits, like weight loss and managing certain conditions. However, a new study revealed that KDs can also lead to harmful effects, including cellular senescence (the cessation of cell division) leading to pro-inflammatory effects.

Researchers, led by CPRIT Scholar David Gius, M.D., Ph.D., professor in radiation oncology and the assistant dean of research at The University of Texas Health Science Center at San Antonio, tested two types of KDs—one based on Crisco and another on cocoa butter—and found that both could trigger cellular aging in mice in multiple organs, including the heart and kidney.

The results of the in vivo mouse experiments, published in Science Advances on May 17, showed that a KD can trigger a chain reaction that activates p53 signaling through AMPK activation combined with inactivation of MDM2, ultimately leading to cellular aging in multiple organs. However, by following an intermittent KD, they reversed these effects. The data revealed that the effects of KD are complex, with both potential benefits and side effects likely due to multiple factors, including the timing, composition of the diet and the genetics, endocrine factors, and health conditions of the individual. The researchers suggest that carefully timed breaks in the diet could enhance its benefits while minimizing risks, supporting a personalized approach to using KD.

The University of Texas Health Science Center at San Antonio recruited Dr. Gius in 2020 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR200112). The Methodist Hospital Research Institute received a $250,000 CPRIT High Impact/High Risk grant

(RP220650) in 2022 to remodel obesity induced tumor inflammation in patients with TNBC.

205. Acute myeloid leukemia (AML) with p53 mutations is resistant to existing therapies, and scientists do not understand how these mutations lead to the development of AML. To learn more, researchers led by Rasoul Pourebrahim, M.D., Ph.D., Michael Andreeff, M.D., Ph.D., Department of Leukemia, along with CPRIT Scholar Peter Van Loo, Ph.D., Department of Genetics at The University of Texas MD Anderson Cancer Center, investigated the complex role of p53 mutations in hematopoietic stem cells (HSCs).

The researchers generated the first preclinical models of p53-mutant clonal hematopoiesis to explore the molecular mechanisms of AML development and progression. Through a series of complementary genetic models, the team showed that age significantly influences how p53 mutations lead to different types of blood cancers in mice. In older mice, mutations were more likely to cause AML, while in younger mice, they led to other blood cancers.

These findings, published in Cell Reports Medicine on May 21, present a valuable mouse model for studying the role of mutant p53 in AML and offer insight for developing potential early therapeutic targets to prevent the development of AML in patients with p53 mutations.

The University of Texas MD Anderson Cancer Center recruited Dr. Van Loo in November 2020 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR210006). MD Anderson received a $6 million CPRIT Multi-Investigator Research Awards grant (RP160693) in 2016 to study acute myeloid leukemia in the immunosuppressed microenvironment.

206. Advances in cancer treatment, such as the introduction of targeted therapies, immunotherapies, and molecular biomarkers, has led to larger patient data sets. Integrating this data from various platforms and using it effectively for large-scale oncology applications is a growing challenge. Dynamic operations platforms allow for cross-platform data extraction, integration, and analysis; however, researchers have not reviewed the application of these platforms to large-scale oncology enterprises.

To address this, researchers at The University of Texas MD Anderson Cancer Center led by CPRIT Scholar John Paul Shen, M.D., assistant professor, Department of Gastrointestinal Medical Oncology, and Abhineet Uppal, M.D., Department of Colon and Rectal Surgery, developed an automated method for extracting, integrating, and validating cross-platform oncology data in patients undergoing treatment for rectal cancer.

Using this system, the team extracted demographic, clinicopathologic, tumor mutation, radiographic and treatment data from the electronic health records of 516 patients with localized rectal cancer treated at MD Anderson Cancer Center between 2016 and 2022. The platform improved accuracy for various data categories, including tumor and lymph node classifications, as well as chemotherapy and radiation therapy data. The study, published in JCO Clinical Cancer Informatics on May 17, demonstrates the potential of automated data integration to increase efficiency in clinical research and to optimize patient outcomes.

The University of Texas MD Anderson Cancer Center recruited Dr. Shen from the University of California, San Diego in 2018 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR180035).

207. Prostate cancer (PCa) is the second most prevalent cancer and the second leading cause of cancer-related deaths among men in the United States. Although effective initially, prolonged androgen deprivation therapy (ADT) promotes neuroendocrine differentiation (NED) and PCa progression.

To understand the mechanisms of NED in prostate cancer cells, Wenliang Li, Ph.D., associate professor at The University of Texas Health Science Center at Houston, and colleagues investigated the links between ADT and key proteins involved in prostate cancer: CREB1, EZH2, and REST. The findings, published in Cell Death Discovery on May 22, revealed that REST, which usually suppresses certain genes, is turned off by EZH2, in neuroendocrine prostate cancer (NEPC). This EZH2-REST interaction is crucial for triggering NED, which makes the cancer more resistant to treatment.

The study also showed a direct link between two important regulators of neuron-related genes, CREB1 and REST, revealing how they work against each other. These discoveries deepen understanding of prostate cancer progression and could lead to new treatments, bridging fields including cancer progression, drug resistance, cellular differentiation, epigenetic regulation, and neurobiology.

The University of Texas Health Science Center at Houston received a $900,000 CPRIT Individual Investigator grant (RP170330) in November 2016 to obtain critical new insights in neuroendocrine prostate cancer (NEPC) biology, to identify new drug targets, and to facilitate the development of effective therapy for NEPC.

208. Children with diffuse midline glioma (DMG) and other treatment-refractory CNS tumors do not respond to conventional treatments. CNS tumors create an immunosuppressive tumor microenvironment that weakens the immune system's ability to fight back, including shutting down CAR T cell therapy, partially due to limited availability of immunostimulatory cytokines.

To improve T cell activity against these malignancies, researchers at Texas Children's Cancer Center and the Center for Cell and Gene Therapy at Baylor College of Medicine modified CAR T cells to include a special receptor called C7R, which boosts their activity, with a constitutively active interleukin (IL)-7 receptor. In this phase I study, the team examined the safety and efficacy of C7R-GD2.CART cell therapy in children with incurable recurrent CNS tumors. The results, published in the Journal of Clinical Oncology on May 21, revealed that the incorporation of C7R into GD2.CARTs appeared to improve clinical benefit and tumor regression in some patients.

"This study shows that this therapy can effectively get to the tumor, and the addition of C7R safely augments antitumor activity," said senior author Bilal Omer, Ph.D., associate professor of pediatrics – hematology and member of the Center for Cell and Gene Therapy and oncologist at Texas Children's Cancer Center. In the next arm of the study, researchers plan to study the best way to

deliver the therapy, intravenously or directly into the spinal fluid, for the best response to treatment and investigate why some patients respond to treatment better than others. Their goal is to improve and extend the treatment's effectiveness for more patients.

Baylor College of Medicine received a $5.3 million CPRIT Core Facility Support Awards grant (RP180785) in August 2018 to manufacture and test vectors that can improve the activity of cell therapies. BCM received a $1.5 million CPRIT Individual Investigator Research Awards for Clinical Translation grant (RP190067) in February 2019 in support of this Phase I clinical trial.

209. Lysosomes act as the cell's recycling centers by breaking down and recycling materials that the cell no longer needs or that come from outside the cell. When lysosomal transport proteins malfunction, they can lead to rare genetic disorders known as lysosomal storage diseases (LSDs). Researchers from The University of Texas Southwestern Medical Center and collaborating institutions set out to understand the mechanisms of these key transport systems to aid in therapeutic development to treat LSDs.

Mutations in Sialin, a member of the solute carrier 17 (SLC17) transporter family, are responsible for two devastating neurodegenerative sialic acid storage disorders: Salla Disease and Infantile Sialic acid Storage Disease (ISSD). Using cryo-electron microscopy, the team captured detailed snapshots of Sialin's activity. The results, published in Nature Communications on May 23, allowed the researchers to map out how the protein works and how mutations disrupt its function, leading to both Salla disease and ISSD. Their findings provide a blueprint for understanding these conditions at a molecular level, which could help in developing new treatments.

The University of Texas Southwestern Medical Center received a $5.5 million CPRIT Core Facility Support Awards grant (RP170644) in August 2017 to establish a new Cryo-Electron Microscopy Core Facility and Service for Structure Determination.

210. Most breast cancer-related deaths occur in cases of estrogen receptor-α-positive (ER+) breast cancer. While current treatments combining Endocrine therapies (ET) and CDK4/6 inhibitors work initially, drug resistance develops in 80% of these cases and can lead to lethal disseminated disease.

Researchers at Baylor College of Medicine and collaborating institutions studied proteins in ER+ breast cancers that are resistant to the combination therapy, focusing on enzymes called kinases, whose expression is typically altered in cancer. The researchers had previously developed a laboratory method they called kinase inhibitor pull-down assay (KIPA) that significantly reduced the time necessary for kinase identification. Using KIPA, the team, including CPRIT Scholar Matthew Ellis, MB BChir, Ph.D., professor and director, Lester and Sue Smith Breast Center, identified a key protein, protein kinase, membrane-associated tyrosine/threonine one (PKMYT1), linked to drug resistance. They found that tumors with high levels of PKMYT1 were less responsive to both endocrine therapy and CDK4/6 inhibition.

"These findings suggested that a high PKMYT1 level could be an indicator for treatment response in ER+ breast cancer tumors," said first author Anran Chen, Ph.D., a post-doctoral associate in the Foulds lab during this project. "Because this kinase is involved in the regulation of cell division, we decided to investigate the effect a PKMYT1 inhibitor in clinical development would have on cancer growth." The findings, published in Molecular Cancer Therapeutics on May 23, also

revealed that PKMYT1 could both predict treatment response and serve as a target for new therapies to treat drug-resistant ER+ breast cancer.

Baylor College of Medicine recruited Dr. Ellis in 2014 from Washington University with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR140033). BCM received two CPRIT Research Training grants (RP210027, RP140102) totaling $5.6 million in support of the Baylor College of Medicine Comprehensive Cancer Training Program.

211. Scientists have been working for years to develop a male contraceptive pill, but none are available yet. Previous research focused on a gene, STK33, which is essential for normal sperm development. Mutations in this gene cause abnormal sperm development and infertility in both men and male mice due to defective sperm shape and motility, making STK33 a viable target for reversible male contraception.

CPRIT Scholars Zhi Tan, M.D., Ph.D., and Mingxing Teng, Ph.D., both from the Department of Pathology & Immunology at Baylor College of Medicine, and team used DNA-Encoded Chemistry Technology to screen their multi-billion compound collection and to discover potent STK33 inhibitors. The researchers identified a small molecule, CDD-2807, that disrupts sperm form and motility in mouse models, leading to infertility. The team housed male mice with female mice for up to six weeks, treating the males with either CDD-2807 or untreated controls.

Compared with the control mice, mice treated with CDD-2807 sired few litters, with fewer pups per litter and sired no litters after the first month. Three weeks after stopping treatment, the treated mice sired offspring at the same rate as control mice. The results, published in Science on May 23, revealed that the compound had no clear effect on the overall health or mortality of the mice, it did not accumulate in the brain, the treatment did not alter testis size, and the contraceptive effect was reversible.

Baylor College of Medicine recruited Dr. Teng in November 2021 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR220012). BCM recruited Dr. Tan in February 2022 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR220039). BCM received a $770,000 CPRIT Individual Investigator grant (RP220524) in February 2022.

212. Epithelial-ovarian cancer (OCa) has the highest mortality rates among gynecologic cancers; 90% of patients experience recurrence and resistance to chemotherapy and ultimately pass away. Researchers have been exploring new treatment options and focused on a pathway involving leukemia inhibitory factor (LIF) and its receptor (LIFR), which are linked to poor outcomes in many solid cancers. However, researchers don’t know exactly how essential LIFR is as a therapeutic target or how blocking LIFR will alter the course of OCa.

In this study, the researchers used a variety of lab and patient-derived models to test EC359, a new drug that blocks LIFR signaling. The data, published in npj Precision Oncology on May 24, revealed that treatment with EC359 significantly reduced the growth and survival of OCa cells and induced ferroptosis (a form of cell death). These findings reveal that LIF and LIFR play a crucial role in driving ovarian cancer growth and survival across multiple subtypes of the disease and suggest that targeting the LIF/LIFR pathway with EC359 could be a promising new treatment strategy for ovarian cancer, especially for patients with chemotherapy-resistant disease.

The University of Texas Health Science Center at San Antonio received a $3.64 million CPRIT Core Facility Support Awards grant (RP210126) in August 2021 in support of the Flow Cytometry Shared Resource of the Mays Cancer Center and the UT Health Science Center at San Antonio,

and a $4 million CPRIT Research Training grant (RP170345) in November 2016.

213. Malignant rhabdoid tumors (MRTs) are a group of highly malignant pediatric cancers with poor survival rates. Mutations of the SMARCB1 gene (a tumor suppressor gene) often cause MRTs, and current treatments - resection, conventional chemotherapy, and radiotherapy- offer limited success.

Corresponding author Raushan Kurmasheva, Ph.D., assistant professor, Department of Molecular Medicine at The University of Texas Health Science Center at San Antonio, and colleagues investigated the DNA damage response as a potential therapeutic approach for MRT. The team focused on targeting PARP1, a protein involved in DNA repair and gene regulation, using a specialized inhibitor called PEG~TLZ (a PEGylated version of talazoparib). When combined with temozolomide (TMZ), a chemotherapy drug that induces DNA damage, the treatment showed significant effectiveness in killing MRT cancer cells and shrinking tumors in experimental models.

In this study, the team reported a new potential biomarker, O6-methylguanine methyltransferase (MGMT), which could help predict how well patients respond to this combined therapy. This novel therapeutic approach, published in Cancers on May 28, not only targets cancer cells more effectively but also reduces side effects, offering a more personalized and less toxic treatment option for children with MRT achieved through the combination of PEG~TLZ and TMZ.

The University of Texas Health Science Center at San Antonio received two CPRIT Core Facility Support Awards grants (RP220599, RP220662) totaling $7.93 million.

214. Researchers have identified a crucial protein, hnRNPM, that helps ensure the accuracy of RNA splicing, a critical step in gene expression. This process is essential for producing the correct instructions to make proteins. Splicing involves removing non-coding regions (introns) from RNA, but the complexity of human introns increases the risk of errors.

Researchers, including CPRIT Scholars Chonghui Cheng, M.D., Ph.D., professor, Department of Molecular and Cellular Biology and Eric Van Nostrand, Ph.D., assistant professor, Department of Biochemistry at Baylor College of Medicine, and fellow researchers discovered that hnRNPM binds to deep introns, preventing cryptic splicing—mistakes where unnecessary sequences are included in the final RNA. Without hnRNPM, these errors can lead to the formation of double-stranded RNA (dsRNA), which can mistakenly activate the immune system, potentially contributing to diseases, including cancer.

“Synthesizing a protein is like putting together the different parts of a machine. If during the assembly process, parts that do not belong are incorporated into the machine, the final product would not fulfill its intended function, disturbing the normal workings of the cell and potentially leading to disease,” said co-corresponding author Dr. Cheng. “Despite the many opportunities for such mistakes, cells make proteins highly accurately and precisely. Here we investigated what helps cells maintain the integrity of this vital process.” The findings, published in Molecular Cell on May 29, not only highlight hnRNPM’s role in maintaining cellular function but also suggest it could be a target for developing new cancer therapies, by preventing the errors that disrupt normal protein production.

Baylor College of Medicine recruited Dr. Cheng in 2015 from the Northwestern University Feinberg School of Medicine with the support of a $4 million CPRIT Recruitment of Rising Stars grant

(RR160009). BCM recruited Dr. Van Nostrand in 2020 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR200040).

215. Researchers have extensively studied how the enteric nervous system (ENS) forms during early embryonic development due to the numerous ENS diseases, including Hirschsprung disease, esophageal achalasia, chronic constipation, and gastroesophageal reflux disease. This study sheds light on the previously unrecognized role of opioid receptors in the development of the ENS.

Led by CPRIT Scholar Rosa Uribe, Ph.D., assistant professor of biosciences at Rice University, researchers used a targeted F0 CRISPR screen and zebrafish embryos, which share many genetic similarities with humans, to identify the genes critical for ENS development. Published in PLOS ONE on May 29, 2024, the results pinpointed twelve genes, that when disrupted, led to various ENS development phenotypes across different F0s, or crispants.

The researchers highlighted the opioid receptors, oprl1 and oprd1b, as key players. Disruption of these genes resulted in severe ENS development defects, revealing a critical role for these receptors beyond their established function in mediating responses to hormones, neurotransmitters, and drugs. Their subsequent investigations confirmed that opioid receptors are not merely involved in signaling pathways but are integral to the developmental establishment of gut nerves. This discovery offers new insights into how the gut's nervous system forms and opens doors to potential therapeutic strategies for addressing ENS-related diseases. Dr. Uribe emphasized the broader implications of this work, suggesting it could transform the understanding and treatment of digestive disorders by targeting the opioid receptor pathways.

Rice University recruited Dr. Uribe in August 2017 from the California Institute of Technology with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR170062).

216. Up to 90% of patients undergoing chemotherapeutic treatments experience chemotherapy-induced intestinal damage. Beyond the manifestation of distressing symptoms like nausea, vomiting, diarrhea, and pain, chemotherapy-induced intestinal damage can compromise the effectiveness of treatments, leading to worse clinical outcomes and potential increased cost of care.

The gastrointestinal tract is particularly sensitive to antineoplastic drugs such as methotrexate (MTX) and 5-Fluorouracil (5-FU) which inhibit cell growth and division. Studies have implicated the role of IL-22 and ILC3s in mucosal repair following MTX-induced intestinal damage, however the role of other immune components and cytokines are less defined.

Researchers from The University of Texas Health Science Center at San Antonio, including Alexei Tumanov, M.D., Ph.D., associate professor, Department of Microbiology, Immunology, and Molecular Genetics, and international colleagues investigated the role of lymphotoxin beta receptor (LTβR) signaling in chemotherapy-induced intestinal damage using animal models of disease. The results, published in Frontiers in Immunology on May 29, revealed a previously unrecognized role for the LTβR-RelB pathway in intestinal epithelial cells which promotes mucosal repair after chemotherapy-induced intestinal damage. These findings provide valuable insights which pave

the way for potential therapeutic interventions.

The University of Texas Health Science Center at San Antonio received three CPRIT Academic Research grants (RP210105, RP220470, RP210126 – core facility) totaling $4.9 million.

217. Scientists have developed numerous lung cancer risk prediction models to identify individuals at high risk of lung cancer and who may benefit from lung cancer screening. Samir Hanash, M.D., Ph.D., director, Department of Red and Charline McCombs Institute for the Early Detection and Treatment of Cancer, and professor, Department of Clinical Cancer Prevention at The University of Texas MD Anderson Cancer Center, and fellow researchers determined that they could use biomarkers to improve lung cancer risk assessment even further.

The team evaluated the performance of a four-marker protein panel (4MP) for predicting lung cancer risk, focusing on a cohort inclusive of never- and ever-smokers. Using blinded pre-diagnostic plasmas collected from 25 cases from participants in the Physicians' Health Study (PHS) cohort, the team analyzed data from cases diagnosed within two years. The findings in this validation study, published in Cancers on May 30, demonstrated that the 4MP could reliably identify individuals at high risk of lung cancer up to two years prior to clinical diagnosis, regardless of smoking status. Notably, this predictive capability was effective regardless of smoking status, emphasizing the panel's potential to address lung cancer risk in a more comprehensive manner.

This early identification can provide a valuable two-year head start in the treatment of lung cancer, allowing for timely interventions that significantly enhance the likelihood of successful outcomes. This advancement underscores the critical role of biomarker-driven approaches in modern lung cancer screening programs, particularly for individuals who might not qualify for traditional screening methods based on smoking history alone.

The University of Texas MD Anderson Cancer Center received a $6 million CPRIT Multi-Investigator Research Awards grant (RP160693) in 2016 to study acute myeloid leukemia in the immunosuppressed microenvironment.

218. In multicellular organisms, aging affects the functions of all types of cells. Scientists are still determining how the changes that come with age differ in various tissues at cellular resolution. Single-cell and single-nucleus RNA sequencing (scRNA-seq and snRNA-seq) are tools that allow scientists to explore gene activity at a cellular resolution, identifying distinct patterns in various cell types.

In this study, CPRIT Scholar Hongjie Li, Ph.D., assistant professor, Department of Molecular and Human Genetics at Baylor College of Medicine, and colleagues analyzed snRNA-seq data from wild-type (WT) adults at different ages and constructed tissue-specific transcriptomic aging clocks, which track molecular changes associated with aging in specific tissues. Additionally, they developed germ cell differentiation trajectory maps, providing detailed insights into how aging influences reproductive cell function. This dual approach, published in Nature Aging on May 30, revealed how aging affects both somatic and germ cells at the molecular level, uncovering the unique mechanisms at play within distinct tissues. The study serves as a critical resource for exploring the diverse pro-longevity mechanisms that contribute to cellular resilience and may inform future strategies for mitigating age-related decline. These findings also highlight the potential for target-

ed interventions to preserve tissue-specific functions as organisms age.

Baylor College of Medicine received a $5.17 million CPRIT Core Facility Support Awards grant (RP180672) in August 2018 to purchase high-end equipment. Baylor College of Medicine recruited Dr. Li in August 2020 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR200063).

219. Neurogenetic disorders can cause cognitive and motor impairments, traditionally attributed to neuronal defects. One such disorder is neurofibromatosis type 1 (NF1), a cancer predisposition syndrome in which affected individuals are also prone to learning, behavioral and motor deficits. In this study, CPRIT Scholar Yuan Pan, Ph.D., assistant professor, Department of Symptom Research at The University of Texas MD Anderson Cancer Center, and colleagues reveal that oligodendrocyte progenitor cells (OPCs) also play a critical role.

Using a mouse model of NF1, the researchers found that the Nf1 mutation delays the development of oligodendrocytes and disrupts the activity-dependent functions of OPCs, which are essential for motor learning. This indicates that the proper adaptation of oligodendrocytes to neuronal activity—a key aspect of brain plasticity—is impaired in NF1. Published in Nature Neuroscience on May 30, these findings show that oligodendroglial plasticity is not only vital for motor and cognitive functions in a healthy brain but also contributes to the neurological dysfunction observed in NF1. This study expands the understanding of NF1 pathophysiology and points to oligodendrocytes as a potential target for therapeutic strategies aimed at mitigating motor and cognitive impairments in NF1 patients.

The University of Texas MD Anderson Cancer Center recruited Dr. Pan in August 2021 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR210085).

220. Purine nucleotides are vital building blocks for making RNA and DNA, sending signals in cells, regulating metabolism, and energy homeostasis. Cells create purines through two main processes: the de novo pathway, which builds purines from scratch, and the salvage pathway, which recycles purines. Scientists believed that rapidly dividing cells use the de novo pathway, while mature tissues use the salvage pathway.

CPRIT Scholar Gerta Hoxhaj, Ph.D., assistant professor in Children's Medical Center Research Institute and the Departments of Pediatrics and Biochemistry at The University of Texas at Southwestern Medical Center, and colleagues used a special technique called isotope tracing to study how purine nucleotides are made and recycled in both normal mouse tissues and various cancers, including breast, kidney, colon, and liver cancers. Normal tissue analyses showed the kidney salvaged the most purines, which might explain why people with kidney disease have a higher risk of gout. Gout, a painful type of arthritis, occurs when uric acid, a byproduct of purine breakdown, builds up in the body.

When conducting the same analyses on tumors, they discovered that cancer cells use both de novo and salvage pathways to meet their high demand for purines. They also found that tumors grew faster when mice consumed a high-purine diet, suggesting that dietary purines can contribute to cancer growth. These findings, published in Cell on May 31, highlight the crucial role the

salvage pathway plays in tumor growth.

“While our food provides sugars, proteins, and fats, it also supplies purine nucleotides, especially from meat products. Our research could pave the way for doctors to include dietary interventions when creating a treatment strategy for cancer patients – restricting nucleotide availability could be a new tool to slow cancer progression,” Dr. Hoxhaj said.

The University of Texas Southwestern Medical Center recruited Dr. Hoxhaj in 2019 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR190087).

221. Pediatric high-grade glioma (pHGG), is an aggressive brain cancer that often spreads widely through the brain, making it hard to treat. Researchers aimed to understand what drives this spread to develop new therapies targeting cancer invasion.

Researchers including Peter Davies, M.D., Ph.D., professor, director, Center for Translational Cancer Research at Texas A&M University System Health Science Center, used ten patient-derived models of pHGG and subjected them to isolation of matching pair of invasive (HGGINV) and tumor core (HGGTC) cells. When the researchers implanted CD57+ cells into mouse brains, the cancer spread widely, mimicking the behavior of pHGG. However, when they removed CD57+ cells, the cancer’s ability to spread dropped significantly.

The findings, published in British Journal of Cancer on June 4, confirmed CD57 as a novel glioma stem cell marker and identified two key types of invasive cells: CD57+CD133− and CD57+CD133+. The data suggests a new dual-mode hierarchy of glioma stem cells driving pHGG invasion, providing valuable insight into how the cancer spreads and offering potential targets for anti-invasion therapies.

Texas A&M University System Health Science Center received two CPRIT Core Facility Support Awards grants (RP200668, RP150578) totaling $9.9 million to support the Combinatorial Drug Discovery Program.

222. Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. HCC occurs most often in people with chronic liver diseases, such as cirrhosis caused by hepatitis B or hepatitis C infection. Doctors across the cancer care continuum have difficulty diagnosing patients with HCC, leading to frequent late-stage diagnoses and high mortality. Amit G. Singal, M.D., professor, Department of Internal Medicine, medical director of the Liver Tumor Program, and chief of Hepatology at The University of Texas Southwestern Medical Center, and colleagues set out to evaluate the effectiveness of mailed outreach invitations plus patient navigation in patients with cirrhosis to promote HCC screening completion.

The team conducted a multicenter, pragmatic randomized clinical trial comparing mailed outreach plus patient navigation for HCC screening (n=1436) versus usual care with visit-based screening (n=1436) among patients with cirrhosis at three United States health systems between April 2018 and September 2021. The primary outcome was screening process completion over a 36-month period, and the secondary outcome was the proportion of time covered by screening. The results, published in BMJ Journals-Gut on June 5, revealed that this intervention increased HCC screening process completion across most subgroups, including age, sex, race and ethnicity. The find-

ings also exhibited that screening completion remained suboptimal in both arms, emphasizing a need for more exhaustive interventions.

Baylor College of Medicine received a $9.77 million CPRIT Multi-Investigator Research Awards grant (RP150587) in 2015 to support the Texas Hepatocellular Carcinoma Consortium.

223. Chemotherapy, such as cisplatin, is a widely used ovarian cancer treatment, but many patients face chemoresistance, where cancer cells stop responding to treatment, particularly in recurrent tumors. Although new FDA approved chemotherapeutic drugs have improved the survival of patients, chemoresistance remains a major challenge in the treatment of recurrent tumors. Researchers have found that proteins in the IL6-family, which includes Oncostatin M (OSM) and its receptor (OSMR), play a role in chemotherapy resistance.

In this study, researchers including Zhiqiang An, Ph.D., professor of Molecular Medicine, chair in the Department of Chemistry, and director of the Texas Therapeutics Institute at the University of Texas Health Science Center at Houston, discovered that the OSMR gene is significantly more active in chemoresistant ovarian cancers. To counteract this, they developed monoclonal antibodies to target the extracellular domain of OSMR, blocking the signals that help cancer cells resist chemotherapy. The results, published in npj Precision Oncology on June 5, reported a significant reduction in the growth of cisplatin-resistant ovarian cancer cells and an improved response to cisplatin in both lab experiments and animal models.

These findings suggest that targeting OSMR with these antibodies could be a powerful way to overcome chemoresistance and make ovarian cancer treatments more effective, offering hope for improved outcomes in patients with recurrent disease.

The University of Texas Health Science Center at Houston received two CPRIT Core Facility Support Awards grants (RP190561, RP150551) totaling $11.2 million.

224. Subclonal reconstruction is the process of analyzing a tumor's genetic mutations to understand the different groups of cancer cells within the tumor. Using this process, researchers can mathematically quantify individual tumor evolution from bulk DNA sequencing data. This helps them understand how cancers begin, progress, and adapt to their environment to develop better treatment strategies. However, the results from subclonal reconstruction can vary substantially from algorithm to algorithm. CPRIT Scholar Peter Van Loo, Ph.D., Department of Genetics at The University of Texas MD Anderson Cancer Center, and colleagues set out to identify which subclonal reconstruction algorithms are most accurate.

Researchers assembled a team of international experts to form the ICGC–TCGA (International Cancer Genome Consortium–The Cancer Genome Atlas) DREAM Somatic Mutation Calling Challenge. Over seven years, they tested 31 subclonal reconstruction algorithms on 51 simulated tumors using cloud computing. The findings, published in Nature Biotechnology on June 11, revealed that only a small number of specific tumor features significantly impact the accuracy of subclonal reconstruction. No single algorithm was a top performer for all tasks and existing ensemble strategies were unable to outperform the best individual methods. These findings provide valuable insights and resources to optimize the use of current subclonal reconstruction methods and guide the improvement and development of more advanced algorithms.

The University of Texas MD Anderson Cancer Center recruited Dr. Van Loo in November 2020 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR210006).

225. Understanding how genes are expressed is crucial for accurately predicting important regulatory functions in cells, such as identifying where genes start and where specific proteins attach to control gene activity. Currently, scientists depend on supervised learning, but this relies on labeled genomic data, which is often scarce and limits the development of robust predictive models.

This study focuses on self-supervised training to improve DNA sequence modeling, particularly for identifying non-coding regulatory elements. Tao Wang, Ph.D., associate professor, Department of Public Health at The University of Texas Southwestern Medical Center, and fellow researchers used their Motif-oriented DNA (MoDNA) pre-training framework to advance DNA language models. MoDNA uses a vast amount of unlabeled genomic data to efficiently learn patterns and representations of DNA. By incorporating DNA motifs—specific sequences that play functional roles—as core domain knowledge, MoDNA demonstrated superior accuracy and computational efficiency compared to existing DNA language models.

The results, published in BioMedInformatics on June 12, highlight MoDNA's potential to advance genomic analysis. In the future, the team plans to extend their training datasets to include a diverse range of organisms and incorporate advanced algorithms that better capture genetic variability and conservation across species.

The University of Texas Southwestern Medical Center received a CPRIT Individual Investigator Research Awards for Computational Biology grant (RP230363) in February 2023 to develop a suite of knowledge-guided deep learning models to predict the binding between T cell receptors (TCRs) and T cell antigens.

226. Gene editing is a groundbreaking technology designed to correct disease-causing mutations in the genome, holding the potential to transform medicine. Although scientists have used stem cell editing for some genetic diseases, challenges remain, including targeting relevant stem cells and efficient editing of cells directly in an organism.

The Siegwart Lab introduced a new approach in 2020 called Selective Organ Targeting (SORT), which uses specialized components in lipid nanoparticles (LNPs) to direct gene-editing tools to specific organs. Although researchers demonstrated that SORT could deliver gene-editing machinery to the lungs, it wasn't clear whether this method could successfully edit lung stem cells.

In this study, Daniel Siegwart, Ph.D., associate professor, Department of Biochemistry at The University of Texas Southwestern Medical Center and co-founder of ReCode Therapeutics, and colleagues expanded SORT to target all lung cell types, including lung stem cells, using patient-derived cells and a mouse model of cystic fibrosis (CF). The team achieved over 70% editing efficiency in mouse lung stem cells, with the effects lasting up to a year.

The results, published in Science on June 13, suggest that gene editing using SORT could provide long-lasting benefits for patients with genetic lung diseases like CF. However, more research is necessary to investigate this approach in animal models that share CF symptoms and to ensure the safety of this prospective therapy.

The University of Texas Southwestern Medical Center received a $4 million CPRIT Core Facility Support Awards grant (RP210099) in August 2021 to support the North Texas Multimodal Small Animal Imaging Core Facility.

227. Glioblastoma is the most common type of primary brain cancer in adults with an approximate

median overall survival of 21 months. For recurrent glioblastoma, there are currently no available treatment options. Recent studies showed that activation of the stimulator of interferon (IFN) genes (STING) pathway increases antitumoral immune responses in gliomas and melanoma. In this study, researchers from The University of Texas MD Anderson Cancer Center and collaborating institutions hypothesized that activating the STING pathway in glioblastoma tumor cells could transform immunosuppressive myeloid cells within the tumor into anti-tumor inflammatory cells that can be detected by the body's adaptive immune system.

By analyzing RNA sequencing datasets and immunofluorescence multiplex imaging of patient glioblastoma samples, co-first author Spencer T. Lea, CPRIT Graduate Scholar, graduate research assistant (Michael Curran, Ph.D.) in the MD Anderson Cancer Center Department of Immunology, and team found that STING pathway activation occurs in subsets of myeloid cells, including microglia, which mediate immune responses. An ex vivo analysis revealed that the agonist, successfully induced immune responses in T-cells and NK (natural killer) immune cells from surrounding lymphatics. The findings, published in the Journal of Clinical Investigation on June 17, revealed that STING agonists have the distinct elements necessary to eradicate the tumor and lend strong support for further investigation in the clinic.

"It's not so much reinvigoration of a prior failed immune response but rather a nucleation of a new response directed toward the tumor," said Michael Curran, Ph.D., associate professor of Immunology at The University of Texas MD Anderson Cancer Center and co-corresponding author of the study. "The trigger of the STING pathway turns an otherwise quiescent, calm bed of cells into one that is highly visible to the immune system and is calling out to be investigated and possibly eliminated."

The University of Texas MD Anderson Cancer Center received a $4 million CPRIT Research Training grant (RP210028) in May 2021 to provide a comprehensive learning environment focused solely on cancer, to position trainees for successful careers in cancer research.

228. Chromosome instability (CIN) and aneuploidy are key characteristics of cancer. Chemotherapy-induced polyploidy (CIP) is a process where cancer cells develop extra chromosomes, making them resistant to treatment and causing more aggressive disease. Interestingly, chemotherapy, the standard treatment for diffuse large B-cell lymphoma (DLBCL), gradually increases ploidy (the number of complete sets of chromosomes in a cell) and is a known mechanism for drug resistance.

The Aurora Kinase (AK) family of enzymes plays a crucial role in proper cell division, ensuring that cells maintain the correct number of chromosomes and reducing the risk of errors that can lead to cancer. In DLBCL, the drug alisertib disrupts the cell cycle, causing cells to develop abnormal chromosome numbers (polyaneuploidy). In this study, corresponding author Eloise Dray, Ph.D., assistant professor, Department of Biochemistry and Structural Biology at The University of Texas Health Science Center at San Antonio, and researchers aimed to counteract this resistance mechanism by combining alisertib with Aurkin A, a drug that blocks interaction between two proteins, Aurora Kinase A (AK-A) and TPX2, which is essential for cell division.

The researchers found that alisertib alone caused nearly half of the cancer cells to develop excessive chromosomes after five days. Using live cell imaging to monitor cell division, the researchers

discovered that this was due to a process called endomitosis, where cells replicate their DNA without dividing properly. However, the addition of Aurkin A prevented endomitosis, reduced polyploidy, and increased cancer cell death.

In mouse models of DLBCL, the combination of Aurkin A and alisertib significantly reduced the number of resistant cells compared to alisertib alone. This combination also allowed for lower doses of alisertib while enhancing its effectiveness. These findings, published in ScienceDirect on June 14, suggest that combining Aurkin A with alisertib could improve treatment outcomes for patients with DLBCL and potentially other cancers that develop resistance through polyploidy.

The University of Texas Health Science Center at San Antonio received a $3.64 million CPRIT Core Facility Support Awards grant (RP210126) in August 2021 in support of the Flow Cytometry Shared Resource of the Mays Cancer Center and the UT Health Science Center at San Antonio.

229. Osteogenesis imperfecta (OI) type V, the second most common form of OI, is a form of brittle bone disease caused by a mutation in the gene IFITM5. The mutation blocks the normal development of bone stem cells into mature cells and leads to the formation of bones that are extremely brittle. Children with this disorder suffer from recurrent fractures, bone deformities, chronic pain, and other complications.

Co-corresponding author Brandan Lee, M.D., Ph.D., professor, chair and Robert and Janice McNair Endowed Chair of molecular and human genetics at Baylor College of Medicine, and fellow researchers created a mouse model of OI type V by introducing the mutant gene during certain stages of bone development. These mice exhibited most of the characteristics of the human condition, allowing the team to analyze the underlying molecular mechanisms. The team discovered that the IFITM5 mutation affects bone stem cells, preventing them from developing into mature bone cells.

“Bone stem cells lead the way in the formation of the skeleton during development and in bone healing after a fracture – first, they give rise to cartilage, which then turns into bone,” Dr. Lee said. “Our findings help explain what we see in patients with OI type V. They not only have bones that break easily, but when stem cells attempt to heal them, they form large calluses of cartilage instead of bone.” The findings, published in The Journal of Clinical Investigation on June 17, aid in understanding how OI type V develops and provide new details which could lead to better treatment of similar but more common skeletal conditions, such as osteoporosis.

Baylor College of Medicine received two CPRIT Core Facility Support Awards grants (RP210227, RP180672) totaling $9.2 million.

230. Methaqualone, commonly known as Quaalude, is a central nervous system (CNS) depressant that doctors prescribed in the 1960s–1980s as a sedative-hypnotic. The drug promotes relaxation, calmness, drowsiness, and euphoria, and is an effective anticonvulsant agent. However, methaqualone is highly addictive and was eventually prohibited, yet it persists as a globally abused substance. Understanding the mechanism of action of methaqualone may contribute to the development of safer sedative and anticonvulsant therapeutics especially for patients with epilepsy.

In this study, researchers sought to understand how the methaqualone family of

drugs act on $GABA_A$ receptors. The team used cryo-EM to pinpoint where methaqualone and a stronger version of it, PPTQ, attach to the $GABA_A$ receptor. These drugs bind to the same spots as some general anesthetics, like propofol and etomidate, within the receptor's structure. Interestingly, methaqualone and PPTQ go deeper into the receptor than other known drugs. When they bind, they cause a part of the receptor to widen, which helps to activate it.

This finding, published in Nature Communications on June 19, helps researchers understand how these drugs work and provides new insights into the effects of similar compounds on the $GABA_A$ receptor. The data can guide scientists in designing new versions of these drugs that reduce the risk of abuse while keeping their beneficial effects.

The University of Texas Southwestern Medical Center received a $5.5 million CPRIT Core Facility Support Awards grant (RP170644) in August 2017 to establish a new Cryo-Electron Microscopy Core Facility and Service for Structure Determination at UT Southwestern Medical Center.

231. CD70, a protein that contributes to tumor progression and immune evasion, is a promising target for CAR NK cell therapy. Researchers from The University of Texas MD Anderson and Navin Varadarajan, Ph.D., the University of Houston, sought to create and improve CAR-engineered natural killer (NK) cells designed to target CD70 for use as cancer cell therapies. However, researchers do not fully understand how these signals affect CAR NK cells.

In this study, the team looked at how different costimulatory signals influence CAR-NK cell activity, specifically using a CD70-targeting CAR. They discovered that the CD28 molecule, which isn't naturally found in mature NK cells, greatly improved the cancer-fighting abilities and longevity of CAR NK cells in lab tests and animal models. The findings, published on June 20 in Cancer Discovery, demonstrate that incorporating CD28 can enhance the effectiveness of CAR-NK cells for cancer treatment, suggesting researchers should consider this engineering approach for future NK cell therapies. Based on these results, researchers at MD Anderson have initiated the first-in-human Phase I/II clinical studies to assess the safety and efficacy of CAR27 NK cells with C28 in patients with CD70+ hematologic malignancies and solid cancers.

Baylor College of Medicine received a $3.98 million CPRIT Core Facility Support Awards grant (RP210227) in 2021. University of Houston received a $1.2 million CPRIT Individual Investigator Research Awards grant (RP180466) in 2018.

232. Targeted therapies, cancer treatments directed at specific proteins in cancer cells, hold promise for achieving more effective results than traditional radiotherapy and chemotherapy. However, FDA-approved cancer drugs target fewer than 200 proteins and doctors still treat most cancer patients with radiotherapy and chemotherapy, which are associated with significant recurrence risks and toxicities. Because proteins are primary targets of these therapies, proteogenomics, which encompasses methods that integrate mass spectrometry (MS)-based measurements of protein abundance, provides a powerful framework for the exploration of existing and future targets for cancer treatment.

In this study, led by CPRIT Scholar Bing Zhang, Ph.D., professor of molecular and human genetics and part of the Lester and Sue Smith Breast Center at Baylor College of Medicine, along with CPRIT Scholar Valentina Hoyos, M.D., assistant professor, Center for Cell and Gene Therapy at the Lester and Sue Smith Breast Center, researchers integrated Clinical Proteomic Tumor

Analysis Consortium (CPTAC) proteogenomics data from 1,043 patients across 10 cancer types with additional public datasets to systematically identify proteins and genes that are important for cancer growth and development. The results, published in Cell on June 24, significantly expanded the list of potential therapeutic targets.

“Our study revealed new opportunities for repurposing drugs currently approved for other conditions,” Dr. Zhang said. “For example, we show that an antifungal drug can also reduce growth of several cancer types, supporting further exploration of the anti-cancer value of this drug.”

Baylor College of Medicine recruited Dr. Velez in 2017 from Johns Hopkins University with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR170024). Baylor College of Medicine recruited Dr. Zhang in 2016 from Vanderbilt University School of Medicine with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR160027).

233. Converting methane into liquid fuels and valuable chemicals is a major challenge in chemistry. Traditional methods are inefficient, but using enzymes or microbes shows promise. Typically, processes that rely on oxygen lose a lot of carbon and energy. However, using methods that don’t require oxygen might be more efficient.

Researchers in the Department of Chemical and Biomolecular Engineering, University of Houston, have developed the first genetically encoded biosensors to detect methane activation using a chemical compound called methylsuccinate (MS). These biosensors are based on modified versions of a protein called ItcR. The original ItcR responds strongly to itaconate (IA) but weakly to MS, while the modified version, Var7, responds strongly to MS and less to IA. This demonstrates how small changes in the protein structure can significantly affect its ability to bind and regulate different molecules.

These new biosensors can help quickly identify effective enzyme variants for methane conversion, and they serve as a starting point for creating more sensors for other related chemical processes. As reported in Biosensors on June 30, this advancement could lead to more efficient ways to convert methane and other short-chain alkanes into useful products.

Baylor College of Medicine received a $5.17 million CPRIT Core Facility Support Awards grant (RP180672) in August 2018 to purchase high-end equipment.

234. Humanized mice, mice modified to have human-like immune systems, face challenges in accurately modeling human immunity, especially with regards to antibody responses. This is because many of the over 1,600 immune response genes in mice do not match their human counterparts, leading to differences in how their immune systems function compared to humans. As a result, there is a strong need for a humanized mouse model that better mimics human immune responses.

Scientists at The University of Texas Health Science Center at San Antonio set out to remedy this insufficiency. The aim of the multi-year project, led by Paolo Casali, M.D., professor, Department of Microbiology, Immunology and Molecular Genetics, was to create a humanized mouse with a fully developed and functional human immune system. Using various human cell sources, like bone marrow, fetal liver, and umbilical cord blood, which is especially rich in hematopoietic

stem cells (HSCs), the team developed a new type of humanized mouse, called TruHuX (for truly human, or THX). TruHuX is a fully developed and fully functional human immune system, including lymph nodes, germinal centers, thymus human epithelial cells, human T and B lymphocytes, memory B lymphocytes, and plasma cells making highly specific antibody and autoantibodies identical to those of humans.

As published on June 25 in Nature Immunology, the new THX mice overcome the limitations of earlier models and offer a powerful tool for studying human immune responses in living organisms. These mice are useful for aiding the development of vaccines and treatments for immune-related conditions, including managing unwanted antibody responses.

Dr. Casali hopes that this discovery will make the use of non-human primates for immunological and microbiological biomedical research obsolete, and that it prompts further research into the topic. “By critically leveraging estrogen activity to support human stem cell and human immune cell differentiation and antibody responses, THX mice provide a platform for human immune system studies, development of human vaccines, and testing of therapeutics,” Dr. Casali said.

The University of Texas Health Science Center at San Antonio received three CPRIT Core Facility Support Awards grants (RP210126, RP160732, RP150600) totaling $10.5 million. The University of Texas MD Anderson Cancer Center received a $3.5 million CPRIT Core Facility Support Awards grant (RP190507) in 2019.

235. Cellular senescence is a stress response that causes cells to stop growing to prevent cancer. This can happen with the activation of certain cancer-related genes such as RAS. Although senescent cells don’t grow, they remain active by secreting chemokines and cytokines, known as the senescence-associated secretion phenotype (SASP). This process helps block cancer development, but scientists are still uncovering how it works.

CPRIT Scholar Rugang Zhang, Ph.D., professor and chair, Department of Experimental Therapeutics at The University of Texas MD Anderson Cancer Center, and colleagues have discovered an enzyme, catalytic methyltransferase-like 3 (METTL3), that plays a key role in senescence. METTL3 helps control gene expression and contributes to cellular senescence by creating chromatin loops, which increase the expression of a gene called Hexokinase 2 (HK2). The team revealed that expression of HK2 promotes a process known as stress granule phase separation which stops the production of certain proteins that promote cell growth. This effectively keeps the cells in a non-dividing senescent state.

The findings, published in Nature Communications on June 26, show METTL3’s role in linking HK2 to senescence and provides new insights into how the body prevents cancer. METTL3 plays a previously unknown key role in this connection, which could lead to better understanding and treatment of cancer growth.

The University of Texas MD Anderson Cancer Center recruited Dr. Zhang in November 2022 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR230005).

236. Immune checkpoint therapies (ICT) improve overall survival of cancer patients but may cause immune-related adverse events (irAEs) such as myocarditis, a potentially life-threatening inflammation of the heart. Previous work showed that using the drug CTLA-4 Ig – which inhib-

its T cell activation – can protect against irAEs. However, there is a potential for compromising the antitumor effects of ICT.

In this study, researchers from The University of MD Anderson Cancer Center and co-led by CPRIT Scholar James Allison, Ph.D., professor and chair, Department of Immunology, director of the Parker Institute for Cancer Research, and director of the James P. Allison Institute, tested two approaches: administering CTLA-4 Ig at the same time as ICT or after ICT treatment completion in mouse tumor models.

The team discovered that treatment with CTLA-4 Ig after checkpoint inhibitors improved the cancer-fighting effects of the treatment, regardless of the type of checkpoint inhibitor used. In contrast, CTLA-4 Ig given at the same time as checkpoint inhibitors reduced their efficacy. CTLA-4 Ig reduced the frequency of immunosuppressive regulatory T cells, which likely explains the responses seen. These results, published in Proceedings of the National Academy of Sciences on June 26, suggest CTLA-4 Ig can help reduce severe side effects without compromising antitumor activity.

The University of Texas MD Anderson Cancer Center recruited Dr. Allison in 2012 with the support of a $10 million CPRIT Recruitment of Established Investigators grant (R1203).

237. Cancer develops due to the accumulation of multiple genetic mutations including changes in the DNA sequence, rearrangements involving the chromosomes, and changes in the number of chromosomes (aneuploidy). Errors in chromosome segregation during cell division (mitosis) can result in aneuploidy, or the formation of micronuclei, which trap mis-segregated chromosomes. These micronuclei often lead to chromothripsis, a chaotic chromosome fragmentation process associated with cancer, though its underlying mechanisms remain unclear.

CPRIT Scholar Peter Ly, Ph.D., assistant professor in the Department of Pathology at the University of Texas Southwestern Medical Center and Simmons Comprehensive Cancer Center, and fellow researchers investigated the process by which specific DNA repair pathways recognize and process DNA lesions.

To determine how specific double-strand break (DSB) repair pathways shape the rearrangement landscape of mitotic errors, the research team, led by Dr. Ly, used CRISPR-CAS9 gene editing and an innovative strategy termed CEN-SELECT. This method allows researchers to control the formation of micronuclei containing the Y chromosome which carries a selectable marker that makes cells resistant to the antibiotic neomycin (the neoR marker). The scientists induced micronuclei containing the Y-encoded neoR marker and analyzed how different DNA repair pathways processed these fragmented chromosomes.

The investigators then used CRISPR/Cas9 gene editing to systematically delete genes involved in DSB repair pathways. As reported in the July 4 issue of Nature Communications, the analysis revealed that the canonical non-homologous end joining (NHEJ) pathway is the predominant mechanism cells use to repair fragmented chromosomes caused by chromothripsis. Without NHEJ, other repair pathways rarely engage, leading to delayed repair, persistent DNA damage, and cell cycle arrest. These findings suggest that targeting NHEJ with drugs, such as inhibitors of the repair protein DNA-PKcs, could be a potential treatment strategy for tumors with chromosomal instability.

The University of Texas Southwestern Medical Center recruited Dr. Ly in 2018 from Ludwig Institute for Cancer Research and University of California, San Diego, School of Medicine, with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR180050).

238. Glioblastoma multiforme (GBM) is a highly aggressive and essentially incurable brain cancer that makes up almost half of all central nervous system cancers. For nearly 20 years, the standard treatment has been a combination of surgery, radiation, and high doses of the chemotherapy drug temozolomide (TMZ). Despite these treatment options, only 6.7% of patients survive beyond two years. One major challenge is that GBM tumors quickly become resistant to TMZ, and extended use doesn't improve outcomes. Additionally, prolonged use and high dosages of TMZ can cause toxicity in GBM patients, highlighting the need to develop alternative treatments for GBM.

Researchers are exploring a natural xanthonoid called α-mangostin (AMN), which has shown promise in fighting GBM. However, AMN is difficult to administer because it doesn't mix well with water. To address this, researchers including co-corresponding author and Biochemistry Ph.D. candidate, Ammar Kapic, Department of Microbiology, Immunology & Genetics at the University of North Texas Health Science Center at Fort Worth, developed a novel delivery system using reconstituted high-density lipoprotein (rHDL) nanoparticles, which are compatible with the body and enhance drug delivery.

The new formulation, rHDL-AMN, was more effective and had fewer side effects compared to unformulated AMN and TMZ. The data, published in the International Journal of Molecular Sciences on July 5, revealed that rHDL-AMN also triggered beneficial cellular processes more in cancer cells than in normal cells, making it a promising, safer alternative for GBM treatment.

University of North Texas Health Science Center at Fort Worth received a $3.9 million CPRIT Research Training grant (RP210046) in 2021 to implement a recruitment plan to recruit and train underrepresented minorities and disadvantaged scholars.

239. RNA binding proteins (RBPs) are essential regulators of gene expression, with 1,500 proteins in the human genome. They play crucial roles in the nervous system, where they regulate the formation of neurons, neuronal function, and nervous system development. Changes in RBP activity are associated with neurological disorders, neurodegenerative diseases, and brain tumor development.

Luiz Penalva, Ph.D., professor, Department of Cell Systems & Anatomy at The University of Texas Health Science Center at San Antonio, and team previously identified SERBP1 (Serpine RNA binding protein 1) as a novel oncogenic RBP in glioblastoma (GBM). High expression of SERBP1 is associated with poor patient prognosis and treatment resistance. In this study, researchers explored the set of molecular interactions of SERBP1. They discovered that SERBP1 is a versatile protein, forming various complexes and interacting with both the cytoplasm and the nucleus.

The team reported their findings in Genetics and Genomics on July 2. Though mostly found in the cytoplasm, SERBP1 interacts with proteins involved in important nuclear functions like RNA splicing, cell division, and ribosome production. The study also discovered a significant interaction

between SERBP1, and another protein called PARP1, suggesting that they regulate each other's activities. This relationship may help explain SERBP1's role in cancer and possibly other conditions such as Alzheimer's disease, because it interacts with other key proteins involved in neurological functions.

SERBP1 helps regulate genes related to neuron development and the formation of synapses, processes often compromised in disease states. It can both promote and repress different translational steps, depending on the context. Additionally, SERBP1 is involved in the processing and modification of ribosomal RNA (rRNA) and contributes to the assembly and function of ribosomes. This regulation occurs through multiple pathways, highlighting SERBP1's versatility and importance in maintaining cellular functions related to protein synthesis and growth.

The University of Texas Health Science Center at San Antonio received a $250,000 CPRIT High Impact/High Risk grant (RP200595) in 2020.

240. Group 3 medulloblastoma (Gr3-MB) is one of the most aggressive forms of brain cancer in children and often leads to metastasis and poor survival. A team of researchers at Baylor College of Medicine, including corresponding author and CPRIT Scholar Michael Taylor, professor of pediatrics, hematology – oncology and neurosurgery, targeted the protogenin-expressing cells that sustain tumor growth with CAR T-cell immunotherapy to help find an effective therapy.

The researchers compared the genes expressed by Gr3-MB cells from six tumors with those expressed by human fetal hindbrain cells during the first trimester of pregnancy. They found cancer stem-like cells in the rhombic lip - a region in the developing cerebellum. When Gr3-MB tumors develop, they recreate the vascular plexus, a vascular network formed by numerous connections between veins, not found in other types of medulloblastoma.

"Instead of attacking the entire tumor, we hypothesized that eliminating the small population of cancer stem-like cells that sustains the tumor would be therapeutic, which is analogous to triggering the dissolution of an army by removing the leader," said Dr. Taylor.

The data, published in Cell on July 5, showed that eliminating the small population of the cells present in Gr3-MB tumors led to tumor shrinkage. The researchers hope that with additional research, this novel approach will lead to new ways to treat children with Gr3-MB.

Baylor College of Medicine recruited Dr. Taylor in May 2022 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR220051).

241. Cellular senescence is an irreversible state of cell death triggered by various stresses, including abnormal oncogene activation, telomere shortening, and DNA damage. Cells experience senescence when a cancer-causing mutation arises, halting uncontrolled cell division and preventing tumors from developing. However, too much senescence contributes to aging and degenerative diseases.

Researchers led by Joshua Mendell, M.D., Ph.D., professor, Department of Molecular Biology at The University of Texas Southwestern Medical Center, used a genome-wide screen to individually inactivate thousands of noncoding RNAs in human cells that carried a cancer-causing mutation. This mutation usually prompts cells to become senescent, but the cells continued to divide due to

inactivation of the noncoding RNA. The team revealed a previously unrecognized regulator of senescence called SNORA13, a member of a family of noncoding RNAs, that is required for multiple forms of senescence in human cells and mice. Additional research showed that SNORA13 also slowed down the construction of ribosomes, cellular machines that produce proteins. As reported in Cell on July 8, when the researchers removed SNORA13, cells ramped up ribosome assembly, blocking the senescence, allowing cells to continue dividing.

With additional research, scientists could eventually control this process and develop new cancer drugs that push cells into senescence. In turn, developing drugs that prevent senescence could help slow the aging process and diseases that typically accompany it, such as cardiovascular diseases, neurodegenerative diseases, and diabetes.

The University of Texas Southwestern Medical Center received a $1.05 million CPRIT Individual Investigator grant (RP220309) in February 2022 to investigate chemical modification of ribosomal RNA.

242. Skin cancer is the most diagnosed type of cancer among fair-skinned populations, but identifying suspicious skin cancer lesions remains challenging. The two most common types of skin cancer are malignant melanoma and non-melanoma skin cancer (NMSC). Currently, treatment involves surgically removing the tumor along with some surrounding healthy tissue, but this approach can miss tumor extensions and subclinical tumor spread, while removing healthy or unaffected surrounding tissue.

In this work, Vladislav Yakovlev, Ph.D., professor, Department of Biomedical Engineering at Texas A&M Engineering Experiment Station, and colleagues aimed to identify and completely remove skin cancer from the patient. The researchers developed an objective image-guided multispectral autofluorescence lifetime imaging (maFLIM)-based strategy to distinguish between benign and malignant skin lesions. The team developed classification models using maFLIM images collected from 30 patients exhibiting benign or malignant skin lesions. These models generated prediction probability maps that doctors could potentially use to classify the lesion as either benign or malignant for screening and diagnosis purposes. In addition, doctors could use these maps to ensure complete removal of cancer cells during skin cancer excision surgery. The findings, published in Biomedical Optics Express on July 9, show that this method could make skin cancer diagnosis and surgery more accurate, potentially improving patient outcomes by reducing recurrence and minimizing unnecessary tissue removal.

Texas A&M Engineering Experiment Station received an $897,394 CPRIT Individual Investigator grant (RP180588) in 2018 to develop a clinical tool for noninvasive, fast and automated in situ detection of early-stage oral cancer and dysplasia vs. benign conditions.

243. Immune checkpoint therapy (ICT) has significantly improved cancer treatment outcomes, leading to long-term durable responses in cancers such as melanoma. However, certain tumor types, such as pancreatic ductal carcinoma (PDAC), have shown poor response to this treatment. Understanding these resistance mechanisms can help develop better treatment combinations with ICT that can help convert unresponsive tumors (cold tumors) to more responsive tumors (hot tumors).

Cancer-associated fibroblasts (CAFs) are the primary component of the tumor environment, and they promote tumor growth through various mechanisms. Although CAFs appear to be promising candidates for enhancing therapy responses, depleting them may not effectively boost anti-tumor responses.

In this work, researchers from The University of Texas MD Anderson Cancer Center, including corresponding author Padmanee Sharma, M.D., Ph.D., professor, Department of Genitourinary Medical Oncology, used single-cell RNA sequencing to analyze both the immune and non-immune compartments of the tumor microenvironment. They found that a molecule called TNF-stimulated gene 6 (TSG-6), secreted by CAFs, is more abundant in pancreatic tumors than in melanoma tumors in both mouse models and patient samples. Importantly, in vivo neutralization of TSG-6 in combination with ICT decreases suppressive immune cells and increases beneficial CD8 T cells in the tumor, leading to improved survival. The results, published in Nature Communications on July 10, identify TSG-6 as a key factor in ICT resistance in pancreatic cancer and suggest that targeting TSG-6 could improve ICT effectiveness in fibrotic tumor types.

The University of Texas MD Anderson Cancer Center received a $4 million CPRIT Research Training grant (RP210028) in May 2021 to provide a comprehensive learning environment focused solely on cancer, to position trainees for successful careers in cancer research.

244. Treating cancer remains a challenge due to tumor heterogeneity, even within the same cell. While genetic mutations have helped identify targets for therapies, tumors often become resistant, leading to relapse. Non-genetic factors, such as the ability of cancer cells to switch between different states (a process called the epithelial-to-mesenchymal, or E-M, transition), also play a key role in resistance. Cancer cell populations show a range of characteristics along the E-M spectrum, but it's not clear what causes these differences and changes over time.

CPRIT Scholar Jason George, Ph.D., assistant professor, Department of Biomedical Engineering at Texas A&M University, and colleagues investigated why breast cancer cells show different behaviors along the E-M spectrum. They studied two types of breast cancer cells using various mathematical models and explored how three factors -- differential growth rates, cell-state switching, and changes in growth or state-transition rates -- affect cancer cell populations. They found that including E-M cell-state transitions was essential to explain the variations in E-M characteristics. Additionally, cell crowding influenced growth rates more than state-switching, a finding supported by data from experiments involving treatments that inhibit specific cellular signaling pathways that promote growth.

The team devised a selection criterion to identify the next most informative time points for which experimental data will optimize the accuracy of the models. The results, published in iScience on July 19 issue, show that heterogeneity in breast cancer cells emerge because of cell-state transitions together with the influence of heterogeneous subpopulations on growth rate. Moreover, the study identifies the population level processes shaping the dynamics of spontaneous E-M heterogeneity in breast cancer, findings that will impact the ability to predict the dynamics of spontaneous and therapy-induced cell transitions, including the acquisition of drug-resistance. This knowledge could lead to better strategies to combat drug resistance and design more effective therapies.

Texas A&M Engineering Experiment Station recruited Dr. George in 2021 from The University of Texas MD Anderson Cancer Center with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR210080).

245. Nucleotides, the main building blocks of nucleic acids including DNA and RNA, rely on non-covalent interactions (such as hydrogen bonding and stacking) to maintain their structure and function. Understanding these interactions is critical for improving molecular models and computational tools used to study nucleic acids. However, due to the complex nature of DNA and RNA molecules, molecular simulations using the current molecular mechanics forcefields have been challenging.

To address this, researchers from the University of Texas at Austin broke down nucleotides into three main parts -- nucleobases, sugars, and phosphate groups -- and analyzed how these parts interact with each other and with water. They compared different quantum mechanical methods to calculate these interaction energies, focusing on two advanced techniques: Symmetry-Adapted Perturbation Theory (SAPT) and Absolutely Localized Molecular Orbitals (ALMO).

SAPT showed that using a higher level of theory or a larger basis set didn't always improve accuracy, making it hard to choose the best combination for a given system. In contrast, ALMO EDA2 provided reliable and consistent results across various computational settings and was faster. These calculations, described in the July 10 edition of Molecules, provide a benchmark for different quantum mechanical methods and offer deeper insights into the forces that stabilize nucleic acid structures, paving the way for more accurate and efficient simulations.

The University of Texas at Austin received a $4 million CPRIT Core Facility Support Awards grant (RP210088) in 2021.

246. Mycobacterium tuberculosis (Mtb) is a deadly human pathogen that causes tuberculosis (TB) in humans and is the leading cause of death among people with HIV-1 infection. To improve the diagnosis and treatment of HIV-TB patients, it is important to understand the mechanisms underlying these conditions.

CPRIT Scholar Shrikanth Gadad, Ph.D., adjunct assistant professor, Department of Biomedical Sciences at the University of Texas Southwestern Medical Center, and colleagues used an integrated genomics approach to determine the long non-coding RNAs (lncRNAs) that are dysregulated in HIV-TB patients and HIV-TB patients undergoing anti-retroviral therapy (ART). The analyses focused on lncRNAs, parts of the genome that don't code for proteins.

The team found that Mtb infection in HIV patients increased the activity of some lncRNA genes and decreased others. When these patients receive anti-retroviral therapy (ART), it reduces the activity of some highly active lncRNA genes. Additional analysis revealed that these lncRNAs are linked to immune system pathways in TB-infected conditions. Interestingly, TB patients receiving ART showed entirely different and non-overlapping pathways. Published in Non-Coding RNA on July 13, the findings revealed that scientists could use the differentially expressed lncRNA genes in HIV-TB and HIV-TB patients undergoing ART to develop diagnostic and prognostic tools.

Texas Tech University Health Sciences Center at El Paso recruited Dr. Gadad in 2017 from The University of Texas Southwestern Medical Center with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR170020).

247. Scientists have known for a long time that cytotoxic T cells need the assistance of helper T cells to become armed and activated. Tumor-specific CD8+ T cells (cytotoxic T cells),

which are supposed to attack tumors, often become dysfunctional and unable to stop tumor growth. Hyun-Sung Lee, M.D., Ph.D., associate professor, Department of Surgery at Baylor College of Medicine, and fellow researchers investigated whether tumor-specific CD4+ T cells (helper cells) can overcome CD8+ T cell dysfunction within tumors.

In this study, published in Cancer Cell on July 8, the researchers discovered that spatial positioning and interactions of CD8+ and CD4+ T cells, but not the number of these T cells, dictate anti-tumor response. For effective anti-tumor responses, CD4+ T cells must interact with CD8+ T cells on the same dendritic cell, forming a three-cell cluster (triad) that enables CD8+ T cells to kill cancer cells. When intratumoral triad formation is disrupted, tumors continue to grow even if there are enough CD8+ and CD4+ T cells present. These triads correlate with improved clinical responses in patients with pleural mesothelioma undergoing immune checkpoint blockade treatment. Therefore, CD4+ T cells and these triad formations are required for CD8+ T cell cytotoxicity to effectively eliminate tumors.

Baylor College of Medicine received a $5.2 million CPRIT Core Facility Support Awards grant (RP180672) in 2018 and an $897,527 CPRIT Individual Investigator grant (RP200443) in 2020.

248. Skin derives its mechanical strength from keratin intermediate filaments (KIFs), rope-like proteins that crisscross the interior of skin cells and form connections between cells. This family of proteins includes 54 members, produced in different combinations depending on the cell's needs. However, research has not yet revealed why there are so many different members in the KIF family and how changes in their relative abundance affect processes such as wound healing.

Scientists often study the roles of specific proteins by mutating or deleting the gene responsible for making them. However, senior author and CPRIT Scholar Gaudenz Danuser, Ph.D., chair and professor in the Department of Bioinformatics and professor in the Department of Cell Biology at The University of Texas Southwestern Medical Center, said that studying KIFs using this strategy weakens skin and makes it impossible to study any other roles the proteins might play. To address this, Dr. Danuser and colleagues genetically engineered two batches of skin cells: one that produced more of the wound-associated keratin K6A and another that made more of the typical keratin K5 found in intact skin. They allowed these cells to grow into skin organoids, which then formed layers typical of natural skin.

The team compared how the cells in each of these organoids behaved and found that cells with higher levels of keratin K6A migrated more readily than those with higher levels of keratin K5, allowing them to close wounds more effectively in the skin organoids. However, cellular migration relies on myosin motors, critical proteins responsible for generating the forces needed for traction, and the operation of these motors is not directly linked to KIFs. Further investigation showed that the relative abundance of K6A influenced the activation of a molecular switch that triggers myosin activity. Increased levels of K6A led to higher myosin activation, prompting cells to roam, while lower levels of K6A prevented the activation of these motors, hindering cell movement.

The study, published in Developmental Cell on July 12, revealed that keratin filaments play a dual role: besides providing mechanical support, they act as signaling scaffolds. These scaffolds, fine-tuned by different keratin isoforms, organize cellular signals that regulate epithelial cell behavior, particularly during processes like wound healing.

The University of Texas Southwestern Medical Center recruited Dr. Danuser from Harvard Med-

ical School in 2012 with the support of a $5 million CPRIT Recruitment of Established Investigators grant (R1225).

249. Aggressive breast cancers, such as triple negative breast cancer, often have mutations in the TP53 gene. These mutations help cancer cells grow and survive by changing how genes are activated. To understand how TP53 mutations in breast cancer contribute to tumorigenesis and progression in vivo, corresponding author Guillermina Lozano, Ph.D., Department of Genetics at The University of Texas MD Anderson Cancer Center, and colleagues created a mouse model with specific Trp53 mutations in breast cells. The mice developed primary mammary tumors reflecting the human molecular subtypes of Luminal A, Luminal B, HER2-enriched, and Triple Negative Breast Cancer with metastases.

By comparing tumors with TP53 mutations to those without, researchers identified different cancer-related pathways activated by these mutations. They also discovered that a gene called Nr5a2 plays a key role in these pathways. Meta-analyses of human breast tumors corroborated these results. In vitro assays demonstrated that mutant p53 increases the activity of specific target genes linked to Nr5a2. Further studies revealed that the mutant TP53 proteins interact with Nr5a2. These findings, published in Cancer Research Communications on July 12, implicate NR5A2 as a novel mediator of mutant p53 activity in breast cancer. Targeting Nr5a2 could be a potential therapy for hard-to-treat breast cancers, including endocrine-resistant tumors and metastatic triple negative breast cancers with TP53 mutations.

The University of Texas MD Anderson Cancer Center received a $900,000 Individual Investigator grant CPRIT (RP180313) in 2018 to understand the changes that cooperate with p53 mutations to yield triple negative breast tumors.

250. Neuroblastoma (NB) is a cancer that affects the peripheral nervous system in children under 15 years of age. It is the most frequently diagnosed cancer during infancy, accounting for approximately 12% of all cancer-related deaths in children. Leucine-rich repeat-containing G-protein-coupled receptor 5 (LGR5) is a membrane receptor linked with tumor growth and metastasis in gastrointestinal cancers. Researchers also found high LGR5 levels in NB tumor cells and LGR5 expression is strongly associated with poor survival.

To better understand the function of LGR5 in NB cells, corresponding author Qingyun Liu, Ph.D., professor and director, IMM-Center for Translational Cancer Research at The University of Texas Health Science Center at Houston, and team explored an antibody–drug conjugate (ADC), which are cancer drugs attached to antibodies that home in on tumor cells and spare normal cells. They developed an ADC targeting LGR5 for the treatment of high-risk NB using the PBD class of the cytotoxin SG3199. The resulting anti-LGR5 ADC was able to inhibit the growth of NB cells expressing LGR5 with high potency and specificity. Importantly, the ADC was able to completely inhibit tumor growth in vivo at a clinically relevant dose. The findings, published in Pharmaceutics on July 15, support the potential of targeting LGR5 using this ADC for the treatment of high-risk NBs.

The University of Texas Health Science Center at Houston received a $4 million CPRIT Core Facility Support Awards grant (RP210119), a $1 million CPRIT Individual Investigator grant (RP220169) and a $250,000 High Impact/High Risk grant (RP210092).

251. The blood-brain barrier (BBB) protects the central nervous system from infectious and neurotoxic agents by preventing transport across the barrier. However, these same properties that protect the brain also prevent the transport of therapeutic agents into the brain. Convection-enhanced delivery (CED) is a method which targets parts of the central nervous system. However, CED has shown mixed results in clinical trials for conditions like glioblastoma and Parkinson's disease.

Robert Rostomily, M.D., professor of neurosurgery at Houston Methodist Research Institute, and colleagues have discovered a more accurate and timely way to deliver life-saving drug therapies to the brain. Electrokinetic convection-enhanced delivery (ECED) is a method that uses electromotive forces to enhance drug delivery. The team used an external electric field to guide therapeutic agents from a specially designed hydrogel placed on the brain's surface into its interior, without the need for traditional infusion techniques like pressurized delivery.

The team demonstrated that ECED enabled deeper and more targeted penetration into brain tissue compared to natural diffusion alone in a rat brain in ex vivo and in vivo experiments. This data, published in Communications Biology on July 17, demonstrates the potential to provide rapid conveyance of therapeutics from doped hydrogels placed at the cortical surface or along surgical resection cavities to allow for increased coverage of tumor margins. This method shows promise in improving gene therapy and tumor treatment, as well as treatment for traumatic brain injury and degenerative diseases.

The Houston Methodist Research Institute received a $200,000 CPRIT High Impact/High Risk grant (RP190587) in 2019.

252. The immune system can detect and eliminate early signs of malignant cell transformation, but cancer cells can develop genetic changes to evade this detection. The protein, interferon regulatory factor 8 (IRF8), plays a crucial role in both myeloid differentiation and B cell development. In diffuse large B cell lymphoma (DLBCL), a common, genetically diverse, and often fatal B cell malignancy, researchers found that mutations in IRF8 can weaken the immune system, affecting genes involved in antigen processing and chromatin modification.

Corresponding author Richardo Aguiar, Ph.D., Division of Hematology and Medical Oncology, Department of Medicine at The University of Texas Health Science Center San Antonio, and fellow researchers investigated how IRF8 mutations contribute to the development of B cell lymphomas. They discovered that these mutations in the IRF8 gene contribute to immune evasion in DLBCL by disrupting antigen presentation pathways.

In mouse models, IRF8 mutations suppressed the activation of CD4 T cells (an essential component of the immune response), but not CD8 T cells, and reduced the levels of proteins necessary for antigen processing, leading to a higher tumor burden. Mice with IRF8 mutant lymphomas had higher tumor burdens and changes in their tumor microenvironment, such as fewer CD4, CD8, and natural killer cells, and more regulatory T cells and T follicular helper cells. Similar immune changes were observed in human diffuse large B cell lymphoma (DLBCL) with IRF8 mutations. The study, published in Science Advances on July 12, added IRF8 to the list of genes that when mutated help lymphomas evade the immune system, promoting cancer growth.

The University of Texas Health Science Center at San Antonio received a $900,000 CPRIT Individual Investigator grant (RP190043) in 2019.

253. Medulloblastoma (MB) is a heterogeneous malignant pediatric brain tumor that is divided into four molecular subgroups. OTX2 is a transcription factor and known driver in many cases of group 3 and group 4 MB subgroups. They are very aggressive and the mechanisms regulating cell fate decisions are poorly understood.

Researchers at Baylor College of Medicine, Texas Children's Hospital, and collaborating institutions conducted a comprehensive screening of the proteins that interact with OTX2 in the cell. The team, including CPRIT Scholar Michael Taylor, M.D., Ph.D., professor, Department of Pediatrics, Section of Hematology-Oncology at Baylor College of Medicine, came upon an unexpected finding in which the protein OTX2 drives the progression of MB. They found that medulloblastoma develops from stem cells early during development of the cerebellum and are the root of the disease.

The researchers also discovered that OTX2 interacts with other proteins called splicing factors and that OTX2-mediated alternative splicing helps maintain the stem cell state, driving the progression of group 3 MB. Importantly, the researchers found that disturbing PPHLN1 gene splicing with an anti-PPHLN1 drug called a morpholino, significantly reduces tumor growth and opens new possibilities for the development of improved treatments. This study, published in Nature Cell Biology on July 18, demonstrates the role of OTX2-mediated alternative splicing in determining cell fate decisions.

The findings have implications beyond cancer. "It is fascinating that a transcription factor would be moonlighting to control splicing, and that this differential splicing should be important in both childhood brain cancer and the normal development of the human fetal hindbrain," said co-corresponding author Dr. Taylor.

Baylor College of Medicine recruited Dr. Taylor in May 2022 with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR220051).

254. Glioblastoma multiforme (GBM) is the most common and aggressive tumor of the central nervous system (CNS) with poor survival rates. An estimated 2.2% of adult GBM patients will survive three years or more after diagnosis, and about 25% of children with this tumor live for five years or more. Unfortunately, therapeutic options for these tumors are still minimal.

Research shows that long-term survivors have more significant infiltration of CD8 T cells in their tumors. These immune cells are good at controlling tumor growth, making immunotherapy a promising treatment approach. In pursuit of novel therapeutic targets for GBM treatment, co-corresponding author Maurício Menegatti Rigo, Ph.D., Kavraki Lab, Department of Computer Science at Rice University, and fellow researchers selected peptides that could still trigger a strong CD8 T cell immune response despite mutations, thereby maintaining a specific CD8 T cell immune response.

In this study, the researchers focused on mutations in GBM that affect immunogenic proteins such as TP53, PTEN, EGFR, and IDH1. Using advanced prediction tools and machine learning, the team identified mutations that do not interfere with the immune system's ability to recognize these proteins, as consistently predicted by in silico tools. Specifically, they also found six peptides from the TP53 protein that remain unaffected by mutations and could be stable targets for immunotherapy.

The simulation results, published in Scientific Reports on July 19, confirmed they were able to discern mutations capable of influencing, or not, the immune response, making them promising targets for GBM therapies, all derived from the TP53 protein.

The University of Texas Medical Branch at Galveston received a $4 million CPRIT Research Training grant (RP170593) in 2016 in support of the Computational Cancer Biology Training Program.

255. Prostate cancer metastasizes primarily to bone. The development of bone metastases in castration-resistant prostate cancer (bmCRPC) signifies the lethal progression of the disease. The incidence of bone involvement in patients with metastatic disease is greater than 85%, and bone lesions can cause significant morbidity, including pain and skeletal-related complications. Radium 223 (Ra-223) is a treatment that targets tumor-induced osteoblasts (bone-forming cells). Ra-223 reduces bone pain and prolongs overall survival in bmCRPC. However, treatment with Ra-223 can cause an increased risk of fractures in bones not affected by cancer.

In this study, Sue-Hwa Lin, Ph.D., Department of Translational Molecular Pathology, and colleagues from The University of Texas MD Anderson Cancer Center aimed to understand how Ra-223 affects healthy bone cells and bone structure in mouse models. Understanding the effects of Ra-223 on non-tumor-affected bone is necessary for optimizing the use of Ra-223, especially in combination with other therapies. Although Ra-223 significantly improves overall survival, it doesn't often lower prostate-specific antigen (PSA) levels, a common marker used to assess prostate cancer progression, while lower levels of alkaline phosphatase, a marker of bone cell activity, are associated with better survival.

Using osteoblast reporter mice to monitor the levels of osteoblasts in vivo, a single dose of Ra-223 led to a rapid and sustained reduction of healthy bone cells, in certain areas of the femur, leading to reduced bone density and altered bone microstructure. Furthermore, Ra-223 treatment also significantly reduced tumor-induced bone cells. This study, published in Cancers on July 21, highlights the importance of protecting healthy bone areas during Ra-223 treatment and reveals the need for further development of Ra-223 combination therapies for treatment of patients with bmCRPC.

The University of Texas MD Anderson Cancer Center received two CPRIT Individual Investigator grants (RP190252, RP230247) totaling $1.95 million to study a novel therapy combination will improve the quality of life and prolong the survival of patients with bone metastasis caused by prostate cancer.

256. Ewing sarcoma affects the bone and soft tissue in children and young adults primarily driven by the protein EWS-FLI1, which has been undruggable. The prognosis for patients with recurrent or metastatic Ewing sarcoma continues to be poor. Despite many attempts, however, scientists have not developed EWS-FLI1-targeted therapy. Previous research on Ewing sarcoma predominantly focused on how EWS-FLI1 regulates intracellular events such as gene transcription and mRNA splicing. Little is known about how EWS-FLI1 impacts the extracellular environment.

In this study, corresponding author Yuzuru Shiio, M.D., Ph.D., associate professor in Biochemistry

& Structural Biology, and fellow researchers from The University of Texas Health Science Center at San Antonio, revealed that Ewing sarcoma depends on a secreted enzyme, sphingomyelin phosphodiesterase 1 (SMPD1), and ceramide for its growth. They found that a receptor called GPR64 responds to ceramide and activates critical growth signaling in Ewing sarcoma. Ceramide induces a part of GPR64 to move to the cell's nucleus, reducing levels of a protein called RIF1 through a tumor-suppressing pathway involving the gene SPOP. Both SMPD1 and GPR64 are regulated by EWS-FLI1, making them key players in Ewing sarcoma growth. These results, published in Cell Reports on July 17, suggest that targeting the SMPD1-ceramide-GPR64 pathway could be a new therapeutic approach for treating Ewing sarcoma.

The University of Texas Health Science Center at San Antonio received two CPRIT Individual Investigator grant (RP160487, RP190385) totaling $2.4 million, and three Core Facility Support Awards grant (RP160716, RP220599, RP160732) totaling $12.6 million.

257. Understanding the genetic causes of diseases requires large amounts of genetic and phenotypic data. As the sample sizes become more heterogeneous, scientists must use complex statistical approaches to correct for the confounders that may bias results. However, sharing this data among institutions can be challenging due to privacy regulations such as HIPAA, which protect sensitive health information. This makes it difficult to conduct high-powered, collaborative studies.

To address these issues, CPRIT Scholar Xiaoqian Jiang, Ph.D., professor and associate vice president of Medical AI, and fellow researchers at The University of Texas Health Science Center at Houston developed a federated genetic association testing tool called FedGMMAT. This tool uses advanced statistical models to account for differences in data and potential biases, ensuring accurate results without the need to share sensitive information. Tests with both simulated and real data revealed that FedGMMAT can match the accuracy of traditional methods while preserving privacy and using practical resources. This approach, described in PLOS Computational Biology on July 24, offers a potential solution for conducting large-scale genetic studies while maintaining data privacy.

The University of Texas Health Science Center at Houston recruited Dr. Jiang from the University of California San Diego in 2018 with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR180012).

258. Endometriosis, a condition where endometrial tissue grows outside the uterus, is often explained by the retrograde menstruation hypothesis. This theory suggests menstrual blood flows backward through the fallopian tubes into the abdomen, allowing endometrial cells to implant and grow.

Researchers have linked abnormal activity of Estrogen Receptor beta (ERβ) in endometrial tissue the development of endometriosis among reproductive-aged women who have experienced retrograde menstruation. ERβ suppresses the Interferon (IFN)-mediated cell death pathways, allowing misplaced cells to survive and spread. However, scientists have not addressed the key question of how ERβ downregulates IFN-mediated cell death pathways. Researchers at Baylor College of Medicine, led by Yuri Park, Ph.D., Department of Molecular and Cellular Biology, explored the role of a protein called N-Myc and STAT Interactor (NMI) in this process. NMI supports immune de-

fenses by promoting interferon-induced cell death, a mechanism that eliminates harmful or abnormal cells.

The results, published in the International Journal of Molecular Sciences on July 26, revealed that NMI suppresses the growth and adhesion of endometrial cells and enhances cell death upon exposure to interferons. Furthermore, NMI's cancer-suppressing roles in various cancers highlight its broader significance. Although the precise role of NMI in the progression of endometriosis remains unclear, NMI emerges as a promising target for understanding and potentially treating endometriosis.

Baylor College of Medicine received a $4 million CPRIT Core Facility Support Awards grant (RP200504) in 2020 to support the Comprehensive Cancer Epigenomics Core Facility.

259. Transthyretin amyloidosis (ATTR amyloidosis) is a debilitating and progressive disorder caused by the abnormal build-up of transthyretin amyloid (ATTR) that leads to organ failure and death. In ATTR, unstable transthyretin protein (TTR) breaks apart, misfolds, and forms amyloid fibrils that can build up and cause damage throughout the body. This conversion is facilitated by mutations in hereditary (ATTRv) amyloidosis or aging in wild-type (ATTRwt) amyloidosis.

Previously, researchers found that the structure of cardiac amyloid fibrils differs between patients with inherited ATTRv amyloidosis but remains identical in those with non-inherited ATTRwt amyloidosis affecting the heart. In this study, led by Binh An Nguyen, Ph.D., and Virender Singh, Ph.D., Department of Biophysics at The University of Texas Southwestern Medical Center, researchers used cryo-electron microscopy to examine fibrils from four ATTRwt amyloidosis patients with heart issues and confirmed their identical structures. The structural homogeneity in ATTRwt fibrils may explain the consistent and predictable clinical presentation in patients, suggesting a link between fibril structure and disease presentation in the case of ATTRwt amyloidosis.

Published in Communications Biology on July 27, the findings suggest that understanding fibril structures can improve identification of the disease and lead to novel targets for treatment and diagnostic tools for ATTR amyloidosis.

The University of Texas Southwestern Medical Center received a $5.5 million CPRIT Core Facility Support Awards grant (RP170644) in August 2017 to establish a new Cryo-Electron Microscopy Core Facility and Service for Structure Determination.

260. The BRCA1 gene, known for its role in breast cancer susceptibility, plays a key role in responding to DNA damage by coordinating various signaling complexes. The A, B, and C complexes of BRCA1 are formed through specific interactions with the BRCA1-C-terminal domains and help in DNA repair and cell cycle checkpoint control. However, scientists do not fully underhand the exact functions of these complexes in DNA damage response, in part because of cellular lethality associated with loss of CtIP protein, which is an essential component in BRCA1-C complex.

To explore the roles of these complexes, researchers led by Junjie Chen, Ph.D., professor and chair of the Department of Experimental Radiation Oncology at The University of Texas MD Anderson Cancer Center, depleted key components in each one. They used the degradation tag system to deplete endogenous CtIP and created cells lacking the proteins RAP80, FANCJ,

and CtIP, both individually and in combination. They found that losing BRCA1-B/FANCJ and BRCA1-C/CtIP, but not BRCA1-A/RAP80, led to slower cell growth and higher sensitivity to DNA damage. Both BRCA1-C/CtIP and BRCA1-A/RAP80 were necessary for BRCA1 to move to DNA damage sites, but BRCA1-A/RAP80 was not essential on its own for this localization. Instead, RAP80 and CtIP have redundant roles in BRCA1 recruitment.

This study, published in Oncogene on July 27, uncovers the distinct functions of the BRCA1-A, -B, and -C complexes and provides new insights into how these complexes contribute to DNA damage response and repair.

The University of Texas MD Anderson Cancer Center received two CPRIT Multi-Investigator Research Awards grants (RP160667, RP180813) totaling $11 million.

261. Scientists have discovered a new way that stomach cancer can become more aggressive by altering ribosomes, the cell's protein factories. Normally, the regulation of gene expression can contribute to cancer. However, CPRIT Scholar Pawel K. Mazur, Ph.D., assistant professor, Department of Experimental Radiation Oncology at The University of Texas MD Anderson Cancer Center, and fellow researchers found that a specific modification on the ribosome also plays a role. The team found that in gastric adenocarcinoma (GAC), the protein SMYD5 modifies a ribosomal component, rpL40, to enhance the production of proteins that fuel cancer growth and spread. High levels of SMYD5 and modified rpL40 were linked to worse outcomes in patients with aggressive stomach cancer.

When researchers blocked this modification in cancer cells, they were able to slow down cancer growth. Suppressing SMYD5 methylation of rpL40 in mouse models reduced GAC growth and made the cancer more vulnerable to certain treatments, such as inhibitors of PI3K and mTOR. When the team combined SMYD5 depletion with PI3K–mTOR inhibition and chimeric antigen receptor T cell administration, they cured an otherwise lethal in vivo mouse model of GAC-derived peritoneal carcinomatosis. The findings, published in Nature on July 24, suggest that targeting SMYD5 could be a potential combination therapy to treat GAC.

The University of Texas MD Anderson Cancer Center recruited Dr. Mazur in August 2016 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR160078). MD Anderson received a $997,500 CPRIT Individual Investigator grant (RP220391) in 2022 to help identify oncogenic mechanisms driving lung squamous cell carcinoma development and progression.

262. Living organisms have built-in mechanisms that help them remain stable despite changes in their environment or genetic makeup known as "canalization." One important mechanism involved in this process is the protein-folding chaperone heat shock protein 90 (Hsp90). Hsp90 acts as a buffer, helping proteins fold correctly and hiding potentially harmful genetic mutations until the organism faces significant stress. However, scientists do not fully understand the mechanisms driving canalization.

Budding yeast, which has been highly successful in evolving to thrive in stressful environments created by humans, such as in beer and bread making, serves as an excellent model to study these processes. Because Hsp90 has multiple functions in yeast metabolism, this study focused

on identifying environmental factors that weaken Hsp90's protective effects, thereby revealing hidden genetic variations that could be crucial for understanding and harnessing yeast's adaptability.

The research, published in Science on July 26, uncovered a key mechanism by which organisms rapidly adapt to environmental stress. To do this, corresponding author Georgios Ioannis Karras, Ph.D., assistant professor, Department of Genetics at The University of Texas MD Anderson Cancer Center, and colleagues compared the robustness of 12 metabolic traits to Hsp90 inhibition across two independent cohorts, totaling 711 domesticated and wild yeast strains. The team explored the mechanisms that contribute to yeast's resilience, identified environmental factors that weaken these protective mechanisms, and tested predictions from five different models of canalization using yeast's fitness data. This comprehensive approach helped the researchers better understand how yeast adapts to stress and provided insights into the broader principles of canalization.

This research demonstrates that the interaction between gene redundancy and Hsp90 buffering allowed yeast to quickly adapt to changes in its environment and highlights how stress can reveal hidden genetic diversity. This discovery also suggests that Hsp90's role in stabilizing proteins could be relevant to understanding diseases and developing new biotechnologies.

Baylor College of Medicine received a $5.17 million CPRIT Core Facility Support Awards grant (RP180672) in August 2018 to purchase high-end equipment.

263. Neurons, the brain's most complex nerve cells, have intricate structures called dendritic arbors that extend from the cell body. Dendritic branching is a fundamental process in neurodevelopment, and aberrations in its execution are associated with multiple human neuronal and cognitive pathologies. The process is carefully controlled by a variety of actin regulatory proteins that control the growth and branching of dendrites. The PDLIM family of proteins plays a key role in this process. In earlier studies, researchers identified a critical role for Pdlim5 in regulating dendritic branching. However, scientists do not fully understand the domain structure of Pdlim5 and how individual domains participate to initiate and coordinate dendritic branching.

In this report, Mark Bedford, Ph.D., professor, Department of Epigenetics and Molecular Carcinogenesis at The University of Texas MD Anderson Cancer Center, and colleagues set out to clarify the contributions of Pdlim5's principal domains to dendritic morphology. The team assessed the functional role of the three established structural regions within Pdlim5, the PDZ, DUF, and LIM domains, in regulating dendritic branching. Results using primary hippocampal neurons reveal for the first time that the Pdlim5 DUF domain plays a dominant role in increasing dendritic branching. Compared to the deletion of either the PDZ or LIM domains, the loss of the central DUF domain displayed greater reductions in branching activity.

Overall, these assays indicate that each domain is relevant to Pdlim5's dendritic functions, as expected. Unexpectedly, however, Pdlim5's central DUF domain appears to stand out in its relevance in regulating dendritic branching. The report, published in the International Journal of Molecular Sciences on July 30, noted that scientists need to conduct additional mechanistic work to test this assertion.

The team also identified a specific part of the DUF domain, a tiny piece called Tyr residue (Y251), which plays an additional regulatory role in dendritic branching. These results reveal a novel mechanism for the regulation of Pdlim5's function in the regulation of neuronal branching, with a

focus on the critical role of the DUF domain in this process.

The University of Texas MD Anderson Cancer Center received a $2.6 million CPRIT Core Facility Support Awards grant (RP180804) to support the Protein Array and Analysis Core.

264. Ependymoma (EPN) is a common and aggressive type of pediatric brain tumor which has proven resistant to chemotherapy. Scientists have struggled to develop effective treatments due to a poor understanding of the disease. Co-corresponding author, Benjamin Deneen, Ph.D., professor and chair in the Department of Neurosurgery, and director of the Center for Cancer Neuroscience at Baylor College of Medicine, and collaborating researchers, investigated whether brain activity played a role in EPN, specifically in a very aggressive type driven by a protein called ZFTA-RELA.

The team developed an animal model to study this pediatric brain tumor and validated these findings in human tumor samples. They discovered evidence of abnormal brain activity in EPN's environment. They found that the tumor cells have a serotonin transporter, which allows serotonin to enter the cells and attach to a protein called histone H3, which is closely linked to DNA. This process, called histone serotonylation, regulates tumor growth. Promoting serotonylation enhanced tumor growth while blocking it slowed down EPN growth in animal models.

This research, published in Nature on July 31, uncovered a new mechanism that drives tumor growth in EPN, suggesting that targeting histone serotonylation could be a potential therapeutic approach. It also shows how neuronal signaling, genetic regulation, and developmental programs work together to promote malignancy in brain cancer.

Baylor College of Medicine received a $3.97 million CPRIT Research Training grant (RP210027) in 2021 to support the Baylor College of Medicine Comprehensive Cancer Training Program, and a $3.98 CPRIT Core Facility Support Awards grant (RP210227) in 2021 to support the Proteomics and Metabolomics Core Facility.

265. Chronic pain development typically involves three phases: initiation of pain, pain maintenance, and either resolution or persistence of hypersensitivity/pain. Bulk RNA-sequencing (RNA-seq) experiments reveal that pain conditions trigger substantial changes in gene expression plasticity within pain-processing tissues including the dorsal root ganglia (DRG) and spinal cord. However, there are still significant gaps in the understanding of these phases, particularly regarding the sex-dependent nature of gene expression during these processes. Understanding these differences could lead to more effective, personalized pain treatments.

This study, led by Armen N. Akopian, Ph.D., professor, Department of Endodontics, Integrated Biomedical Sciences (IBMS) Program at The University of Texas Health Science Center at San Antonio, explored the complex mechanisms underlying chronic pain, particularly the differences in gene expression between male and female mice during the progression of persistent neuropathic pain induced by paclitaxel (PTX), a chemotherapy treatment.

The team focused on the time course of gene expression plasticity in the hind paws and dorsal root ganglia (DRG) of male and female mice as they progressed through the stages of persistent painful neuropathy caused by PTX treatment. Using transcriptomic profiling, the researchers revealed that pain persistence in PTX-treated mice is associated with either degenerative or regen-

erative processes in the DRG and hindpaw skin. Notably, degeneration was linked to a reduction in immune processes, while regeneration involved an increase in immune system activity. These processes varied significantly between males and females at all stages of the pain condition. Surprisingly, during the maintenance phase of pain, the researchers observed only minimal inflammation, challenging the idea that inflammation must always accompany ongoing pain.

The study, published in Scientific Reports on July 30, highlights significant sex-dependent differences in how pain progresses at the molecular level, providing new insights into chronic pain mechanisms and paving the way for more tailored pain treatments. Further research is necessary to confirm these results and explore their implications.

The University of Texas Health Science Center at San Antonio received a $3.64 million CPRIT Core Facility Support Awards grant (RP210126) in August 2021 in support of the Flow Cytometry Shared Resource and a $3.68 million Core Facility Support Awards grant (RP160732) in support of the UTHSCSA Cancer Genome Sequencing and Computation Core.

266. Cancer cells frequently have defects in DNA repair pathways, leading to instability in their genetic material. For example, cells with non-functional BRCA1 or BRCA2 genes—important for repairing DNA—experience high levels of chromosomal instability. Poly (ADP-ribose) polymerase (PARP) inhibitors exploit these defects, selectively killing cancer cells with BRCA mutations while sparing normal cells. This study explored the effectiveness of the PARP inhibitor talazoparib for treating patients with advanced or metastatic cancers, particularly those with defects in DNA repair pathways. Talazoparib works by targeting cancer cells that struggle to fix DNA damage, such as those with BRCA1/2 mutations.

Funda Meric-Bernstam, M.D., chair of the Department of Investigational Cancer Therapeutics and the medical director of the Institute for Personalized Cancer Therapy at The University of Texas MD Anderson Cancer Center, and colleagues conducted a phase II study to formally evaluate whether talazoparib achieves clinical benefit in metastatic or inoperable locally advanced or locally recurrent cancer patients. Researchers tested talazoparib in patients grouped based on specific genetic changes: somatic BRCA1/2 mutations, other DNA repair pathway alterations, PTEN mutations, or germline BRCA1/2 mutations.

The findings, published in npj Precision Oncology on July 31, revealed that talazoparib provided significant benefits, like shrinking tumors or stabilizing the disease, in some patients. However, patients with PTEN mutations showed reduced survival and a tendency for faster disease progression, indicating limited benefit from talazoparib. Further research is necessary to clarify whether PTEN mutations can predict a patient's response to PARP inhibitors and to refine patient selection for these therapies.

The University of Texas MD Anderson Cancer Center received a $6 million CPRIT Core Facility Support Awards grant (RP150535) in 2015 in support of the Precision Oncology Decision Support Core.

267. Inflammation and synapse loss have been associated with deficits in social behavior and are involved in pathophysiology of many neuropsychiatric disorders. Synapse loss, marked by a reduction in dendritic spines, can severely disrupt communication between brain cells and impair the neural circuits that control social behavior. Chronic stress is a known trigger for the loss

of dendrites and spines in the prefrontal cortex (PFC), a brain region crucial for regulating social interactions. However, scientists do not fully understand the underlying mechanisms.

Zhongming Zhao, Ph.D., professor, Department of Psychiatry and Behavioral Sciences at The University of Texas Health Science Center at Houston, and colleagues investigated the role of type I Interferon (IFN-I) signaling in chronic unpredictable stress (CUS)-induced synapse loss and behavior deficits in mice. The researchers focused on the PFC and found that when they subjected mice to chronic stress, a type of immune signaling in the brain involving IFN-I increased. This signaling contributed to the loss of synapses and the resulting social behavior problems. However, when they blocked this immune signaling in microglia (specialized immune cells in the CNS), the mice did not experience synapse loss and their social behavior remained normal. Additionally, it preserved the function of key genes involved in synaptic plasticity, the brain's ability to adapt and change over time. The results, published in Molecular Psychiatry on August 2, suggest that microglial IFN-I signaling plays a critical role in the effects of chronic stress and could be a target for preventing stress-related brain changes and social behavior issues.

The University of Texas Health Science Center at Houston received a $4.4 million CPRIT Core Facility Support Awards grant (RP180734) in August 2018 for the UTHealth Cancer Genomics Core.

268. The novel coronavirus (SARS-CoV2) pandemic has had a profound impact on the world, but the rapid development of vaccines has been an impressive response. Unfortunately, incomplete vaccination and persistent viral mutations have hampered attempts to eradicate this disease, and ultimately vaccination therapy alone is not a viable long-term strategy. To address this, researchers are looking into developing broad-spectrum antiviral drugs that can fight not only COVID-19 but also other similar respiratory viruses.

Scientists have studied a class of compounds called histone deacetylase inhibitors (HDACi) for their potential in treating cancer and HIV. Valproic acid (VPA), a well-known HDAC inhibitor commonly used to treat seizures and bipolar disorder, has shown antiviral activity against a range of viruses. In this study, researchers from The University of Texas Health Science Center at San Antonio and collaborating institutions found that VPA has a novel anti-coronavirus activity. Further investigation found that VPA can be used in combination with Docosahexaenoic acid (DHA), an omega-3 fatty acid, to make the antiviral effects stronger. The VPA-DHA combination activates natural antiviral mechanisms normally repressed by coronaviruses. The team presented evidence from epidemiologic data that supports VPA as a potential antiviral agent against coronaviruses, despite previous predictions that it would be ineffective based on in vitro high-throughput screening assays. The researchers observed these screening methods to identify any shortcomings and explored the antiviral mechanisms using a less pathogenic coronavirus (HCoV-229E) as a model.

Patients tested for COVID-19 demonstrated that a correlation exists between a reduced infection rate in patients treated with VPA of up to 25%, a decreased rate of ER visits, a decreased rate of hospitalization if they contract COVID-19, a decreased rate of ICU admissions, and a decreased rate of mechanical ventilation. These findings, published in PLOS One on August 2, demonstrate an interaction between HDAC inhibition and the potent activation of cellular antiviral responses and lay the groundwork for further clinical evaluation of VPA + DHA for treating coronaviruses.

The University of Texas Health Science Center at San Antonio received a $3.68 million Core Facility Support Awards grant (RP160732) in support of the UTHSCSA Cancer Genome Sequencing

and Computation Core.

269. Wilms tumor is the most common pediatric kidney cancer and resembles embryonic renal progenitors, stem cells that give rise to the kidney during the development of an embryo. Currently, there are no specific treatments that can target the genetic mutations that cause this cancer, especially those involving a gene called DROSHA, which helps regulate gene expression.

In this study, CPRIT Scholar Kenneth S. Chen, M.D., assistant professor, Department of Pediatrics at The University of Texas Southwestern Meical Center, and fellow researchers used a "multiomics" approach to explore the impact of DROSHA mutations and were able to categorize Wilms tumor mutations into four mutational subclasses, each with unique effects on gene expression.

The results, published in Molecular Cancer Research on August 2, revealed that DROSHA mutations lead to the activation of genes that encourage cancer cells to grow, divide, and remain in a more primitive and flexible state. When DROSHA expression was reduced in a Wilms tumor cell line, there was an increase in a protein called cyclin D2 (CCND2), which promotes cell division. DROSHA mutations also make cancer cells less able to handle oxidative stress. Importantly, the study discovered that Wilms tumor cells lacking microRNAs are more vulnerable to ferroptosis (cell death), which occurs when cells can't properly detoxify harmful lipid peroxides. This vulnerability to ferroptosis highlights a potential therapeutic target for treating a specific subset of Wilms tumor by exploiting the cells' inability to detoxify lipid peroxides.

The University of Texas Southwestern Medical Center recruited Dr. Chen in 2018 with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grant (RR180071). UT Southwestern received a $5.4 million Core Facility Support Awards grant (RP180805) in 2018 in support of the Pediatric Cancer Data Core.

270. Hybridization, where different species interbreed, plays a significant role in evolution, but studying its genetic impact on vertebrates has been challenging due to a lack of appropriate experimental systems. Scientists propose that fish from the genus Xiphophorus, known for their use in research, have evolved with multiple ancient and ongoing hybridization events, making them a valuable model for studying evolutionary biology and human diseases like cancer.

In this study, co-corresponding author Manfred Schartl, Dr. rer. nat., visiting professor, Department of Biology at Texas A&M University, and fellow researchers created a complete genomic resource for all 26 recognized Xiphophorus species and three additional, yet undescribed taxa. They investigated the molecular evolution of genes related to cancers such as melanoma and for the genetic control of puberty timing. Their focus was on genes that could influence hybridization by affecting reproductive isolation.

One key finding was the significant size variation in certain gene families, which persisted even though these species have undergone rapid speciation and complex evolutionary histories. The study also clarified the hybridization history of the entire genus, settling debates about the hybridization events in two Southern swordtail species. The research, published in Nature Communications on August 4, revealed that hybridization of Xiphophorus fish has been a common occurrence throughout their evolution, significantly contributing to the formation of new species, the development of physical traits, and their adaptation to different environments. This work enhances our un-

derstanding of how hybridization influences evolution and speciation in vertebrates. More detailed studies are necessary to explore how specific lineages of the 26 known Xiphophorus species have adapted over time.

Texas State University received a $248,458 High Impact/High Risk CPRIT grant (RP200657) in August 2020 to identify previously unknown genes involved in melanoma progression that are potentially important for personalized therapies.

271. Metastatic pancreatic cancer is a particularly aggressive form of cancer that quickly spreads to vital organs. The disease is typically diagnosed at an advanced stage, which limits treatment efficacy and lowers survival rates. Chemotherapy, the main treatment option, generally offers a seven-month average survival time before disease progression.

Chad Tang, M.D., associate professor, Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, and fellow researchers hypothesized that adding comprehensive metastasis-directed therapy (MDT) to chemotherapy would improve progression-free survival (PFS) over chemotherapy alone among patients with limited metastatic (or oligometastatic) pancreatic ductal adenocarcinoma (PDAC). MDT, which has proven effective in multiple cancer types, focuses on targeting metastases with high-dose ablative radiation therapy.

The EXTEND trial (ClinicalTrials.gov identifier: NCT03599765) is a Phase II randomized basket trial for multiple solid tumors. The team focused on examining the effects of MDT on the immune system following earlier findings that suggested MDT could enhance the immune response. Between 2019 and 2023, researchers evaluated 40 patients with five or fewer metastatic sites in the pancreatic cancer basket of the trial. These patients were randomly assigned 1:1 to MDT plus systemic therapy versus systemic therapy. Disease progression was defined by radiologic criteria, clinical progression, or death. The primary end point was PFS in the per-protocol population, evaluated after all patients achieved at least six months of follow-up.

At a median follow-up of 17.3 months, PFS was 10.3 months in patients who received MDT plus chemotherapy compared to only 2.5 months in those who received standard chemotherapy. The results, published in the Journal of Clinical Oncology on August 5, revealed that MDT is effective and safe for patients with PDAC and is associated with improved PFS. The induction of a radiotherapy induced systemic immune response is a possible mechanism of benefit. Based on these findings, MD Anderson will lead the Phase III EXPAND trial to test whether MDT improves both PFS and overall survival for patients with PDAC, which will open in late 2024.

The University of Texas MD Anderson Cancer Center and Dr. Tang received a $2.4 million CPRIT Individual Investigator Research Award for Clinical Translation grant (RP180140) in 2018 in support of a randomized phase II basket trial to assess local control of oligometastatic disease.

272. Approximately 50% of all women with advanced triple-negative breast cancer (TNBC) will be diagnosed with brain metastases. Treatment involves surgery, radiotherapy, and systemic therapies but is limited by several factors, including blood-brain barrier, the tumor's complex biology, and the difficulty of targeting the tumors without harming surrounding brain tissue. Glioblastoma multiforme (GBM) is the most common and most aggressive primary brain tumor, with a median survival of only 20.9 months. As such, there remains an unmet need for both recurrent GBM (rGBM) and breast cancer with brain metastasis (BCBM).

This study, co-led by William Kelly, M.D., assistant professor, Department of Neuro-Oncology at The University of Texas Health Science Center San Antonio, focused on a drug called Sacituzumab Govitecan (SG), an antibody-drug conjugate (ADC) which targets Trop-2 for the selective delivery of SN-38 to tumors. Trop-2 is found on the surface of many cancer cells, including 95% of glioblastoma samples, but not in normal brain tissue. Unlike chemotherapy, it targets and kills tumor cells while sparing healthy cells.

In this phase 0 window-of-opportunity trial, scientists treated 25 patients with BCBM and rGBM with SG one day prior to tumor-tissue removal and on days 1 and 8 of 21-day cycles following recovery. The results, published in Nature Communications on August 7, revealed that SG could achieve concentrations of inhibitors inside the tumors sufficient to benefit patients with minimal side effects. Additionally, a xenograft model confirmed intracranial activity in mice. This data supports ongoing investigation in a phase 2 clinical trial (NCT04559230) of this drug in recurrent glioblastoma.

The University of Texas Health Science Center at San Antonio received a $1.5 million CPRIT Early Clinical Investigator grant (RP210164) in 2021 to test Sacitizumab, a novel antibody drug conjugate targeting the epithelial glycoprotein Trop2, in the treatment of recurrent glioblastoma.

273. The formation of the blood system is a complex and highly regulated process requiring the specification and maintenance of hematopoietic stems cells (HSCs) capable of producing nearly all blood and immune cells in adults. The mitochondrial permeability transition pore (mPTP) is a key player in this process, with roles in mitochondrial function and cell death. The contribution of the mPTP to normal physiology remains debated, although evidence suggests that it plays a part in reshaping the mitochondria as cells develop into blood cell precursors.

Researchers from the Department of Integrative Biology & Pharmacology at The University of Texas Health Science Center at Houston investigated how changes in mitochondrial structure affect the ability of these precursor cells to function as they mature. The researchers found that during a critical stage, the endothelial-to-hematopoietic transition (EHT), where cells switch from being part of blood vessel linings to becoming blood cells, there is strict regulation of the mPTP. Just before cells commit to becoming blood cells, the activity of the mPTP is limited, and then it is restored after the cells have changed identity.

When the team treated embryos with NIM811, a molecule that prevents the mPTP from opening too easily, it boosted the cells' energy production through a process called oxidative phosphorylation (OXPHOS) and increased the production of blood cells in the embryo. These findings, published in Communications Biology on August 9, highlight the importance of the mPTP in shaping the mitochondria during the formation of blood cells and suggest that manipulating the mPTP could influence the development of the blood system.

The University of Texas Health Science Center at Houston received a $598,472 Shared Instrumentation Awards grant (RP110776) in 2011 to purchase and supported use of a shared custom fluorescence activated cell sorter.

274. Glioblastoma (GBM), the most common and aggressive primary brain tumor, remains difficult to treat due to its resistance to conventional chemotherapy and the role of glioblas-

toma stem cells (GSCs) in tumor development and recurrence. Natural killer (NK) cells, part of the innate immune system, can target and kill GSCs and other tumors and researchers are exploring ways to enhance their effectiveness.

In this study, first author Mayra Shanley, Ph.D., principal research scientist at The University of Texas MD Anderson Cancer Center, and co-authors used multiple models to treat GSCs with NK cells engineered to express either IL-21 or IL-15, immune-signaling molecules used to boost NK cell activity. The team found that while IL-15 NK cells were highly toxic and ineffective at tumor control in vivo, the IL-21 NK cells were safe and resulted in long-term anti-tumor activity. Researchers also found that the effectiveness of IL-21 NK cells was linked to specific changes in gene expression, particularly CEBPD, a protein critical for maintaining their killing power and metabolic health. When researchers deleted CEBPD, the potency of IL-21 NK cells decreased, while overexpression of CEBPD in NK cells further improved their ability to target and destroy GSCs.

These findings, published in Cancer Cell on August 12, highlight the potential of IL-21 to enhance NK cell therapy for GBM through epigenetic reprogramming. Based on these findings, researchers at MD Anderson plan to launch a clinical trial of IL-21-engineered NK cells for GBM patients in late 2024, offering hope for more effective treatment.

The University of Texas MD Anderson Cancer Center received a $4.9 million CPRIT Core Facilities Support Awards grant (RP180684) in August 2018 to establish an Integrated Single Cell Genomics (SCG) Core Facility.

275. Glioblastoma (GBM) is a highly aggressive brain cancer with a median survival of only 8–16 months and accounts for nearly half of all malignant brain and central nervous system tumors. Current diagnosis and treatment evaluation methods, such as histology and MRI, often detect the disease in its later stages, limiting treatment effectiveness. Researchers hope that artificial intelligence (A.I.) can provide an opportunity for early diagnosis.

Co-corresponding author Pratip K. Bhattacharya, Ph.D., associate professor, Department of Cancer Systems Imaging at The University of Texas MD Anderson Cancer Center, and colleagues focused on hyperpolarized magnetic resonance spectroscopy (HPMRS), a technique which holds promise for early GBM detection or predicting treatment effects but remains costly. In this study, published in MDPI Metabolites on August 14, the team developed a deep learning model that integrates multiple types of tumor information to predict tumor progression and evaluate treatment effects. This model detected GBM progression two weeks earlier than conventional MRIs and a week earlier than HPMRS alone. It accurately predicted in vivo biomarkers using ex vivo information such as conventional MRIs, HPMRS, and tumor size data.

The model demonstrated the ability to predict treatment outcomes and has the potential to expand the range of metabolites that scientists can analyze in live studies. These advancements could lead to earlier GBM diagnosis and better treatment strategies.

The University of Houston received a $1.6 million CPRIT Research Training Award Continuation grant (RP140113) in 2014. The University of Texas MD Anderson Cancer Center received a $4 million CPRIT Research Training grant (RP170067) in 2016, and a $1.05 million CPRIT Individual

Investigator grant (RP220270) in 2022. The University of Texas Health Science Center at Houston recruited Dr. Jiang from the University of California San Diego in 2018 with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR180012) and received a $915,256 CPRIT Individual Investigator grant (RP220313) in 2022.

276. Mitochondrial alterations are a common feature of renal cell carcinomas (RCCs), but scientists do not fully understand how these mutations affect nutrient metabolism in human RCCs. In this study, corresponding author Ralph DeBerardinis, M.D., Ph.D., CRI Professor and Howard Hughes Medical Institute (HHMI) Investigator, and first author Divya Bezwada, Ph.D., collaborated with surgeons from the Department of Urology at The University of Texas Southwestern Medical Center to investigate how nutrient metabolism, particularly mitochondrial function, evolves in RCCs as they progress from primary tumors to metastases.

The researchers infused over 80 kidney cancer patients with labeled carbon nutrients during tumor removal surgery to track nutrient utilization directly within the tumor. The results revealed a stark contrast in mitochondrial activity: primary kidney tumors suppress mitochondrial metabolism, but once these tumors metastasized to other organs like the liver, lungs, and brain, mitochondrial activity increased.

The study, published in Nature on August 14, revealed that a shift in energy production strategies occurs as the cancer spreads. These findings challenge the century-old Warburg hypothesis, which suggested that cancer cells downregulate mitochondrial metabolism in favor of glycolysis for energy production. Instead, the study demonstrated that reactivation of mitochondrial metabolism is a key driver of metastasis. This discovery opens new avenues for therapeutic interventions aimed at targeting mitochondrial activity in metastatic RCC and potentially other cancers.

“For a century, the dominant idea in cancer biology was that aggressive tumors turn off mitochondrial metabolism to grow and spread. The new research – which studied cancer metabolism directly in patients – shows the opposite: Activating mitochondrial metabolism drives metastasis,” Dr. DeBerardinis said. “Metastasis is the most important cause of cancer-related deaths in patients with cancers of the kidney and most other organs. Metastatic tumors are the ones we most need to treat.”

The University of Texas Southwestern Medical Center received a $6 million CPRIT Multi-Investigator Research Awards (Version 2) grant (RP180778) in 2018 to identify new therapeutic strategies that inhibit melanoma progression by exacerbating oxidative stress or by increasing the effectiveness of immunotherapy by modulating immune cell metabolism within tumors.

277. Liver regeneration after injury involves both metabolism and the immune system. Neutrophils, a type of immune cell, play a key role in this process, but it is unclear how the liver signals to the bone marrow to release neutrophils after injury and how reparative neutrophils signal to hepatocytes to reenter the cell cycle.

In this study researchers including Hao Zhu, M.D., director of Children Research Institute’s Tissue Regeneration Program and a co-leader of the Development and Cancer Research Program in the Simmons Comprehensive Cancer Center, report that loss of the liver tumor suppressor Lifr in mouse hepatocytes impairs, whereas overexpression of leukemia inhibitory factor receptor (LIFR) promotes liver repair and regeneration after partial hepatectomy or toxic injury. When the liver is

damaged, LIFR in liver cells triggers the release of cholesterol and a signaling molecule (CXCL1). These signals, through a pathway involving the protein STAT3, cause neutrophils from the bone marrow to travel to the liver. Once there, cholesterol activates neutrophils to release a substance called hepatocyte growth factor, which promotes liver cell regeneration.

This study published in Nature Metabolism on August 15, reveals a bidirectional hepatocyte–neutrophil communication system, where liver damage prompts neutrophils to help repair the liver.

The University of Texas Southwestern Medical Center received a CPRIT High Impact/High Risk grant (RP220614) in 2022 to investigate the impact of immunity on pre-malignant somatic mosaicism and cancer prevention.

278. Small cell lung cancer (SCLC) is a difficult-to-treat cancer with neuroendocrine origins, an interconnection between the endocrine and nervous systems, and treatment options have not significantly changed over the years. In this study, researchers from The University of Texas Southwestern Medical Center used preclinical models to identify a new potential treatment approach by targeting a family of enzymes called Jumonji lysine demethylases (KDMs).

To determine if SCLC lines in culture reflected expression patterns similar to patient specimens, researchers used preclinical models to identify a promising therapeutic vulnerability in small cell lung cancer (SCLC) by targeting the Jumonji lysine demethylase (KDM) family. By studying expression patterns in 78 patient-derived cell lines and 87 tumor specimens, the researchers discovered that Jumonji demethylase inhibitors effectively block SCLC growth, particularly in cases resistant to the chemotherapy drug etoposide. These inhibitors cause stress in the cancer cells' endoplasmic reticulum (a structure important for protein production), leading to cell death and reduced levels of proteins critical for SCLC progression, such as INSM1, Secretogranin-3, ASCL1, and NEUROD1.

This study also highlights that Jumonji inhibitors decrease levels of proteins that drive SCLC growth, like INSM1, Secretogranin-3, ASCL1, and NEUROD1. The findings, published in Oncogene on August 18, further reveals that small molecule inhibitors, JIB-04 and SD70 suppress tumor growth in animal models of SCLC, reinforcing their potential as therapeutic agents.

With the advent of clinical trials for this drug class with the KDM4 inhibitor TACH101 currently open for the first time (NCT05076552), the translation of these findings to the clinical setting may be within the foreseeable future. This drug class holds promise not only for SCLC but also for other tumors with similar molecular vulnerabilities, especially those lacking functional RB1. By addressing mechanisms of therapy resistance and targeting fundamental cellular stress pathways, Jumonji inhibitors could represent a significant advance in cancer treatment.

The University of Texas Southwestern Medical Center received a $4 million CPRIT Research Training grant (RP160157) in 2016 to support the Cancer Intervention and Prevention Discoveries program to train scientists capable of conducting independent cancer research with a deep understanding of the science, public health, and clinical problems of human cancer.

279. Mutations or defects in BRCA2 predispose the affected individuals to breast, ovarian, and other cancers. BRCA2 plays a critical role in repairing damaged DNA by interacting with a protein called RAD51. Together, they help repair DNA breaks through a process called homolo-

gous recombination. BRCA2 also protects perturbed DNA replication forks from nucleolytic degradation (replication fork protection, RFP), preventing damage and the buildup of harmful DNA-RNA hybrids (R-loops). When BRCA2 is defective, cells become unstable, more prone to DNA damage, and highly sensitive to certain stressors. However, the molecular mechanism(s) governing BRCA2's targeting of nucleic acid substrates during these processes remains elusive.

DSS1, a protein linked to various cancers, forms a stable partnership with BRCA2. This study, led by corresponding author Weixing Zhao, Ph.D., assistant professor, Department of Biochemistry and Structural Biology at The University of Texas Health and Science Center San Antonio, highlights how DSS1 fine-tunes BRCA2's ability to help RAD51 bind to single-stranded DNA (ssDNA) instead of double-stranded DNA (dsDNA). This interaction improves BRCA2's effectiveness in repairing DNA through homologous recombination (HR), protecting DNA during replication, and preventing harmful R-loops.

The potential therapeutic implications of these findings are significant. The team proposed that targeting the interaction between DSS1 and BRCA2 with small molecules or peptides could serve as effective sensitizers for DNA-damaging therapies. Scientists could potentially integrate these agents into existing radiotherapy or chemotherapy regimens or used alongside PARP inhibitors to enhance the killing of tumor cells. This approach, published in Nature Communications on August 17, represents a promising avenue for improving cancer treatment outcomes, particularly in cancers driven by BRCA2 mutations or deficiencies.

The University of Texas Health Science Center at San Antonio received a $250,000 CPRIT High Impact/High Risk grant (RP210102) in August 2021 to study the key functions of BRCA1 and to provide the foundation for formulating new treatment regimens.

280. The alternative lengthening of telomeres (ALT) mechanism is a hallmark of certain cancers, including sarcomas, and is associated with distinct patterns of therapy resistance and sensitivity. A key feature of ALT cancers is the presence of telomeric DNA C-circles, which are self-primed circular telomeric repeats. These C-circles serve as a highly specific and sensitive biomarker for ALT cancers and scientists can detect them using the real-time PCR C-circle assay (CCA).

Previous research identified the ALT phenotype in 23% of high-risk neuroblastomas. In this study, the team led by C. Patrick Reynolds, M.D., Ph.D., director of the School of Medicine Cancer Center at Texas Tech University Health Sciences Center, shifted the focus to assessing the prevalence of ALT in other sarcoma types—Ewing's family sarcoma (EFS), rhabdomyosarcoma (RMS), and osteosarcoma (OS)—by analyzing DNA extracted from fresh frozen primary tumor samples using the CCA.

The study aimed to refine the understanding of ALT prevalence across the sarcoma subtypes, offering insights into their biology and potential for therapeutic targeting. The team used a sample cohort which included DNA from 94 EFS, 187 RMS, and 87 OS primary tumors. The findings revealed that there were no ALT cases detected in EFS; in RMS, ALT was detected in 2.7% of tumors; and in OS, ALT was observed in 71% of tumors. The high prevalence of ALT in OS compared to EFS and RMS underscores the significant variability in telomere maintenance mechanisms across sarcoma subtypes. The data, published in Frontiers in Oncology on August 18, suggests that the real-time PCR CCA can identify ALT in sarcomas, and it has potential as a companion diagnostic assay for ALT-targeted therapies in RMS, and especially OS, patient popu-

lations.

The Texas Tech University Health Sciences Center received a $1.34 CPRIT Individual Investigator Research Awards for Cancer in Children and Adolescents grant (RP220460) and a $6 million Texas Regional Excellence in Cancer Award (RP210154) in 2021.

281. In Alzheimer's disease (AD), the buildup of β-amyloid proteins causes dysfunction in the early stages of pathology. The hippocampus, a region critical for memory, is affected early in the pathogenesis of AD, however the impact of soluble β-amyloid on the dentate gyrus (DG) subregion of the hippocampus and its interaction with nicotinic acetylcholine receptors (nAChRs) within this region are not known.

In this study, CPRIT Scholar John Wood, department chair, Robert A. Welch Distinguished Professor of Chemistry & Biochemistry, and co-director, Baylor Synthesis and Drug Lead Discovery Lab at Baylor University, and fellow researchers focused on how soluble β-amyloid affects the DG and its interaction with nAChRs. The team found that overexpression of β-amyloid in mice led to increased neuron activity and memory problems. Interestingly, the researchers discovered that certain subtypes of nAChRs play a key role in controlling activity in the DG, both in healthy and diseased conditions. By inhibiting these receptors, they were able to reverse memory deficits caused by β-amyloid.

While neurogenesis and synaptic function were not severely impacted, reducing the function of a specific nAChR (β2-containing) promoted the growth of young neurons, suggesting a potential protective response. This study, published in Molecular Psychiatry on August 20, sheds light on how the DG region changes during the early stages of Alzheimer's and suggests that targeting nicotinic receptors could help alleviate some of the negative effects of β-amyloid buildup.

Baylor University recruited Dr. Wood from the Colorado State University in 2013 with the support of a $4.2 million CPRIT Recruitment of Established Investigators grant (R1309).

282. According to the American Cancer Society, clinicians will diagnose nearly 21,000 new cases of acute myeloid leukemia (AML) in the U.S. in 2024, with a poor outlook for many types of AML, especially in older patients. A global team of scientists, including CPRIT Scholar Bruno Di Stefano, Ph.D., and other researchers from Baylor College of Medicine, has discovered how AML cells help themselves grow. These new findings, published online on August 21 in Nature Cell Biology, shed light on how AML cells survive and offer potential for new cancer treatments.

Previous research showed that leukemia cells influence the process of translating mRNAs into proteins to aid their growth, but the details were unclear. The investigators employed the powerful CRISPR technology to systematically turn off genes in both healthy and leukemia cells to uncover key differences. These studies revealed that a class of genes that regulate the function of "P-bodies" are crucial for AML cells, and that that leukemia cells had more P-bodies than normal cells.

First recognized two decades ago, P-bodies are a type of biomolecular condensate inside cells that serve as reservoirs sequestering specific mRNAs from the cellular machinery that translates them into proteins until the cells need them. By adjusting the stability of P-bodies, the scientists demonstrated that P-body formation is essential for AML to develop and survive. When they removed a protein called DDX6, which is crucial for creating P-bodies, the leukemia cells died in

models of human AML, while normal blood cells were unaffected. This highlights the potential for targeting P-body formation as a treatment for AML.

AML is a complex disease and discovering a molecular pathway that might serve as its Achilles' heel has several important implications. These findings provide novel insights into the little studied mechanism of controlled mRNA translation in the context of cancer development. Since the DDX6 protein is a drug target, this opens the door to developing new cancer therapies focused on this mechanism.

Baylor College of Medicine recruited Dr. Di Stefano (RR200079) and co-author Eric Van Nostrand, Ph.D. (RR200040) to Texas in 2020 with CPRIT Recruitment of First-Time, Tenure-Track Faculty Members grants. BCM received a $5.2 million CPRIT Core Facility Support Awards grant (RP180672) in 2018 to support the CPRIT Cytometry and Cell Sorting Core.

283. Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer and often has worse clinical outcomes and high early recurrence rates compared to other breast cancer subtypes. TNBC is known for its lack of expression of common hormone receptors making it very difficult to treat with hormone receptor-specific therapies like tamoxifen.

Epithelial-to-mesenchymal transition (EMT) is a process where cells change from a stable, non-invasive state (epithelial) to a more mobile and aggressive form (mesenchymal). While EMT is a normal part of development, cancer cells utilize EMT to invade and migrate to other sites during metastasis. In this study, researchers including corresponding author Bruce A. Bunnell, Ph.D., Department of Microbiology, Immunology and Genetics, University of North Texas Health Science Center, explored new treatments, including drugs called kinase inhibitors, which block signals that help cancer grow. Their aim was to identify novel kinase pathways that affected breast cancer cell proliferation and metastatic capabilities to find new targets for breast cancer treatment.

The team tested a library of 187 kinase inhibitors and found 14 compounds that slowed the growth of TNBC cells. Three drugs—THZ531, THZ1, and PFE-PKIS 29—were especially effective across different TNBC cell types. The results, published in Anti-Cancer Drugs on August 21, highlight new potential drug targets to help stop TNBC from spreading.

University of North Texas Health Science Center at Fort Worth received a $3.9 million CPRIT Research Training grant (RP210046) in 2021 to recruit and train underrepresented minorities and disadvantaged scholars.

284. Otopetrin (OTOP) proteins, which are proton-activated channels, play a role in allowing protons to move across cell membranes, and changes in acidity (pH) outside the cell trigger their activity. Humans have three types: OTOP1, OTOP2, and OTOP3, each found in specific tissues. Scientists have found lower levels of OTOP2 expression in colorectal cancers, implying a possible contribution to cancer development. However, the structural mechanisms underlying some basic functional properties of the OTOP channels remain unresolved, including extracellular pH activation, proton conducting pathway, and rapid desensitization.

In this study, published in Nature Communications on August 23, researchers at The University of Texas Southwestern Medical Center studied the structures of OTOP proteins from Caenorhabditis elegans (CeOTOP8) and mice (mOTOP2). Corresponding author Youxing Jiang, Ph.D., pro-

fessor, Department of Physiology | Biophysics at The University of Texas Southwestern Medical Center, and team combined data from both channels and proposed a step-by-step model of how OTOP channels undergo conformational changes to conduct protons efficiently. Understanding these structural mechanisms helps explain how OTOP channels function and could inform future research into their roles in physiological processes or diseases, potentially leading to targeted therapeutic strategies.

The University of Texas Southwestern Medical Center received a $5.5 million CPRIT Core Facility Support Awards grant (RP170644) in 2017 to establish a new Cryo-Electron Microscopy Core Facility and Service for Structure Determination at UT Southwestern Medical Center.

285. Idiopathic pulmonary fibrosis (IPF), a disease that causes lung scarring, is associated with a low life expectancy, few treatment options, and is a major cause of death. Currently, lung transplantation is the only effective treatment, but many patients are unable to receive an organ donation due to a shortage of suitable lungs and a high risk of mortality from the transplant procedure.

In this study, researchers led by CPRIT Scholar Yair Reisner, Ph.D., professor, Department of Stem Cell Transplantation, Division of Cancer Medicine at The University of Texas MD Anderson Cancer Center, investigated the efficacy of lung stem cell transplantation using single-cell suspensions of an entire lung in two distinct in vivo models of lung fibrosis. The transplant successfully slowed disease progression, resulting in improved lung function and a reduction of fibrotic tissue compared to untreated controls. The use of two distinct models suggests promising clinical potential for treating lung fibrosis, whether caused by chemotherapy-induced lung injury or genetic factors leading to the depletion of progenitor cells in IPF. The results, published in Science Advances on August 23, offer proof-of-concept for further investigation into the treatment of lung fibrosis using lung cell suspensions and highlight the potential for lung stem cell transplants as a new therapeutic option for patients with limited treatment choices.

The University of Texas MD Anderson Cancer Center recruited Dr. Reisner in 2017 from the Weizmann Institute with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR170008).

286. Immunodeficiency, centromeric instability, and facial anomalies (ICF) syndrome is a rare autosomal recessive disease characterized by facial dysmorphism, immunoglobulin deficiency, and branching of chromosomes 1, 9, and 16. Cell Division Cycle Associated 7 (CDCA7), a protein coding gene, is mutated in ICF syndrome, but its role in DNA methylation, a chemical modification of DNA, is unknown.

Researchers led by CPRIT Scholar Xiaodong Cheng, Ph.D., professor, Department of Epigenetics and Molecular Carcinogenesis at The University of Texas MD Anderson Cancer Center, discovered how CDCA7 interacts specifically with non-B DNA that contains a CpG sequence, a common DNA pattern in the genome. CDCA7 has a unique region (CRD) that allows it to recognize and bind to these structures in a precise way, especially when one strand of the DNA is partially methylated—a chemical modification important for gene regulation.

The team found that, compared to other proteins that bind methylated DNA, CDCA7 has a distinct

mechanism. Instead of flipping the DNA base out of the strand like some proteins, CDCA7 binds best to these non-B DNA structures when one DNA strand is partially methylated. In ICF syndrome, CDCA7 mutations disrupt this ability, leading to improper DNA methylation and instability in these regions. These findings, published in Science Advances on August 23, help explain how CDCA7 influences DNA methylation and stability and shed light on its role in certain genetic disorders like ICF syndrome, where DNA regulation is disrupted.

The University of Texas MD Anderson Cancer Center recruited Dr. Cheng in 2016 from Emory University School of Medicine with the support of a $6 million CPRIT Recruitment of Established Investigators grant (RR160029).

287. Spatial transcriptomics (ST) measures gene expression while preserving the spatial information, which is crucial for exploring the tumor microenvironment (TME) and understanding how cellular composition varies across different tumor regions. However, most existing analytical tools lack critical tissue-level features and rely on matched single-cell RNA sequencing data. This reliance limits their ability to fully capture the complexity of the TME, including spatial organization and interactions between cells in their native context.

To address the demand for better profiling of different cell types and their behaviors within the TME, researchers developed a framework that systematically analyzes cancer cells and cells of the TME by incorporating spatial gene expression, tissue histology, and prior knowledge of cancer and TME cells. Humam Kadara, Ph.D., professor, Department of Translational Molecular Pathology, and colleagues at The University of Texas MD Anderson Cancer Center introduced the Morphology-Enhanced Spatial Transcriptome Analysis Integrator (METI), an end-to-end framework, which provides considerable advantages in terms of flexibility and applicability across various datasets.

The team evaluated the performance of METI on ST data generated from various tumor tissues, including gastric, lung, and bladder cancers, and premalignant tissues. They also conducted a quantitative comparison of METI, published in Nature Communications on August 25, with existing clustering and cell deconvolution tools, demonstrating that METI outperforms these existing tools. By seamlessly integrating with existing clinical diagnostic and treatment planning tools, METI has the potential to complement and enhance current diagnostic workflows, facilitating more informed decision-making in clinical settings. While METI presents a useful framework for in-depth cancer cell and TME cell profiling, it is important to recognize its limitations and the need for further studies.

The University of Texas MD Anderson Cancer Center received a $831,561 CPRIT Individual Investigator grant (RP220101) in 2022 to unravel an “atlas” of KRAS-mutant lung cancer evolution in space and in time and of its response to early immune-based treatment.

288. The circadian clock (CC) is an internal timing system which plays a crucial role in regulating metabolism, immunity, and hormonal functions in mammals. Scientists have discovered that perturbation of CC function in murine models causes diverse pathologies including chronic liver disease and cancer.

Hepatitis C virus (HCV) is a major cause of chronic liver disease and hepatocellular carcinoma

(HCC). Despite significant strides, scientists have a limited understanding of the molecular basis of HCV-induced liver disease and HCC development. In this study, researchers investigated the role of the hepatic clock in liver disease biology using an advanced mouse model with human liver cells, along with data from HCV-infected patients to study how HCV disrupts the liver's normal daily rhythms.

CPRIT Scholar Yujin Hoshida, M.D., Ph.D., director of the Liver Tumor Translational Research Program at The University of Texas Southwestern Medical Center, and colleagues used a state-of-the-art in vivo model system. Their data, published in Nature Communications on August 29, show that the disruption of the liver's circadian rhythms due to HCV impacts biomarkers associated with liver cancer risk. These disruptions may serve as early indicators of liver cancer risk in HCV patients. Since compounds targeting the CC have slowed liver disease progression in animal models, these findings could pave the way for developing CC-based biomarkers to predict HCC risk and identify novel therapeutic targets for cancer prevention.

The University of Texas Southwestern Medical Center recruited Dr. Hoshida in 2018 from the Icahn School of Medicine at Mount Sinai with the support of a $4 million CPRIT Recruitment of Rising Stars grant (RR180016). UT Southwestern Medical Center received a $2.5 million Collaborative Action Program to Reduce Liver Cancer Mortality in Texas: Investigator-Initiated Research Awards grant (RP200554) in August 2020.

289. Multiple myeloma (MM) is a cancer of plasma cells within the bone marrow and remains incurable. The tumor microenvironment (TME) in MM houses a complex range of elements that support tumor progression, immunosuppression, and drug resistance. Recently, researchers have focused on boosting the immune system, specifically targeting macrophages (immune cells).

IL-10 is a key immunosuppressive cytokine that leads to recruitment and development of tumor-associated macrophages (TAMs). In the context of cancer, TAMs are a prominent population within the TME, especially in MM, and correlate negatively with patient survival. In this study, corresponding author and CPRIT Scholar Abdel Kareem Azab, Ph.D., associate professor, Department of Biomedical Engineering at The University of Texas Southwestern Medical Center, and colleagues investigated the role of IL-10 in MM TAM development as well as the therapeutic application of IL-10/IL-10R/STAT3 signaling inhibition.

The results show that MM cells release high levels of IL-10, which transforms macrophages into tumor-supporting cells that promote growth and drug resistance. This creates a harmful cycle that helps the tumor thrive. By blocking the IL-10 signaling pathway with an anti-IL-10R mAb reversed this effect, stopping the tumor-supporting activity of the macrophages and reducing tumor growth and drug resistance.

Published in Leukemia on August 30, these findings present a novel strategy reprogramming TAMs to stop supporting tumors and instead use their natural ability to fight cancer. alongside current MM treatment. This approach could improve MM treatment and potentially benefit patients with other cancers, like breast cancer, where macrophages play a similar role in drug resistance. Further research is needed to confirm its effectiveness in clinical settings.

The University of Texas Southwestern Medical Center recruited Dr. Azab in 2022 from Washington University, St. Louis, with the support of a $2 million CPRIT Recruitment of Rising Stars grant (RR220088).

290. The inner lining of the colon consists of cells that form a protective barrier, keeping harmful substances like bacteria and toxins out of the body. When this barrier is damaged due to infection, inflammation, chemical or physical insults, or ischemia, the body normally has a system in place to heal the wound and restore the protective layer. However, when this healing process is disrupted, it can lead to conditions like inflammatory bowel disease (IBD), characterized by recurrent or chronic impairment of mucosal barrier integrity, bacterial infiltration into the bowel wall, pronounced inflammation, and compromised wound healing.

Researchers have identified two important molecules, cystathionine gamma-lyase (CSE) and TNF-α, as key regulators of intestinal maintenance and wound healing. While both are known to influence biological processes in the colon, how they interact with each other has been unclear. In this study, Mark Hellmich, Ph.D., professor, Department of Surgery at The University of Texas Medical Branch at Galveston, and fellow researchers explored these interactions using lab models of healthy human colon cells.

The research revealed that TNF-α quickly activates CSE, increasing endogenous CSE-derived H2S production, which is important for cell function. In return, CSE activity helps amplify TNF-α's ability to promote healing responses, but did not affect the p38 MAPK signaling pathway. This data, published in Antioxidants on August 31, suggests that CSE activity is essential during intestinal injury response, and that targeting the regulation of CSE and its related signaling pathways may offer promising therapeutic strategies for treating colon diseases such as IBD. By enhancing CSE activity, it may be possible to improve wound healing and restore the integrity of the colon's epithelial barrier.

The University of Texas Medical Branch at Galveston received a $1.6 million CPRIT Bridging the Gap: Early Translational Research Awards grant (DP150074) in 2014 to make new and better drugs for patients with colorectal cancers, particularly those with tumors that express KRAS or BRAF mutations.

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