**FY 2021 Published Research Findings Supported by CPRIT Grant Awards**

- CPRIT Scholar Kyle Miller, Ph.D., associate professor of molecular biosciences at The University of Texas at Austin, and his colleagues discovered a protein that drives treatment resistance in aggressive cancers. Patients with low levels of this protein, called PCAF, are more likely to experience cancer growth and metastasis. Using PCAF as a molecular marker, doctors can predict which patients will become resistant to PARP inhibitors—a class of drug commonly used to treat BRCA-deficient tumors. The study, published in the journal *Molecular Cell* on **September 22, 2020**, shows that BRCA-deficient tumors are better able to resist PARP inhibitors when they have low levels of PCAF. "A major issue with cancer treatments is the development of resistance," said Dr. Miller. "When treatments stop working for patients, it's incredibly demoralizing and it's been a huge drive in research to understand these resistance mechanisms." With the help of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty grant (R1116), the University of Texas recruited Dr. Miller from the University of Cambridge in England.

- Researchers from The University of Texas MD Anderson Cancer Center led a Phase 1 clinical trial with promising results for patients with advanced solid cancers, such as non-small cell lung cancer and colorectal cancer, who often receive a poor diagnosis. The researchers used sotorasib, a small-molecule inhibitor, to treat patients with KRAS G12C cancer mutations—one of the most common types of cancer-promoting KRAS mutations. During the study, published in *The New England Journal of Medicine* on **September 24, 2020**, patients who received targeted therapy with sotorasib experienced tumor shrinkage and disease stabilization. In June of 2021, the U.S. Food and Drug Administration approved sotorasib to treat patients with non-small cell lung cancer, making it the first FDA approved therapy to target KRAS mutations. In 2015, the MD Anderson Cancer Center received a $6 million CPRIT Precision Oncology Decision Support Core award (RP150535) to conduct patient-specific research on cancer genomics.

- Led by Lydia Kavraki, Ph.D., researchers from the Brown School of Engineering at Rice University developed a new computational tool that simulates human metabolic reactions to test the safety and efficacy of drug compounds. This tool, called the Metabolite Translator, uses a rule-free, end-to-end learning-based method that can analyze a broad range of enzymes and metabolites, unlike customary rule-based systems that can only analyze a limited number of chemicals. And as recorded in *Chemical Science* on **September 24, 2020**, this new tool predicts small molecule sequences as reliably as rule-based systems. "Using a machine learning-based method, we are training a system to understand human metabolism without the need for explicitly encoding this knowledge in the form of rules," said Dr. Kavraki, Noah Harding Professor of Computer Science, and director of the Ken Kennedy Institute at Rice University. With access to a greater range of chemical reactions, scientists can use the Metabolite Translator to develop new innovative drugs and treatments. In 2016, CPRIT awarded a $900,000 Individual Investigator Academic Research award (RP170508) in support of Dr. Kavraki's work at Rice University.

- CPRIT investigator Andy Futreal, Ph.D., professor of genomic medicine at The University of Texas MD

Anderson Cancer Center, and his colleagues discovered that cancerous cell mutations accumulate in region-specific genome patterns. Published on **October 5, 2020**, in *Nature Genetics*, the research shows that this accumulation process depends highly on a cell's genome structure and mutational cause. Using more than 3,000 pairs of sequencing samples across 42 cancer types, the researchers examined the rate of mutation in cells that organize in active and inactive regions. (Commonly used genes organize in active regions while seldom used genes organize in inactive regions.) They discovered that mutations in inactive regions occurred more often. In further experiments, they found that external cancer-causing factors (e.g., ultraviolet light and tobacco smoke) drove mutations within inactive regions, but internal cancer-causing factors (e.g., random errors in DNA repair) drove mutations within active regions. By shedding light on this mutation-accumulation process, this study can lead to new precision targeting therapies. With the help of a $7 million Recruitment of Established Investigators award from CPRIT (R1205), granted in 2011, the MD Anderson Cancer Center recruited Dr. Futreal from Wellcome Trust Sanger Institute in England.

- Researchers from The University of Texas MD Anderson Cancer Center Linghua Wang, M.D., Ph.D., and Sattva Neelapu, M.D., led a study on the efficacy and toxicity of chimeric antigen receptor (CAR) T cell therapy in patients with large B-cell lymphoma (LBCL). While highly effective against LBCL, CAR T cell therapy can cause serious adverse effects in some patients. The study, published in *Nature Medicine* on **October 5, 2020**, identifies DNA signatures that indicate how individuals with LBCL will respond to CAR T cell therapy. During the 24-patient study, the researchers found that individuals whose DNA expressed memory signatures within the first week of therapy responded positively, while those whose DNA expressed certain exhaustion signatures within the first week responded poorly. "This study also tells us that some rare and unexpected cells identified by single-cell analysis could be biologically important," said Dr. Linghua Wang. "Going forward, we plan to functionally characterize these monocyte-like cells to better understand their specific biological mechanisms driving these clinical results." In support of their innovative work on CAR T cell immunotherapy, CPRIT granted $900,000 Individual Investigator Academic Research awards to Dr. Wang, assistant professor of genomic medicine, in August of 2020 (RP200385) and to Dr. Neelapu, professor of lymphoma and myeloma, in February of 2015 (RP150316).

- OncoNano Medicine Inc. announced positive results from a Phase 2a study of ONM-100, a novel imaging agent used in solid tumor surgeries. ONM-100 is one of the few imaging tools that allow doctors to identify small tumors that metastasized. The data, presented at the World Molecular Imaging Congress 2020 virtual program on **October 7–10, 2020**, show that surgeons can use ONM-100 to take feasible images of breast, prostate, ovarian, and head and neck cancers. "These data indicate that ONM-100 was well-tolerated and was able to visualize various solid tumor types," said Ravi Srinivasan, Ph.D., president of OncoNano Medicine. In August of 2020, Southlake-based OncoNano received a $10 million CPRIT Product Development Research award (DP200081) to develop the surgical imaging tool ONM-100 for breast, head, neck, and skin cancers.

- Collaborating with scientists from the University of North Carolina at Chapel Hill, researchers from Baylor College of Medicine engineered immune cells to fight neuroblastoma—a common type of pediatric cancer. In their study, published in *Nature Medicine* on **October 12, 2020**, the researchers presented results from an ongoing clinical trial which suggest that the engineered cells are safe and

effective. During the study, the researchers genetically modified natural killer T cells (NKT cells) with a chimeric antigen receptor (CAR) and an IL-15 protein to attack tumors directly and support NKT cell survival. “Our initial results show that NKT cells can be expanded to clinical scale with high purity, genetically engineered to express a CAR and IL15, and used to safely treat patients with advanced neuroblastoma,” said Leonid S. Metelitsa, M.D., professor of pediatrics-oncology at Baylor College of Medicine. In 2015, Baylor College of Medicine received a $4 million Academic Research award (RP160283) in support of its comprehensive cancer training programs. CPRIT grantee Kuur Therapeutics licensed this CAR-NKT platform.

- In an international study, researchers from The University of Texas MD Anderson Cancer Center, Baylor College of Medicine, and the University of Houston identified a protein that plays a key role in cancer progression. The study, published in *Nature Communications* on **October 14, 2020**, shows that the protein TAp63, which typically suppresses tumor growth, directly affects IncRNA, an RNA molecule that promotes cancer growth and metastasis. The less active TAp63 proteins are, the more active IncRNA molecules become; this leads to more cancer-causing genes like the TROLL-2 and TROLL-3 expressions that occur in breast cancer. Scientists can use these early results to develop better diagnostic tools and treatments against metastatic cancers. The Houston-based contributors received two CPRIT awards. Stephanie Watowich, Ph.D., professor of immunology at the UT MD Anderson Cancer Center received a $1.7 million Research Training Award in February of 2014 (RP140106) for leading clinical cancer care and translational cancer research. In February of 2015, Chunru Lin, Ph.D., assistant professor of molecular and cellular oncology at MD Anderson, received a $900,000 CPRIT Individual Investigator Academic Research award (RP150094) for her research on mammary tumor progression and metastasis.

- In a multi-institutional research project, scientists from Texas A&M University College of Medicine, Baylor College of Medicine, and Texas Children’s Hospital developed a new method for monitoring medulloblastoma—the most common type of pediatric brain cancer. Current monitoring methods, such as MRI scans and tumor biopsies, test for biomarkers that do not consistently predict a patient’s response to treatment. However, this new method detects epigenetic abnormalities that are unique to pediatric brain cancer; by screening for these biomarkers, doctors can monitor patients’ progress with greater accuracy. As recorded in *Science Advances* on **October 16, 2020**, this method allows doctors to detect DNA methylation, an epigenetic marker found in cerebrospinal fluid, to monitor tumors as patients continue their treatment plans. “This is essentially a completely novel way of detecting DNA methylation in circulating DNA and using it for biomarker detection and quantitation in childhood cancer,” said study co-author Peter Davies, M.D., Ph.D., director of the Center for Translational Cancer Research at the Texas A&M Institute of Biosciences and Technology. In support of this work, CPRIT has granted two Core Facility Support awards (RP150578, RP200668), a Recruitment of First-Time, Tenure-Track Faculty grant (RR140053), and an Individual Investigator Research award (RP180131), totaling approximately $13 million.

- A team of researchers from Rice University and Baylor College of Medicine developed a new platform that isolates specific cells and their unique properties. This platform, called SPOTlight, monitors cellular expression using a method that is more reliable and more efficient than those used in comparable tools. With the SPOTlight tool, synthetic biologists can engineer new proteins, nucleic

acids, and cells, all of which could lead to new cancer prevention, diagnostic, and treatment methods. This study is available in the **October 23, 2020**, issue of *Science Advances*. Several CPRIT Scholars at Baylor College of Medicine (RR150005, RR150093, RR170023, RR180072, RR190043) conducted research.

- In a collaborative work, researchers from The University of Texas Southwestern Medical Center conducted a clinical trial of itraconazole—an antifungal drug with cancer-fighting qualities—in 13 patients with lung cancer. As recorded in the **November 2020** edition of *Clinical Cancer Research,* patients with the highest traces of itraconazole in their blood experienced the greatest results; remarkably, the drug's efficacy did not depend on factors known to affect drug dosing, such as body mass and kidney or liver function. Patients who received the highest doses of itraconazole (with the max dose at 7,094 ng/g) had the greatest degree of tumor shrinkage (with a max reduction of 26%). Researchers conducted the blood and tissue assays for this study at the North Texas Clinical Pharmacology Cancer Core at the Texas Tech University Health Sciences Center in Dallas. Core director William (Trey) Putnam, Ph.D., received a $2.5 million CPRIT Core Facility Support award (RP170003) in September of 2016 to fund the lab that made this study possible.

- A team led by John Abrams, Ph.D., professor of cell biology at The University of Texas Southwestern Medical Center, discovered a mechanism in p53 gene mutations that can lead to new diagnostic and treatment methods for various cancers. The study, published in the **November 1, 2020,** issue of *Genes & Development*, reveals that the p53 gene blocks retrotransposons from triggering other cancer-causing mutations. The researchers discovered that retrotransposons, or jumping genes, were more active in cells with missing or mutated p53, a mutation that occurs in most human cancers. "There's been long-standing literature associating retrotransposons with cancer," says Dr. Abrams. "What this work does is deliver the first empirical link between p53 and retrotransposons in humans." In experiments confirming this link, the researchers used a drug to stop retrotransposons from replicating, which prevented the inflammatory response commonly seen in p53 mutant cancers. Further studies will help determine whether drugs that target retrotransposon can slow or stop growth in existing cancer cells. In August of 2017, Dr. Abrams received a $816,000 CPRIT Individual Investigator Academic Research award (RP170086) to study the role the p53 gene plays in promoting cancer.

- Arvind Dasari, M.D., associate professor of gastrointestinal medical oncology at The University of Texas MD Anderson Cancer Center, and his colleagues design clinical trials to study minimal residual diseases in colorectal cancer. Their goal is to help specialists determine whether patients will benefit from post-surgery therapy. "The idea is that if we're able to detect any of this tumor DNA after a patient has had treatment, then we know there is residual cancer somewhere that we're just not able to pick up on scans," Dr. Dasari said during an interview on **November 2, 2020**. "We know some are cured with surgery alone and, in others, this chemotherapy doesn't prevent recurrence. So, there are patients that don't benefit from the post-surgical therapy but still experience all the side effects." CPRIT awarded a $2.4 million Individual Investigator award (RP200356) to Dr. Dasari in February of 2020 in support of his research on minimal residual disease in colorectal cancer.

- Building on prior research, Rana Gupta, Ph.D., associate professor of internal medicine at The University of Texas Southwestern Medical Center, and his colleagues identified blood vessel cells

that play a key role in the inflammation process that drives disease and cancer. Published in *Nature Metabolism* on **November 2, 2020**, the findings suggest that fibro-inflammatory progenitors, blood vessel precursor cells that make mature fat cells, cause fat cells to make molecules that promote inflammation. If the researchers observe similar results in late-stage clinical trials in humans, this research could lead to new avenues for disease and cancer prevention therapies. In support of this work, UT Southwestern received a $5.6 million CPRIT Core Facility Support Award (RP150596) in May of 2015.

- A team of researchers from The University of Texas MD Anderson Cancer Center developed the largest protein drug response data model currently available to scientists. To create this one-of-a-kind, large-scale data model, the researchers combined 168 different compounds with more than 200 proteins across more than 300 post-treatment cell lines. Available in the **November 5, 2020**, issue of *Cancer Cell*, the data model supplies proteomic profiles (important protein statistics) for cell lines that are associated with many forms of cancer—including breast, ovarian, uterine, skin, prostate, and blood cancers. "We've seen a number of perturbation studies that look at gene expression changes following drug treatments or CRISPR-mediated changes, but there is a significant gap in terms of proteomic profiling," said lead author Han Liang, Ph.D., professor of bioinformatics and computational biology at MD Anderson. "We hoped to fill that gap by profiling changes in major therapeutic target proteins, which provides a lot of insight in terms of drug resistance and designing drug combinations." CPRIT granted $8.4 million in Academic Research awards (RP170640, RP170593, RP160015) to the authors of this study for their collaborative work in bioinformatics.

- OncoNano Medicine Inc. reported positive results from its preclinical study of ONM-400, a novel interleukin-2 (IL-2) encapsulating pH-activated nanoparticle that targets metabolic acidosis in cancerous tumors. The data, presented on **November 9, 2020**, at the Society for Immunotherapy of Cancer's 35th Anniversary Annual Meeting, demonstrate successful tumor acidosis-driven accumulation that provides a high local concentration of IL-2 within tumors potentially resulting in an improved therapeutic index for this cancer immunotherapy. The Southlake-based company received a $6 million CPRIT Product Development award in 2014 (DP140072) and a $10 million award in 2020 (DP200081) to develop novel technologies that help surgeons detect and image breast, head, neck, and skin cancers.

- Immatics N.V. presented Phase 1 results from their ACTolog program IMA101 at the 35$^{th}$ Annual Society for Immunotherapy of Cancer Meeting, held virtually on **November 9–14, 2020**. The ACTolog program is a pilot study of a personalized multi-TCR-T approach. This approach is meant to help alleviate immunotherapy challenges, such as tumor heterogeneity and tumor immune escape. The company's data show that the multi-TCR-T approach is feasible and well tolerated in heavily pretreated patients; case studies warrant further testing of the approach with potent high-affinity TCRs. Houston-based Immatics US Inc. received a $19.7 million CPRIT Product Development award (DP150029) in 2015 to develop personalized cellular therapies that target multiple cancer types.

- Researchers at Baylor College of Medicine led a study on iron regulation that could serve as a blueprint for precision treatments that target ferroportin—the only gene known to export iron into the bloodstream. Ferroportin mutations often result in too much or too little iron in the bloodstream, and both conditions can cause serious diseases. To learn more about ferroportin's

regulation process, the researchers studied ferroportin in tarsiers (a Philippine primate), which are 92% identical to the ferroportin in humans. When they began the study, the researchers thought that the tarsier gene had only one iron-binding site. The results, published in *Nature Communications* on **November 10, 2020**, reveal a second iron-binding site; this finding explains why prior attempts to alter the other (and at the time, the only known) site had little effect on the gene's structure. "We are using these new structural and functional findings to identify small molecule candidates that can regulate ferroportin," said study-leader Ming Zhou, Ph.D., professor of biochemistry and molecular biology. With the help of CPRIT's $4.5 million Recruitment of Rising Stars grant (R1223), Baylor College of Medicine recruited Dr. Ming Zhou from Columbia University Medical Center in August of 2012.

- CPRIT Scholar and chemist Julian West, Ph.D., and his colleagues at Rice University developed a new method for creating drug compounds which is less expensive and more eco-friendly than current conventional methods. This work, available in the **November 11, 2020**, issue of the *Journal of the American Chemical Society*, presents a technique called cooperative hydrogen atom transfer (cHAT) that allows scientists to reduce alkenes into drug compounds. The cHAT technique uses a dual-catalyst approach: a two-step chemical reaction that causes hydrogen atoms to interact with other molecules to form new chemical variants. "Through teamwork, we introduced a strategy to get us to new variations of our products," said Dr. Julian West. "By combining dirt-cheap iron with an organic sulfur compound, we were able to cobble together a nice win-win. The iron catalyst tees up the process by giving it one hydrogen atom and gets out of the way. Then the sulfur can come in and give it the second one." As Rice scientists continue to create new products in greater quantities, their findings could help experts produce drugs at lower costs. With support from CPRIT's $2 million Recruitment of First-Time, Tenure-Track Faculty grant (RR190025), Rice University recruited Dr. West from the California Institute of Technology in 2019.

- Researchers from Rice University and The University of Texas MD Anderson Cancer Center identified secondary peptide interactions in the SARS-Cov virus that can help improve immunotherapy treatments and COVID-19 vaccines. Peptides must bind with certain proteins to activate the immune cells that fight cancers and viruses. This study is the first to reveal models of unbinding mechanics, which affect a key component of the immune system, and it is the first to provide atomic resolution of binding and unbinding models. The findings, published in the *Proceedings of the National Academy of Sciences* on **November 12, 2020**, reveal that binding sites once thought to be insignificant are crucial to the mechanisms that allow patients to fight cancer and viral infections and, thus, may lead to significant advances in immune targeting therapies. In support of her work on structural peptide modeling for the prevention and early detection of melanoma, study co-author Lydia Kavraki, Ph.D., received a $900,000 CPRIT Individual Investigator Academic Research award (RP170508) in 2016.

- A team of researchers from The University of Texas Southwestern Medical Center identified a cellular mechanism that scientists can use to combat cancer and infectious diseases. Micro-RNAs (miRNAs) are molecules that breakdown complementary sequences of messenger RNA (mRNA), and, when they linger inside a cell, miRNAs can prevent mRNA sequences translating into proteins. Lingering miRNA biomarkers are indicative of certain cancers. "For over a decade, researchers have

been searching for mechanisms through which cells degrade miRNAs," said Jaeil Han, Ph.D., postdoctoral research fellow at UT Southwestern. To better understand miRNA degradation, using CRISPR-Cas9 gene editing technology, the researchers examined how cells get rid of unneeded miRNAs. Published in *Science Daily* on **November 12, 2020**, the study reveals that proteins encoded by miRNA-destroying genes accumulate into large masses called ubiquitin ligase that trigger the sequence of events that destroys lingering miRNAs. Understanding how to control miRNA degradation may lead to development of novel treatments for a variety of diseases and infections. In 2015, UT Southwestern received a $5.6 million CPRIT Core Facility Support Award (RP150596) for its bioinformatic research and discoveries.

- Aravive Inc., a clinical stage oncology company based in Houston and Palo Alto, received a $20 million CPRIT Product Development Research award in 2015 (DP150127) for the development of AVB-500, an engineered AXL decoy receptor, as a treatment for ovarian cancer. The company is also conducting clinical trials to test AVB-500 as a treatment for kidney and pancreatic cancer.

  On **November 19, 2020**, Aravive reported that the U.S. Food and Drug Administration provided guidance on the design of a Phase 3 trial to test AVB-500 as a treatment for platinum resistant ovarian cancer. The global, randomized, double-blind, placebo-controlled adaptive trial will evaluate the efficacy and tolerability of AVB-500 at a dose of 15 mg/kg in combination with paclitaxel. The trial is set to begin in the first quarter of 2021 with an interim analysis expected a year later. "We look forward to advancing AVB-500 into a pivotal Phase 3 trial in platinum resistant ovarian cancer, following the promising results from our Phase 1b trial and productive conversations with the FDA," said Gail McIntyre, Ph.D., chief executive officer of Aravive. The adaptive Phase 3 trial will enroll 300 to 400 patients who received one to four prior lines of therapy to treat their advanced ovarian cancer. The company plans to conduct the clinical trial across 100 sites throughout the United States and Europe and, on **April 27, 2021**, reported dosing the first patient in the Phase 3 trial for platinum resistant ovarian cancer with AVB-500.

  On **May 6, 2021**, Aravive announced recent corporate updates and first quarter financial results; the company also shared its plan to initiate a Phase 1b/2 clinical trial in first-line metastatic pancreatic cancer to test AVB-500 in combination with gemcitabine and nab-paclitaxel. Phase 1b of the clinical trial will assess the combined compounds' safety, tolerability, and clinical activity. Phase 2 of the trial will be a randomized, controlled study that tests AVB-500 in combination with gemcitabine and nab-paclitaxel against gemcitabine and nab-paclitaxel alone. The Phase 1b portion of the clinical trial will begin in the second half of 2021.

  On **March 8, 2021**, Aravive Inc. announced that the first patient in the Phase 1b/2 clinical trial for clear cell renal cell carcinoma (ccRCC) received their first dose of AVB-500. And on **June 24, 2021**, the company reported that patients tolerated AVB-500 during the Phase 1b portion of the study. In hopes of initiating Phase 2 of its clinical trial, upon the Data and Safety Monitoring Board's approval, the company intends to expand dosing evaluations to additional patients. "We are pleased to announce the favorable results in the first cohort of our clear cell renal cell carcinoma Phase 1b study, as we continue to advance AVB-500 and evaluate its ability to address an urgent, high unmet medical need in patients with advanced kidney cancer who have very low survival rates," said Dr. Gail McIntyre, Aravive CEO. "We are enthusiastic about the clinical data with AVB-500 in combination with anticancer therapies that continue to show consistent PK/PD data and a favorable

safety profile. These combinations may have the potential to be used in a range of different cancers."

- Researchers from The University of Texas MD Anderson Cancer Center developed a new therapy drug called POMHEX, an enolase inhibitor combined with a prodrug, which targets genetic defects in malignant cells to stop cancer from growing. During the study, published in *Nature Metabolism* on **November 23, 2020**, the researchers tested POMHEX using a treatment strategy that exploits collateral lethality, which occurs when tumor suppressor genes are deleted, an incident observed in nearly all cancers. In this proof of principle study (an early stage of clinical development for promising drug compounds), the researchers designed POMHEX to target ENO2 in malignant brain tumors in mice. ENO2 is one of two enzymes that are essential to glycolysis, a metabolic pathway that promotes cancer growth. In several cancers, including glioblastoma, the ENO1 gene is absent from malignant cells; the researchers chose to target ENO2 over ENO1 for this reason. The POMHEX drug was well tolerated, and the researchers hope to develop a sister enolase inhibitor that targets ENO1 deletions, which commonly occur in cancers with poor prognoses, such as liver, bile duct, and large-cell neuroendocrine lung cancers. In support of this work, CPRIT awarded study co-author Ronald DePinho, Ph.D., professor of cancer biology in the Division of Basic Sciences at MD Anderson, a $900,000 Individual Investigator Academic Research grant (RP140612) in 2014.

- Researchers at The University of Texas Southwestern Medical Center identified a metabolic vulnerability in an aggressive form of non-small cell lung cancer that could lead to new precision targeting treatments. Their findings, published in the **November 30, 2020**, issue of *Nature Metabolism*, reveal that distinct gene mutations have specific metabolic needs that only certain pathways can provide, invalidating the longstanding notion that most tumors use the same few metabolic pathways to grow. The researchers discovered that the hexosamine biosynthetic pathway produces a key ingredient that the KRAS and LKB1 genes need to mutate into therapy-resistant tumors (KL tumors). Patients with KL tumors often receive a poor diagnosis and do not respond to immunotherapy. Understanding how specific mutations occur can help doctors create better treatment plans for patients with therapy-resistant tumors. In support of this work, CPRIT granted a $900,000 Individual Investigator Research award in 2019 (RP160089) to study leader Ralph DeBerardinis, M.D., Ph.D., holder of the Joel B. Steinberg Distinguished Chair in Pediatrics at the Children's Medical Center Research Institute at UT Southwestern.

- CPRIT award recipient Livia Eberlin, Ph.D., assistant professor of chemistry at The University of Texas at Austin, led a study on the use of desorption electrospray ionization mass spectrometry imaging (DESI-MSI) in minimally invasive fine needle aspiration (FNA) biopsies to differentiate lung cancer subtypes from one another. As reported in the **November 2020** edition of the journal *Clinical Chemistry*, DESI-MSI is a spray-based ambient imaging technique that doctors use to collect biological samples directly from a cell's surface. Clinicians used FNA biopsies to diagnose specific histologic subtypes of lung cancer. DESI-MSI can improve this diagnostic process by allowing doctors to analyze small tissue samples faster and with greater accuracy. With the DESI-MSI technology, we can find the best methods for detecting and treating distinct subtypes of cancer. In 2016 and 2018, CPRIT granted Dr. Eberlin academic research awards (RP160776, RP170427, RP180381) of approximately $2.2 million in support of her work on molecular diagnostic techniques.

- With the help of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty grant (RR200009), Baylor College of Medicine recruited Gloria Echeverria, Ph.D., to Houston to lead breast cancer research and development projects. Since the Gloria Echeverria Lab opened in January of 2020, her research team has focused on studying metastasis and treatment resistance in triple negative breast cancer (TNBC), building on Dr. Echeverria's life's work. In a 2019 study on chemotherapy resistance in TNBC tumors, Dr. Echeverria and her colleagues discovered that cancer masses that survived chemotherapy entered a peculiar defensive state using a metabolic pathway called oxidative phosphorylation that helps cancer cells regrow at an alarming rate. The team delayed this process using an oxidative phosphorylation inhibitor drug, a finding that could pave the way for new pharmaceutical therapies. For instance, in November of 2020, scientists from The University of Texas MD Anderson Cancer Center conducted Phase 1 trials to test the oxidative phosphorylation inhibitor, IACS-010759, as a treatment for patients with lymphoma and advanced solid cancers. On **December 1, 2020**, *The Scientist* published an article that showcases the innovative breast cancer research that Dr. Echeverria has conducted throughout her career.

- A study led by researchers from The University of Texas Southwestern Medical Center reveals that basic cell maintenance biomarkers are indicative of cell fate, a finding that can help us better predict patients' responses to pharmaceutical treatments. During the study, published in the **December 1, 2020**, edition of *Cell Reports*, the researchers intermittently deprived modified yeast cells of life-sustaining nutrients; they then analyzed protein biomarkers associated with cell maintenance, i.e., cell cycling, stress response, intracellular communication, and nutrient signaling. "Our results show that factors not traditionally associated with cell fate can, in fact, play an important role in this process, and gets us closer to answering the question of why this phenomenon takes place and how we might control it," said study co-leader N. Ezqi Wood, Ph.D., a postdoctoral fellow at UT Southwestern. A $1.9 million Recruitment of First-Time, Tenure Track Faculty grant (RR150058). CPRIT award to help UT Southwestern Medical Center recruit the late Andreas Doncic, Ph.D., from Stanford University in 2015 helped support this study. Dr. Doncic passed away in 2018. Through this study, his colleagues at UT Southwestern continue his work.

- A team of researchers led by Jun Wu, Ph.D., assistant professor of molecular biology at The University of Texas Southwestern Medical Center, created intermediate pluripotent stem cells (PSCs), called XPSC, by isolating a new type of PSC in mice, horses, and humans. Their findings could lead to advancements in regenerative medicine, reproductive technology, and basic biology. This study, published in *Cell Stem Cell* on **December 2, 2020**, shows that XPSC can generate chimeras and germ cell precursors that allow scientists to study gene signatures preserved through the history of evolution. Offering new insight into chimera cell communication, this work can possibly lead to advancements in stem cells to accelerate the rate of development in tissues and organs, which would benefit those in need of transplants and advanced infertility treatments. In 2017, the UT Southwestern Medical Center recruited Dr. Wu to Dallas with the help of a $2 million CPRIT First-Time, Tenure-Track Faculty grant (RR170076).

- CPRIT Scholar and chemist Julian West, Ph.D., and his colleagues at Rice University developed a new way to create valuable drug compounds using mild B12 catalysts during dehydrohalogenation. Dehydrohalogenation is a process in which hydrogen atoms become more susceptible to chemical

reactions that create new, useful molecule compounds. This process typically requires harsh conditions or rare noble metals, which makes it less practical for synthesizing useful drugs. This new dehydrohalogenation process uses a mild B12 catalyst to make hydrocarbons, compounds existing entirely of hydrogen and carbon, that scientists use to create and study drug precursor molecules. As recorded in *Chemical Science* on **December 8, 2020**, the new method uses blue light to trigger carH, a light-sensitive bacterial enzyme, which then activates the mild cobalt and B12 catalysts that make hydrocarbons. "Instead of needing heat and strong bases, it only needs light energy," said Dr. West, assistant professor of chemistry. This new process could help scientists create and study a greater variety of drug compounds and interactions at lower costs. With support from a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty grant (RR190025), Rice University recruited Dr. West from the California Institute of Technology in 2019.

- Medicenna Therapeutics Corp., a clinical stage immunotherapy company based in Toronto and Houston, announced positive results from a Phase 2b trial evaluating MDNA55 (a protein synthesis inhibitor that targets interleukin-4 receptors) in patients with recurrent glioblastoma—the most common, and most lethal, form of brain cancer. The company published peer-reviewed clinical data from its Phase 2b clinical trial in the **July 2021** issue of *Clinical Cancer Research*. "This Phase 2b trial has generated compelling data, and we are very pleased to have them published in such a prestigious peer-reviewed journal," said Fahar Merchant, Ph.D., the chief executive officer of Medicenna. "[We are currently] pursuing a partnership strategy to continue the Phase 3 development."

- At the 2nd Annual Glioblastoma Drug Development Summit on **December 10, 2020**, Medicenna presented an overview of its planned Phase 3 trial registration to test MDNA55. The company will use an open-label hybrid design to implement matched external control for two-thirds of the Phase 3 trial's control group; it expects that this hybrid design will help it reach clinical goals faster and at lower costs compared to traditional randomized control trials.

- In 2015, Medicenna received a $14.1 million CPRIT New Company Product Development award (DP150031) to develop novel immunotherapy treatments for recurrent glioblastoma and other brain cancers.

- A team led by researchers from The University of Texas Southwestern Medical Center identified a gene that plays an important role in viral autophagy, a recycling process that destroys cellular invaders (e.g., pathogens, bacteria, and cancer-causing proteins). Using bioinformatical tools, the researchers homed in on a gene called sorting nexin 5 (SNX5). While examining the function of SNX5 in several viruses, they found that removing the gene reduced the cells' viral autophagy response without changing the cells' normal autophagy response; this finding suggests that cells follow a unique pathway for viral autophagy. "By learning how cells naturally take up and degrade viruses, we could discover ways to augment this process, creating a more general strategy for developing broad-spectrum antiviral therapeutics that combat an array of different viral infections," said study co-author Xiaonan Dong, Ph.D., assistant professor of internal medicine. A $5.4 million Core Facility Support award (RP180805) and two CPRIT Multi-Investigator Academic Research grants (RP120718-P1, RP120718-P2) supported the study, published in the journal *Nature* on **December 16, 2020**. With this research, the UT Southwestern scientists continue the work of the late Beth Levine, M.D., the

former director of the Center for Autophagy Research, holder of the Charles Cameron Sprague Distinguished Chair in Biomedical Science, and a pioneer in research on autophagy and its effect on human diseases. “This is a beautiful study that further cements the legacy of Dr. Levine and work from her lab members,” says Julie Pfeiffer, Ph.D., study co-author and professor of microbiology.

- On **December 21, 2020**, Molecular Templates Inc. announced safety and efficacy results for MT-5111, a next-generation of engineered toxin bodies (ETBs) that target HER2 positive tumors. The results from the Phase 1 study include dose escalation data collected from 16 study subjects across five cohorts. “We are encouraged by the safety profile of MT-5111 to date in these heavily pretreated study subjects. Based on preclinical data, we believe that the study has reached clinically active dose levels,” said Eric Poma, Ph.D., the chief executive and chief scientific officer of Molecular Templates. “Given that HER2 positive breast cancer patients have generally had the highest response rates to other HER2-targeted therapies, we look forward to generating data from both the HER2-positive breast cancer cohort as well as the broader HER2-positive cohort enrolling all tumor types. We expect to provide an update on results from the subject currently on treatment as well as higher dose cohorts from the dose escalation portion of the Phase 1 study in 1H21.” Molecular Templates Inc. received a $10.6 million CPRIT Product Development Research grant (CC121020) in November of 2011 in support of this work.

- Philip Lupo, Ph.D., associate professor of pediatrics at Baylor College of Medicine, led a multicenter study to find genes that predispose children to rhabdomyosarcoma (RMS), the most common type of childhood soft tissue sarcoma. Despite RMS’s high rate of malignancy, we know little about genetic susceptibility in RMS. During this study, published in the **December 29, 2020**, issue of the *Journal of the National Cancer Institute*, the researchers examined 615 patients with recent RMS diagnoses. Of the participants with RMS, 7.3% had clinically significant variant changes in cancer-predisposition genes; in the control groups (participants without a diagnosis), only 1.4% exhibited such changes. The researchers intend to study whether genetic changes impact RMS patient outcomes, including response to therapy, likelihood of relapse, and overall survival. “RMS is a tumor for which we have not seen a lot of improvement in available therapies over the last 30 years compared to other pediatric tumors,” said Dr. Lupo. “We need these large-scale studies and collaborations to move the needle when it comes to improving outcomes for these children.” In support of his work on pediatric rhabdomyosarcoma, Dr. Lupo received a $1.5 million CPRIT Individual Investigator Academic Research award (RP170071) in November of 2016.

- Researchers from The University of Texas Southwestern Medical Center developed a new statistical model called Tessa that allows researchers to analyze T cell receptors (TCRs), the molecules responsible for recognizing viruses, bacteria, and cancer. Unlike the individual receptors in other immune cells which recognize many different invaders, each T cell receptor only recognizes a few disease-specific molecules. Using Tessa, scientists can pinpoint the molecular functions that make some receptors more effective than others. Tessa combines two existing technologies: TCR analysis and single-cell RNA analysis. (The former measures the diversity of a person’s T cell receptors; the latter identifies the gene sequences activated in a T cell.) With this tool, scientists can observe how TCRs react to disease-specific molecules and how those reactions affect T cell function. Their findings, published in *Nature Methods* on **January 6, 2021**, can help scientists develop personalized

TCR-based immunotherapies. In 2019, CPRIT awarded study co-author Tao Wang, Ph.D., assistant professor of population and life sciences, a $900,000 Individual Investigator Research award (RP190208) to support his immunotherapy research. The UT Southwestern Medical Center recruited study co-collaborator Todd Aguilera, M.D., Ph.D., assistant professor of radiation oncology, from Stanford University in 2017 with the help of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty grant (RR170051).

- Researchers from Rice University and Baylor College of Medicine developed a modeling method that will allow biologists without engineering expertise to study bacteria and pathogenic biochemicals in the intestinal tract—a complex system not easily replicated. Led by K. Jane Grande-Allen, Ph.D., Isabell C. Cameron Professor of Bioengineering, the researchers developed transparent millifluidic perfusion cassettes (mPCs), which allow scientists to study several conditions in gut models without disrupting the replicas' chemical environment. "Devices like these are often not user-friendly and practical for biologists," said co-author Anthony Maresso, Ph.D., an associate professor of molecular virology and microbiology at Baylor. "This one was designed to be easy to use by scientists with less engineering know-how. The hope is it will lower barriers between engineers and medical researchers." A $1.4 million CPRIT Multi-Investigator Academic Research award (RP120713-P2) helped fund the study, published in *Annals of Biomedical Engineering* on **January 6, 2021**.

- On August 21, 2019, CPRIT awarded a $900,000 Individual Investigator Academic Research award (RP190358) to Weibo Luo, Ph.D., assistant professor of pathology and pharmacology at The University of Texas Southwestern Medical Center. With the help of this grant, Dr. Luo and his colleagues discovered that the ZMYND8 gene in breast cancer strongly correlates with mortality: the higher levels of ZMYND8, the lower the chance of survival. "ZMYND8 can control tumor progression and spread, or metastasis. The protein is very important, at least in breast cancer, and if we can find inhibitors, we can combine them with other therapies for breast cancer treatment," said Dr. Luo. During a mice model experiment, the researchers removed the ZMYND8 gene from breast cancer cells that had been resistant to the antitumor responses of immune cells; thereafter, the immune cells attacked the cancer cells and prevented tumor growth and metastasis. This early-stage study, available in the **January 2020** issue of *Cancer Research*, suggests promising news for precision therapy treatment in breast cancer. With the help of CPRIT's $ 2 million Recruitment of First-Time, Tenure-Track Faculty grant, awarded in 2014, the UT Southwestern Medical Center recruited Dr. Luo from Johns Hopkins University School of Medicine (RR140036). CPRIT also awarded study co-author Yingfei Wang, Ph.D., assistant professor of pathology and neurology at UT Southwestern, a $200,000 Academic Research award (RP170671) in support of her research on triple-negative breast cancer.

- CPRIT Scholar Bing Zhang, Ph.D., professor in the Department of Molecular and Human Genetics at Baylor College of Medicine, and his colleagues identified three molecular subtypes in head and neck squamous cell carcinoma that can possibly lead to better cancer therapeutics. The Baylor team, with collaborators from Johns Hopkins University and the National Cancer Institute's Clinical Proteomic Tumor Analysis Consortium, published their findings in the **January 7, 2021**, edition of the journal *Cancer Cell*. The researchers used proteogenomic analyses (a large-scale examination of proteins, genomes, and RNA transcripts) to find biomarkers that could help scientists and doctors match patients to clinical trials and effective therapies—including EGFR inhibitors, CDK inhibitors, and

immunotherapy. Baylor College of Medicine recruited Dr. Zang to Texas in 2017 from Vanderbilt University School of Medicine with the help of a $4 million CPRIT Rising Star Award (RR160027).

- In a collaborative work led by CPRIT investigators Guo-Min Li, Ph.D., and Yang-Xin Fu, M.D., Ph.D., researchers at The University of Texas Southwestern Medical Center discovered an immune response in cGAS-STING pathways that made treatment-resistant tumors more susceptible to immunotherapies. The study, published in *Cancer Cell* on **January 11, 2021**, suggests that treatment-resistant cancer cells respond better to immunotherapies (such as immune check-point inhibitors) if with radiation, which releases DNA inside the cells, prior to the immunotherapy. This finding has the potential to help doctors determine which patients will benefit from immunotherapy. This research builds on the foundational work of Zhijian (James) Chen, Ph.D., study co-author and professor of molecular biology at UT Southwestern, who won the 2019 Breakthrough Prize in Life Sciences for his discovery of the cGAS enzyme. The UT Southwestern Medical Center recruited Dr. Li, professor of radiation therapy, and Dr. Fu, professor of pathology, to Dallas with support from two $6 million Recruitment of Established Investigator grants (RR160101, RR150072). Dr. Chen has also received multiple CPRIT Academic Research grants (RP110430, RP120718-P3, RP120718-C2, and RP150498) in support of his research.

- Researchers at The University of Texas MD Anderson Cancer Center developed a novel computational tool called CopyKAT that allows scientists to differentiate cancerous cells from normal cells in tumors when studying large datasets of single-cell RNA sequences. Traditionally, researchers studied tumors as a conglomeration of cells, both healthy and cancerous. Now, single-cell RNA sequencing technology allows scientists to study cancerous cells with much greater specificity. Nevertheless, single-cell RNA sequencing is only effective if scientists use a reliable computational approach—a feat researchers at MD Anderson accomplished. Led by Nicholas Navin, Ph.D., associate professor of genetics and bioinformatics and computational biology, the CopyKAT creators accurately predicted copy changes and differentiated cancer cells from healthy cells in datasets from pancreatic cancer, triple-negative breast cancer, and anaplastic thyroid cancer. “We developed CopyKAT as a tool to infer genetic information from the transcriptome data. By applying this tool to several datasets, we showed that we could unambiguously identify, with about 99% accuracy, tumor cells versus the other immune or stromal cells present in a mixed tumor sample,” said Dr. Navin. “We could then go one step further to discover the subclones present and understand their genetic differences.” Developed with support from CPRIT’s $4.9 million Single Cell Genomics Core Facilities Grant (RP180684), CopyKAT is likely to lead to significant advancements in single-cell RNA sequencing cancer research. This work, published in *Nature Biotechnology* on **January 18, 2021**, includes the CopyKAT tool available to the public therein.

- In a study with promising results for solid cancer immunotherapies, researchers from The University of Texas Southwestern Medical Center discovered that removing a single gene from exhausted immune cells revitalized their cancer-fighting abilities. The study, published in the *Journal for Immunotherapy of Cancer* on **January 18, 2021**, examines genetically engineered cancer-fighting T cells called chimeric antigen receptor cells (CAR-T cells). Once inside a solid tumor—like those present in colon, breast, and lung cancer—some CAR-T cells lose their cancer-fighting abilities. Venuprasad Poojary, Ph.D., associate professor of internal medicine and immunology at UT

Southwestern, and his colleagues found a highly active gene, called Cbl-b, in exhausted CAR-T cells. After the researchers used CRISPR gene editing technology to cut the Cbl-b gene from exhausted cells, they found that the exhausted immune cells regained their cancer-fighting abilities. “Our study is a major step forward in developing CAR-T cells to fight solid tumors,” Dr. Poojary said. “This could overcome the limitations of some current immunotherapy strategies for cancer.” CPRIT has granted Academic Research awards (RP160577, RP190527) of approximately $632,000 in support of Dr. Poojary’s and his colleagues’ efforts to combat colorectal and other solid cancers.

- With support from a $900,000 Individual Investigator Academic Research award (RP120298) for his research on lymphoma, Carlos Ramos, M.D., led a team of researchers at Baylor College of Medicine in a study for a new cellular therapy platform. Collaborating with Kuur Therapeutics, a clinical stage biopharmaceutical company based in Houston, the researchers conducted a Phase 1 study with promising outcomes for neuroblastoma patients. “We are encouraged by the evidence of clinical activity with an allogeneic approach, especially at such a low dose,” said Dr. Carlos Ramos, principal investigator of the ANCHOR study, professor of Medicine at the Center for Cell and Gene Therapy (CAGT) at Baylor College of Medicine, and member of the Dan L. Duncan Comprehensive Cancer Center. “We look forward to advancing the program and treating additional patients.” Kuur Therapeutics reported updates regarding the Phase 1 clinical trials **on January 21, 2021**.

- Researchers from The University of Texas Health Science Center at Houston and The University of Texas Medical Branch at Galveston discovered a promising new antibody therapy to treat COVID-19. The study, published in *Nature Communications* on **January 21, 2021**, reveals that combining protein antibodies CoV2-06 and CoV2-14 can possibly stop the spread of COVID-19. “By leveraging the unique antibody drug discovery capabilities at UTHealth and the strong virology expertise at UTMB, we started to generate SARS-CoV-2-neutralizing antibodies in February of last year,” said Zhiqiang An, Ph.D., professor of molecular medicine and Robert A. Welch Distinguished University Chair in Chemistry at McGovern Medical School at UTHealth. “The lead antibody combination out of our research is now being developed with a biotech partner for the treatment of COVID-19.” Dr. An received a $5.9 million CPRIT Core Facility Support award in August of 2019 (RP190561) and a $900,000 Individual Investigator Academic Research award in February of 2015 (RP150230) in support of his work on antibody therapeutic strategies.

- Led by Pushkar Lele, Ph.D., assistant professor in the Artie McFerrin Department of Chemical Engineering, scientists at Texas A&M University in College Station discovered a new technique for studying pathogenic bacteria that could lead to new therapies for gastric diseases and cancer. Gastric cancer is the second leading cause of cancer-related deaths. Helicobacter pylori (H. pylori) are pathogenic bacteria that cause inflammation in the stomach and the intestines that can result in ulcers, cancer, and other serious gastric diseases. Doctors use antibiotics to treat conditions associated with H. pylori; however, the bacteria are growing more resistant to these antibiotics. Shortcomings in current techniques used to study H. pylori limit the understanding of the bacteria’s function and, therefore, limit clinicians’ ability to treat diseases associated with H. pylori. The novel approach developed by Dr. Pushkar Lele and his colleagues focuses on the clockwise and counterclockwise rotation of the bacteria’s flagella. The research, published in *eLife* on **January 25, 2021**, reveals new information about the functional characteristics of H. pylori and the intracellular

chemical signaling method they use to reach their target environments. According to Dr. Lele, understanding this signaling and cultivation process can help scientists develop new treatment methods to combat gastric diseases. In August of 2017, scientists from the Texas A&M Engineering Experiment Station received a $200,000 CPRIT Academic Research grant (RP170805) for their research on gastric diseases.

- CPRIT Scholar David Taylor, Ph.D., assistant professor of molecular biosciences at The University of Texas at Austin, co-authored a study that examines remdesivir, a nucleoside analog antiviral medication approved by the FDA to treat COVID-19. The study, published in *Molecular Cell* on **January 28, 2021**, reveals the key blocking mechanism that remdesivir uses in genes to stop COVID-19 from spreading throughout the body, a finding that could revolutionize antiviral drugs. Remdesivir targets the mechanism that allows the virus to replicate and spread, essentially stalling this process. “We were able to identify the point where that paper jam happens,” said Dr. Taylor. “We know now exactly what’s creating this block. So, if we want to make the blockage even worse, we could do so.” This discovery can help scientists develop safe, more effective antivirals in the future. The University of Texas received a $2 million Recruitment of First-Time, Tenure-Track Faculty award (RR160088) in 2016, which helped the university recruit Dr. Taylor from the University of California, Berkeley.

- Houston-based biotech company Pulmotect Inc. received approval from the FDA to initiate Phase 2 trials for PUL-042, an aerosol-delivery drug that activates immune cells on the surface of the lungs to fight respiratory pathogens that cause coronaviruses. As reported in **January of 2021**, the Department of Defense signed a $6 million agreement to fund these Phase 2 trials. “We appreciate the support to evaluate PUL-042, which not only has the potential to be effective against SARS-CoV-2 but also has potential for use against other pathogens that infect the respiratory tract,” said Colin Broom, M.D., chief executive officer of Pulmotect. In 2012, Pulmotect Inc. received a $7.2 million CPRIT Product Development Research grant (CP120014) in support of its work on immunotherapy treatments.

- Researchers from The University of Texas Southwestern Medical Center discovered a coronavirus protein called Nsp1 that promotes viral replication and suppresses cells’ immune response against SARS-COV-2—the coronavirus that causes COVID-19. Their findings, published in *Science Advances* on **February 5, 2021**, confirmed that the coronavirus protein Nsp1 functions like the NS1 protein present in the influenza virus. The Nsp1 coronavirus protein inhibits our cells’ immune response by binding to NXF1, a messenger RNA (mRNA) export receptor, to block mRNA nuclear export—a process necessary for the immune system to attack invading viruses. “If you find a way to block the interaction between Nsp1 and NXF1 or increase the amount of NXF1 in the cell, you'll get mRNAs out of the nucleus and may get a protective effect, as suggested by our experiments,” said Beatrix Fontoura, Ph.D., study co-author and professor of cellular biology at UT Southwestern. Understanding this replication and immune suppression process can help scientists develop new strategies for treating COVID-19. In support of these findings, CPRIT awarded two Multi-Investigator Academic Research grants (RP120718-P2, RP120718-AC), totaling approximately $1.98 million, in August of 2012.

- A team led by CPRIT Scholar Bert O'Malley, M.D., professor of molecular and cellular biology at

Baylor College of Medicine, discovered that a protein called the steroid receptor coactivator 3 (SRC-3/NCOA3) plays an important role in regulating antitumor immunity. The SRC-3/NCOA3 protein is a prognostic marker in aggressive cancers. While studying the role SRC-3/NCOA3 plays in immune T regulatory cells (Tregs), the researchers discovered that inhibiting the protein stopped T cells from suppressing activities of other immune cells, including their ability to fight cancer. On the other hand, Tregs stop immune activity that could otherwise harm healthy cells and cause autoimmune diseases. "We experimentally show that SRC-3 is significantly enriched in both murine and human Tregs," said co-first author Prashi Jain, Ph.D., instructor of molecular and cellular biology at Baylor. "Working with human Tregs, we used our small molecule inhibitor SI-2 to effectively inhibit SRC-3 in Tregs. As a result, Tregs greatly reduced their ability to inhibit the activation of other immune cells that help in maintaining antitumor immunity." This study, published in the **February 9, 2021**, issue of the journal *Scientific Reports*, could possibly lead to new treatments that inhibit Tregs activity. Dr. O'Malley has received multiple CPRIT grants (RP100348, RP101251-P2, and RP170500) for his work on small molecule inhibitors.

- CPRIT Scholar Isaac Hilton, Ph.D., assistant professor of bioengineering and biosciences, and his colleagues at Rice University developed a new tool that identifies the exact molecule sequences that cause genetic mutations. His group created a synthetic protein to deliver chemical payloads at precise spots near human genes. The researchers then used this tool to identify genes linked to melanoma resistance. This work, reported in the **February 9, 2021**, issue of *Nature Communications*, provides insight for how normal cellular processes go awry in human diseases. In 2017, Rice recruited Dr. Hilton from Duke University with the support of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty grant (RR170030).

- On **February 10, 2021**, OncoNano Medicine Inc., a Southlake-based biotech company, presented research on a nanoparticle drug designed to enhance patients' immune responses to various cancer treatments. Developed by a team of scientists from The University of Texas Southwestern Medical Center, and licensed by OncoNano, the pH-sensitive nanoparticle drug activates STING (stimulator of interferon genes). And STING enhance the body's immune pathways during treatment. "We are excited about the study published by our colleagues at UT Southwestern demonstrating that the STING activating polymeric micelle can be selectively triggered in the endosomes and enter the cytoplasm of phagocytic cells to achieve robust antitumor immunity," said Marty Driscoll, chief executive officer of OncoNano. In support of its work on tumor specific immunotherapy treatment in multiple cancers, OncoNano Medicine Inc. received a $15.4 million CPRIT Product Development Research award (DP190066) in August of 2019.

- On **February 11, 2021**, Houston-based biotech company DNAtrix Inc. published data in the December 19, 2020, journal *Clinical Cancer Research* from a preclinical trial on DNX-2410. DNX-2410 is an oncolytic adenovirus immunotherapy specifically engineered to eliminate cancer cells, which suggest early but promising results for treating pediatric brain tumors. "These preclinical data for DNX-2401 show encouraging signals of anti-tumor activity against devastating CNS cancers that we had not previously studied," said Jeffrey Knapp, chief executive officer of DNAtrix. "We now have preclinical and clinical data of DNX-2401's efficacy across a range of difficult-to-treat adult and pediatric tumors, thus further establishing the activity of this potent immunotherapy. We look

forward to the continued advancement of DNX-2401, as well as our pipeline of other oncolytic immunotherapies being developed for the treatment of solid tumors." In support of the company's advancements in brain cancer treatment, CPRIT granted DNAtrix a $10.8 million Product Development Research award (CP130013) in February of 2014.

- Researchers from Baylor College of Medicine identified rare hereditary genes that increase a carrier's risk of lung cancer. The findings, published in *Nature Precision Oncology* on **February 16, 2021**, revealed 25 rare gene variants that increase lung cancer susceptibility. "Many studies have looked at lung cancer risk genes, but the function of those genes has not been well understood," said Jun Xia, Ph.D., study co-author and postdoctoral associate of molecular and human genetics. "In our study, we found that dysregulation or mutations in these candidate genes showed increased DNA damage, suggesting that their potential cancer-causing role might be due to genome instability at the DNA level." CPRIT's $6 million Recruitment of Established Investigators award (RR170048), awarded in 2017, helped Baylor College of Medicine recruit study co-author Christopher Amos, M.D., Ph.D., from the Dartmouth Geisel School of Medicine. In further support of this research, CPRIT awarded study co-author Susan Rosenberg, Ph.D., Ben F. Love Chair of Cancer Research at Baylor College of Medicine, a $9000,000 Individual Investigator Academic Research grant (RP140553).

- Building on prior hypertension studies, researchers at Baylor College of Medicine discovered that fasting can help reduce blood pressure. Prior research confirmed that fasting has a direct effect on gut microbials and that microbial disruption is not just an effect but a cause of high blood pressure. In this study led by David Durgan, Ph.D., assistant professor of anesthesiology and cellular and molecular physiology, researchers found significantly lower blood pressure in hypertensive subjects that fasted intermediately. Hypertensive subjects that received microbiota transplants from subjects that fasted experienced significantly lower blood pressure, confirming the positive correlation between fasting and low blood pressure. "We applied whole genome shotgun sequence analysis of the microbiota as well as untargeted metabolomics analysis of plasma and gastrointestinal luminal content. Among the changes we observed, alterations in products of bile acid metabolism stood out as potential mediators of blood pressure regulation," said Dr. Durgan. "Fasting schedules could one day help regulate the activity of gut microbial populations to naturally provide health benefits." A $5 million CPRIT Core Facility Support award (RP170005) supported this research, published in *Circulation Research* on **February 18, 2021**.

- Jie Zheng, Ph.D., professor of chemistry and biochemistry at The University of Texas at Dallas, and his colleagues designed gold nanoparticles that can detect early signs of liver damage, kidney disease, and cancer. As shown in the **February 19, 2021**, issue of the online journal *Science Advances*, this new detection method is less invasive than a liver biopsy, the most common method for diagnosing liver disease, and can detect damage with greater accuracy than conventional blood biomarkers. The researchers infused an organic fluorescent dye called indocyanine green (ICG) into their nanoparticles to track glutathione, a key chemical produced in the liver. With a simple blood test, doctors can determine the amount of ICG that remains on the surface of the gold particles: The more ICG that remains, the less glutathione in the liver; the less glutathione in the liver, the greater the damage. "Our goal is to make it simple for family doctors to easily catch liver injury earlier," said

Dr. Zheng. “If they can detect and treat such injury earlier, the patient has a better chance of faster recovery.” In support of his work in nanomedicine, CPRIT granted Dr. Zheng a $900,000 Individual Investigator Academic Research award (RP200233) in February of 2020 and a $1.2 million Individual Investigator Academic Research award (RP120588) in November of 2011.

- Scientists at Rice University developed a simple, inexpensive method for creating drug precursors, which typically require precious metal catalysts. In their research, available in the **February 21, 2021,** issue of *Chemical Communications*, the scientists produced fluorine ketone, or fluoroketone, precursors using cerium-based ceric ammonium nitrate (CAN) instead of silver. Earth’s crust contains approximately 800 times more cerium than it does silver, and CAN is able to produce functional precursors in 30 minutes in easily replicable environments. By eliminating the need for precious metals, this new method could lead to more sustainable synthesis processes. “Ketones are a gateway functional group in molecules that you can use to make different things, like anti-cancer compounds,” said study leader Julian West, Ph.D., assistant professor of chemistry at Rice University. “We want to put fluorine in specific places in the molecule where we know it will make a difference, and this ketone functional group allows us to do it.” With the help of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty grant (RR190025), Rice University recruited Dr. West from the California Institute of Technology in 2019.

- CPRIT Scholar Sean Morrison, director of the Children’s Medical Center Research Institute at The University of Texas Southwestern Medical Center, and his colleagues discovered a new way by which exercise strengthens bones and immune functions, a finding that could revolutionize the treatment of bone diseases. Dr. Morrison’s work counters the insulation theory (the long-held belief that bones insulate the inner marrow from mechanical forces). The study, published in the journal *Nature* on **February 24, 2021**, reveals that mechanical forces, induced by running and other forms of exercise, directly affect bone marrow by stimulating growth factors, a naturally occurring substance that creates bone- and immune-cell precursors. Mechanical forces travel through arteriolar blood vessels that run from the surface of the bone to the marrow which stimulate growth factors called Osteolectin. “Therapeutic interventions that expand the number of Osteolectin-positive cells could increase bone formation and immune responses, particularly in the elderly,” said Bo Shen, a post-doctoral fellow in the Morrison laboratory. In 2011, the UT Southwestern Medical Center recruited Dr. Morrison to Texas from the University of Michigan with the help of a $10 million CPRIT Recruitment of Established Investigators award (R1109). CPRIT has also awarded Dr. Morrison three additional grants (RP170114, RP170633, and RP180778) totaling more than $7 million for the study of melanoma.

- In a study led by CPRIT Scholar Hao Zhu, M.D., associate professor at the Children’s Medical Center Research Institute, scientists from The University of Texas Southwestern Medical Center identified the cells responsible for restoring and maintaining liver tissue, solving a longstanding biological mystery. This study, published in *Science* magazine on **February 26, 2021**, compares the different cells produced in the liver (called hepatocytes). The researchers found that the cells ultimately responsible for liver restoration and maintenance originate in one region of the liver; those cells then distribute throughout the organ to restore tissue as needed. “The identification of zone 2 hepatocytes as a regenerative population answers some fundamental questions about liver biology

and could have important implications for liver disease," Dr. Zhu said. "In addition, the tools we created to study different types of hepatocytes can be used to examine how different cells respond to liver damage or to genetic changes that cause liver cancer." The Hao Zhu laboratory at UT Southwestern received two $900,000 Individual Investigator Academic Research awards in support of this work: one in August of 2017 (RP170267), and one in February of 2018 (RP180268).

- Salarius Pharmaceuticals Inc., a Houston-based, clinical stage biopharmaceutical company, is testing its lead drug candidate seclidemstat as a treatment for pediatric cancers, solid tumors, and hematologic cancers. Seclidemstat is a novel, oral reversible inhibitor of the lysine-specific histone demethylase 1 enzyme (LSD1), an enzyme that plays a key role in the development and progression of certain cancers.

  In February of 2021, the company announced the expansion stage of a Phase 1/2 clinical trial of seclidemstat in patients with Ewing sarcoma, Ewing-related sarcomas, and relapsed and refractory Ewing sarcoma—a rare and deadly pediatric bone and soft tissue cancer. Salarius is also enrolling patients with advanced solid tumors in a Phase 1/2 trial of seclidemstat. "The completion of dose escalation in Ewing sarcoma patients and establishment of the [maximum tolerated dose] represent important milestones in our clinical development of seclidemstat," stated David Arthur, the president and chief executive officer of Salarius Pharmaceuticals. "We are encouraged by data from the dose-escalation phase and look forward to continuing development of seclidemstat for difficult to treat cancers."

  In June of 2021, during the American Society of Clinical Oncology Virtual Annual Meeting, Salarius disclosed results from its ongoing clinical trials which include data on seclidemstat's safety, dosing, and early efficacy signals. The results suggest that seclidemstat has a manageable safety profile, anti-tumor effects in heavily pre-treated patients with advanced sarcomas, and no significant hematological toxicities—a common limitation of LSD1 inhibitors. Single-agent treatment with seclidemstat showed signs of drug activity in patients with Ewing sarcoma, Ewing-related sarcomas, and other solid cancers. This is significant because single-agent treatments are likely to generate less toxicity than combination treatments and are often associated with better life quality.

  On June 15, 2021, Salarius announced its plan to initiate a Phase 1/2 clinical trial, led by Guillermo Montalban Bravo, M.D., assistant professor in the department of leukemia at The University of Texas MD Anderson Cancer Center, to investigate seclidemstat as a potential treatment for hematologic cancers. During the open label study, the researchers will test the safety, tolerability, and maximum tolerated dose of seclidemstat when used in combination with azacytidine as a treatment for Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukemia (CMML). Salarius received an $18.7 million CPRIT Product Development Research award (DP160014) in 2016 for its development of epigenetic drugs that treat rare pediatric cancers.

- In a preclinical study, researchers from Baylor College of Medicine examined new strategies for treating MECP2 duplication syndrome (MDS), a cognitive neurodevelopmental disorder that primarily affects adolescent boys. The chief protein implicated in this class of brain condition, MeCP2, operates sufficiently only if it is expressed in strict and stabilized quantities, which is why MDS is so difficult to treat. During the study, published in *Science Translational Medicine* on **March 3, 2021**, using humanized mice models, the researchers tested a MeCP2-targeting treatment, called

MECP2-ASO, which uses antisense oligonucleotide (ASOs), a class of nucleotides that can deliver chemicals with high precision and few side effects. After one week, they observed a 50% reduction in MECP2 mRNA levels; after five weeks, they observed a reversal in the expression of several genes regulated by the MeCP2 protein; and after ten weeks, they observed significant improvements in their subjects' behavioral symptoms, such as locomotion and learning deficits, which are common in MD patients. These findings, while early, suggest that ASO strategies could help treat MDS and other childhood developmental genetic-duplication disorders. In 2016, study co-author Zhandong Liu, Ph.D., associate professor of quantitative and computational bioscience at Baylor College of Medicine, received a $890,000 CPRIT Individual Investigator Academic Research award (RP170387) in support of his bioinformatic research efforts.

- CPRIT Scholar Daniel J. Leahy, Ph.D., Nancy Lee and Perry R. Bass Regents Chair in Molecular Biology at the College of Natural Sciences in The University of Texas at Austin, played a pivotal role in recruiting the team that developed the first COVID-19 vaccine in the United States. With the help of a $6 million CPRIT Recruitment of Established Investigators grant (RR160023), the University of Texas recruited Dr. Leahy from John Hopkins University School of Medicine in 2016. Shortly thereafter, the other members of this all-star research team, including Jason McLellan, Ph.D., Golden Goose award recipient and associate chair for graduate education in the department of Molecular Biosciences, made their way to The University of Texas. "It was clear that to stay relevant in structural biology, you had to be able to do electron microscopy and have access to one of these state-of-the art facilities, and UT Austin had one that was brand new," said Dr. McLellan, who join the faculty at UT Austin in January of 2018.

- Researchers from the University of Houston identified a two-step process that can help explain why healthy p53 proteins, which normally suppress tumor growth, transform into mutant clusters that cause cancer and neurological disease. Breast cancer cell imaging, conducted in the lab of Navin Varadarjan, Ph.D., professor of chemical and biomolecular engineering, helped confirm this two-step process in a p53 mutant variant called R248Q. In support of this collaborative work, published in the *Proceedings of the National Academy of Sciences* on **March 9, 2021**, CPRIT has granted $3.9 million in Individual Investigator Academic Research grants (RP130570, RP180466, RP100602) to this study's contributors, including Dr. Varadarjan.

- Leading a multi-institutional study, researchers from The University of Texas MD Anderson Cancer Center discovered that certain patients with high tumor mutation burdens (TMBs) respond poorly to immune checkpoint treatments. According to their findings, published in *Annals of Oncology* on **March 15, 2021**, patients with high TMB status do not necessarily respond better to treatment than patients with low TMB status. When observing the tumors of patients with a weak TMB to T cell infiltration ratio, the researchers found that high-TMB patients had an overall response rate of only 15.3%—a worse overall response rate than that of low-TMB patients. "While TMB status does show value in predicting response to immune checkpoint blockade in several cancer types, this was not generalizable across all cancers," said Daniel J. McGrail, Ph.D., postdoctoral fellow of systems biology. Pembrolizumab, an anti-PD-1 therapy for patients with high TMB, recently received FDA approval based on a trial that failed to include several important types of cancer, including breast, prostate, and brain cancer. "The FDA approval of pembrolizumab for patients with high TMB

certainly provides an important option for many patients," said study leader Shiaw-Yih (Phoebus) Lin, Ph.D., professor of systems biology at MD Anderson. "However, we felt that it was important to look more closely at TMB status in a broader group of cancer types and establish approaches to harmonize TMB across various assays to enable clinicians to best utilize the recent FDA approval." This research was supported in part by a $5.9 million CPRIT Core Facility Support award (RP170668) and a $6 million CPRIT Multi-Investigator Academic Research award (RP160710).

- On **March 17, 2021**, Immatics N.V. presented data from dose escalation cohorts in its ongoing ACTengine cell therapy programs. The ACTengine product candidates IMA201, IMA202, and IMA203 use proprietary cancer-targeting receptors inside genetically engineered T cells to detect and destroy specific cancers. Treatment with ACTengine product candidates at initial dose levels indicated early anti-tumor activity, with nine out of ten patients showing disease control and eight out of ten patients showing tumor shrinkage, including one partial response. The clinical observations were consistent with robust engraftment, persistence, and tumor infiltration of infused ACTengine T cells. "While the focus of this readout was to evaluate safety and initial biological activity, these unexpected observations on first anti-tumor activity indicate the therapeutic potential for our ACTengine platform in solid cancer patients with considerable tumor burden," said Harpreet Singh, Ph.D., chief executive officer of Immatics. "We look forward to completing dose escalation and sharing first data at target dose in the latter part of this year." Houston-based Immatics US Inc. received a $19.7 million CPRIT Product Development Research award (DP150029) in 2015 for the development of personalized cellular therapies targeting multiple cancer types. The clinical stage biopharmaceutical company is active in the discovery and development of T cell-redirecting cancer immunotherapies.

- Results from a Phase 1 clinical trial conducted by biotechnology company and CPRIT grant recipient ImmunoGenesis show that the prodrug evofosfamide is an effective alleviator of tumor hypoxia—a condition that causes treatment resistance in certain tumors. As reported in *Clinical Cancer Research*, published **March 22, 2021**, when treating tumor hypoxia in patients with advanced cancer, using evofosfamide together with ipilimumab—an immune checkpoint inhibitor—is more effective than using ipilimumab alone. Michael Curran, Ph.D., associate professor of immunology, and David S. Hong, M.D., professor of investigational cancer therapeutics at The University of Texas MD Anderson Cancer Center, led the clinical study. The results revealed a response rate of 17% and a disease control rate of 83% in patients with advanced pancreatic cancer, advance head and neck cancer, treatment resistant prostate cancer, and treatment resistant melanoma. "The efficacy of the combination in these heavily pre-treated patients appears superior to checkpoint monotherapy and provides strong rationale for the use of evofosfamide as a tumor conditioning agent," said Dr. Curran, who is also the founder of ImmunoGenesis. In August of 2020, CPRIT granted ImmunoGenesis a $15.5 million Product Development Research award (DP200094) to support the company's development of novel immunotherapy drugs.

- A team of engineers led by B.J. Fregly, Ph.D., professor of mechanical and bioengineering at Rice University, conducted a study that will likely advance the design of prosthetic joint implants. This work, available in the **March 2021** issue of *Biotribology*, is the first to incorporate all four modes of physics—fluid dynamics, contact mechanics, wear dynamics, and particle dynamics—in a study on

joint implants. By analyzing factors that increase the rate of deterioration in implants (such as the lack of synovial fluid, the extracellular lubricant that allows natural joints to function without pain), these engineers are working to improve the lives of patients in need of joint replacements. Inspired in part by his father's knee surgery, Dr. Fregly's extensive work on human motion in post-surgery patients laid the groundwork for this research. Dr. Fregly invited co-collaborators Fred Higgs, Ph.D., and his engineering team at the Particle Flow and Tribology Lab at Rice to co-author this study. CPRIT issued a $5.1 million Recruitment of Established Investigators grant (RR170026), which helped Rice University recruit Dr. Fregly from the University of Florida in 2017.

- Researchers from The University of Texas Health Science Center at Houston discovered a defect in mice models that test human tumors, called patient-derived xerograph (PDX) models, which could explain why certain cancer drugs are ineffective in human trials. Published in *Nature Communications* on **April 1, 2021**, the researchers examined data from 184 samples of PDX mice models and found that 170 of the 184 samples were compromised by mouse viruses. "What we found is that when you put a human tumor in a mouse, that tumor is not the same as the tumor that was in the cancer patient," said study leader W. Jim Zheng, Ph.D., associate professor of computational biomedicine at the UTHealth School of Biomedical Informatics. "We all share the common goal of hoping to find a cure for cancer. There are 210 ongoing NIH-funded projects relevant to PDX models, with a combined annual fiscal year budget of over $116 million. We need to tighten up quality control and use models that are not compromised so that the treatments we give to future patients are effective." In support of the work conducted at the UT Health Science Center, CPRIT granted Core Facility Support awards in 2015, 2017, and 2019 (RP170668, RP150551, RP190561), totaling approximately $16.8 million.

- Perimeter Medical Imaging AI Inc. announced on **March 30, 2021**, that Northern Arizona Healthcare Verde Valley Medical Center will conduct a study that evaluates Perimeter's Optical Coherence Tomography (OCT) Imaging System in breast conserving surgery. Perimeter created the OCT Imaging System to use as an imaging tool in the evaluation of excised human tissue microstructure by providing two-dimensional, cross-sectional, real-time depth visualization with image review manipulation software for identifying and annotating regions of interest. The company, based in Dallas and Toronto, is also making significant progress within its ATLAS AI Project, an initiative aimed at advancing Perimeter's next-gen artificial intelligence (AI) and machine learning tools through clinical development. Perimeter trained its proprietary ImgAssist AI technology with more than 400 volumes of images of excised breast tissue collected during the first stage of its ATLAS AI project. In April, the United States Food and Drug Administration granted the company a Breakthrough Device Designation for the OCT Imaging System coupled with ImgAssist AI. This designation allows for accelerated interactions with the FDA during product development and prioritized review of future regulatory submissions. Perimeter received a $7.4 million CPRIT Product Development Research award (DP190087) in 2019 to develop an optical tissue imaging system for breast conserving surgery.

- A preclinical study led by researchers from The University of Texas MD Anderson Cancer Center shows promising results for the future of precision targeting therapy for osteosarcoma, the most common type of bone tumor in young adults and adolescents. The researchers used bicycle toxin

conjugates (BTCs) to target highly expressed proteins on the surface of osteosarcoma cells. Using integrated bioinformatic data collected from hundreds of mice and thousands of human tumor samples, the researchers were able to destroy osteosarcoma tumors without damaging healthy cells. In mice models, 50% of the subjects treated with the BTC drug showed a 100% improved response. Richard Gorlick, M.D., head of the division of pediatrics at MD Anderson, presented the findings in **April of 2021** at the American Association for Cancer Research (AACR) Annual Meeting. "This discovery represents a paradigm shift that will help us to move forward more rapidly," said Dr. Gorlick. "I anticipate that there will be an influx of other drugs that can be tested, and because the drugs are targeted to a particular surface protein, they are potentially more effective and have fewer side effects." In support of the precision targeting therapy research conducted at the MD Anderson Cancer Center, CPRIT granted a $4.5 million CPRIT Core Facility Support award (RP130397) in 2012.

- CPRIT Scholar Esra Akbay, Ph.D., assistant professor of pathology, and her colleagues at The University of Texas Southwestern Medical Center discovered a missing protein in immune cells of patients with small cell lung cancer (SCLC) which could help explain why some tumors are resistant to treatment. Patients with SCLC often receive a poor diagnosis, and current immunotherapy drugs typically extend survival by only a few months. While comparing the surface proteins in small cell lung cancer against surface proteins in non-small cell lung cancer (NSCLC), the researchers discovered that the protein NKG2DL was missing from SCLC cells. Using mice models to examine SCLC animal tumors with missing NKG2DL proteins, the researchers genetically altered the SCLC cells, forcing the cells to produce the NKG2DL protein on their surfaces. The experiments, available in the **April 2021** issue of *Cancer Research*, resulted in smaller tumors that were less likely to spread. "The more we know about how the immune system interacts with cancer, the more we can take advantage of the body's inherent defense system to fight this disease," said Dr. Akbay. In 2016, UT Southwestern Medical Center recruited Dr. Akbay from the Dana-Farber Cancer Institute of Harvard Medical School with the support of CPRIT's $2 million Recruitment of First-Time, Tenure-Track award (RR160080).

- Researchers from Rice University and Baylor College of Medicine are joining a national project to improve genome-editing research and technology in disease-specific somatic cells. As described in an article published in *Nature* on **April 7, 2021**, the United States of Health (NIH) Somatic Cell Genome Editing Consortium (SCGE) wants to develop and distribute new genome editors, delivery methods and technologies, and animal models to the biomedical research community. Directing an SCGE project, CPRIT Scholar and professor of bioengineering at Rice University Gang Bao, Ph.D., is leading a team that will engineer adeno-associated viruses to deliver genome-editing enzymes to the endothelium—the tissue that makes up important vascular cells throughout the body. Researchers at Baylor, led by Mary Dickinson, Ph.D., Jason Heaney, Ph.D., and William Lagor, Ph.D., are hosting a small animal testing center where they will develop reporter mice that detect editing events in somatic genomes. With the help of CPRIT's $6 million Recruitment of Established Investigators Grant, Rice University recruited Dr. Bao in 2014 (RR140081). In support of the Houston-based researchers' contribution to the SCGE's project, CPRIT awarded an additional $1.06 million (RP120713-P3), $1.4 million (RP150081), and $900,000 (RP200402) in academic research grants from 2012 to 2020.

- New research led by CPRIT Scholar Jian Xu, Ph.D., associate professor of pediatrics at The University of Texas Southwestern Medical Center, reveals a surprising role for jumping genes. Jumping genes, also known as transposons, are a source of genetic mutations responsible for several human diseases. Transposons are DNA sequences that can jump from one location in the genome to another when activated. Activation of transposons often leads to mutations that can cause cancer. The study, published in the journal *Nature Genetics* on **April 8, 2021**, shows that activation of a particular type of transposon can protect against certain blood cancers. "Our initial finding was a surprise because it's been long thought that activated transposons promote cancer development by generating genetic mutations. We found it was the opposite for blood cancers, and that decreased L1 activity was associated with worse clinical outcomes and therapy resistance in patients," says Jian Xu, Ph.D., associate professor in CRI and senior author of the study. "Our discovery that L1 activation can suppress the survival of certain blood cancers opens up the possibility of using it as a prognostic biomarker, and possibly leveraging its activity to target cancer cells without affecting normal cells." The discovery can possibly provide a mechanistic explanation for the unusual sensitivity of myeloid leukemia cells to DNA damage-inducing therapies that oncologists currently use to treat patients. CPRIT awarded four grants to support this work (RR140025, RP180504, RP180826 and RP190417).

- In a multi-institutional study, researchers from The University of Texas MD Anderson Cancer Center discovered a protein interaction that directly promotes metastasis and tumor growth in roughly 70% of patients with pancreatic cancer. The researchers found that mutant genes KRAS and p53, two of the most common mutations in all human cancers, directly interact through a protein called CREB1 to promote metastasis. Mutant KRAS activates CREB1, which works with mutant p53 to cause cellular abnormalities. "To our knowledge, this is the first study to show how these two major genetic drivers work together to promote tumor growth and metastasis," said Michael Kim, Ph.D., assistant professor of surgical oncology and genetics at MD Anderson. "This discovery provides not only a new therapeutic target but unveils a vast transcriptional network that is activated downstream of these mutant proteins." These findings were published in *Cancer Discovery* by the American Association for Cancer Research on **April 10, 2021**. In support of this work, CPRIT granted a $2.1 million Individual Investigator Academic Research award (RP200173) in February of 2020. CPRIT also granted academic research awards (RP180313, RP170231) in 2018 and 2016 for the investigative work on mutant gene p53 conducted at MD Anderson.

- As part of a multi-laboratory study, researchers from the Peter O'Donnell Brain Institute at The University of Texas Southwestern Medical Center discovered a neurodegenerative protein that can improve understanding of strokes and their aftereffects. In the study, published in *Molecular Neurodegeneration* on **April 14, 2021**, the researchers identified an alternative form of the apoptosis-inducing factor (AIF) protein; they named this protein AIF3. While experimenting on mice models and human brain tissue, the UT Southwestern researchers and their co-collaborators found that, after a stroke, the brain stops producing AIF and starts producing AIF3, which ultimately leads to mitochondrial dysfunction and cell death. In their mice models, this alternative splicing effect (i.e., the reduction of AIF and production of AIF3) resulted in severe progressive neurodegeneration, an observation that could help explain the connection between strokes and dementia. "Our study provides a valuable tool to understand the role of AIF3 splicing in the brain and a potential therapeutic target to prevent or delay the progress of neurodegenerative diseases," said study

leader, Yingfei Wang, Ph.D., assistant professor of pathology and neurology and a member of the O'Donnell Brain Institute at UT Southwestern. In 2017, Dr. Wang and her team at UT Southwestern received a $200,000 Academic Research grant (RP170671), which helped fund this discovery.

- Iterion Therapeutics Inc. recently completed enrollment and dosed the final patient in its multicenter Phase 1/2a dose expansion clinical study of Tegavivint in patients with desmoid tumors. On **April 13, 2021**, the company announced that the expansion study confirmed the safety of Tegavivint, a novel, potent and selective nuclear beta-catenin inhibitor. Rahul Aras, CEO of Iterion, explained, "The completion of enrollment in the dose expansion phase of our desmoid tumor clinical trial and demonstration of safety and clinical activity at the RP2D represent important milestones in our clinical development of Tegavivint. We look forward to advancing the clinical development of Tegavivint in desmoid tumors as this disease target is greatly underserved. The results of this study also provide a green light to initiate clinical development of Tegavivint in additional, high-value cancer settings, including AML, NSCLC, and certain pediatric cancers that are characterized by nuclear beta-catenin overexpression." Houston-based Iterion received a $15.9 million CPRIT Product Development Research award (CP130058) in 2014 to develop Tegavivint for desmoid tumors and acute myeloid leukemia.

- Hummingbird Bioscience Inc. presented pre-clinical data on its BCMA-TACI dual-specific T cell engager, HMBD-009, at the 2021 American Association for Cancer Research (AACR) Annual Meeting on **April 13, 2021**. The company also developed a new cancer therapy, HMBD-002-V4, for patients resistant to cancer immune-oncology (IO) drugs. HMBD-002-V4 is designed to treat a branch in the immune system called myeloid-derived suppressor cells (MDSCs), which is one of the most prominent causes of cancer resistance. MDSCs can deactivate cancer-killing cells that IO drugs are designed to stimulate. In some prior cases, HMBD-002-V4 completely reversed IO therapy resistance in patients. Hummingbird Bioscience, based in Houston, San Francisco, and Singapore, received a $13.1 million CPRIT Product Development award (DP190027) in 2019 to develop a first-in-class anti-VISTA monoclonal antibody to treat MDSC-mediated suppression of anti-tumor immunity in solid tumors and lymphomas.

- Heather Y. Lin, Ph.D., and J. Jack Lee, Ph.D., professor of biostatistics at The University of Texas MD Anderson Cancer Center, co-authored a study on genetic abnormalities in head and neck cancer, reported in *Proceedings of the National Academy of Sciences* on **April 26, 2021**. Knowing which patients will respond poorly to a particular method of treatment will save patients from wasting time and money on ill-suited clinical therapy. The study, supported in part by a $900,000 CPRIT academic research award (RP140464), identified immune cell makeup that dictates a tumor's responsiveness to immune checkpoint inhibitors.

- A recent study reveals that a CPRIT-funded, at-home colorectal cancer (CRC) screening project led by Michael Pignone, M.D., director of the cancer prevention and control program at The University of Texas at Austin Dell Medical School, is fiscally and clinically effective. The project is designed to screen for CRC in low-income and uninsured individuals in Travis County using fecal immunochemical testing (FIT) kits—which are mailed to and from a patient's home—along with inexpensive follow-up reminders (e.g., texts and postcards). Applying preventative medicine and health economics principles, a team of researchers from Dell Medical School and the LBJ School of

Public Affairs analyzed the benefits and costs of testing more than 20,000 adult participants. The results, published in the *Journal of Internal Medicine* on **April 30, 2021**, reveal that 20% of the patients who received at-home FIT kits followed the screening process, which had an average direct cost of approximately $55 per person screened. “There are very few interventions that are cost-saving like this one is, and if adopted widely, this outreach model could be transformative for protecting a vulnerable sector of the population from colorectal cancer,” said Dr. Pignone. “The idea of reaching people in their home, to complement work being done in the clinic, is very appealing for its effectiveness and its convenience.” Dr. Pignone initiated the CRC screening program in 2017 with the help of a $2.3 million CPRIT Cancer Prevention Services award (PP170082). In support of the program’s expansion, The University of Texas at Austin received an additional $2 million Cancer Prevention Services award (PP200066) in August 2020.

- In work analyzing POT1, a gene whose carriers are at high risk for glioma (the most common type of malignant brain tumor), researchers from Baylor College of Medicine found evidence suggesting that sex influences tumor characteristics, immune response, and ultimately, survival rate in glioma patients. “We observed that, in the absence of POT1, there was a sex-specific effect on expression of genes involved in the immune response, both in mice and humans,” said Ali Jalali, M.D., Ph.D., assistant professor of neurosurgery at Baylor. “Some of these genes are known to contribute to the activation of immune cells, such as T cells and macrophages, which have been shown to play a role in cancer growth. We also took a closer look at the tumors and found that female mice lacking the Pot1 gene had less immune cell infiltration into the tumors compared to males. This suggested the possibility that a sex-dependent change in immune response contributed to the observed gender differences in tumor aggressiveness driven by loss of Pot1.” In support of this research, available in the **May 2020** edition of *Cancer Research*, CPRIT granted approximately $12 million through its 2015 (RP150578) and 2017 (RP170719) Core Facility Support Awards.

- On **May 3, 2021**, Aeglea Biotherapeutics Inc. announced that it completed patient randomization for PEACE (Pegzilarginase Effect on Arginase 1 Deficiency Clinical Endpoints), the pivotal Phase 3 clinical trial investigating pegzilarginase for the treatment of Arginase 1 Deficiency. The Austin-based company received a $19.8 million CPRIT Product Development Research award (DP140031) in 2014 to develop an engineered human arginase targeting multiple cancer types.

- Researchers at The University of Texas MD Anderson Cancer Center developed a groundbreaking artificial intelligence tool that could lead to new solutions for drug-resistant cancers. This tool, called SCMER, can isolate rare groups of cells in single-cell datasets. Most modern tools can generate a great deal of data but cannot easily pinpoint the genes or proteins that play important roles in biological phenomena, such as drug resistance. Scientists can use SCMER (which stands for single-cell manifold preserving feature selection) to study minimal residual diseases, drug resistance, and distinct populations of immune cells invading a cancer, and in many other practices that advance the field of oncology. Ken Chen, Ph.D., associate professor of bioinformatics and computational biology at MD Anderson, led the group that developed SCMER. Their work is available in the **May 20, 2021**, issue of *Nature Computational Science*. In support of his work, CPRIT granted Dr. Chen a $900,000 Individual Investigator Academic Research Award for Computational Biology (RP180248) in 2018. Study co-author Weiyi Peng, M.D., Ph.D., assistant professor of biology and biochemistry at the

University of Houston, received a $250,000 CPRIT Academic Research award (RP200520) in 2020 for her development of genetic screens for single-cell RNA sequences.

- Researchers from The University of Texas Health Science Center at Houston and The University of Texas Medical Branch at Galveston engineered a new therapeutic antibody with high potency against the SARS-CoV-2 (COVID-19) virus and its prevalent variants. Clinicians will administer the new antibody formula by nasal spray, supplying direct access to the nasal passages and lungs—the primary sites of viral infection. The preclinical studies in mice suggest that the new antibody fight COVID-19 better than existing antibody treatments, especially against new, increasingly prevalent variants. This study, led by Zhiqiang An, Ph.D., professor at The University of Texas Health Science Center at Houston and Pei-Yong Shi, Ph.D., professor at The University of Texas Medical Branch at Galveston and available in the **June 3, 2021**, edition of the journal *Nature Communications*, received two CPRIT Core Facility Support awards (RP150551, RP190561) in 2015 and 2019, totaling approximately $11.2 million. The researchers licensed this new antibody to IGM Biosciences for further development and clinical testing.

- Scientists know that hypoxia, or a lack of oxygen, is a characteristic of cancerous tissue. The more hypoxic a tumor, the worse it tends to respond to chemotherapy and radiation. Using magnetic resonance imaging in animal models, researchers at The University of Texas Southwestern Medical Center used oxygen levels to predict how tumors would respond to radiation therapy. The findings, published in the Interna*tional Journal of Radiation Oncology, Biology, and Physics* on **June 9, 2021**, can help improve personalized therapies for patients who receive radiation treatments. This work was supported in part by a $900,000 CPRIT Individual Investigator Academic Research award (RP140285), granted to Dr. Ralph Mason in August of 2014.

- CPRIT Scholar K.C. Nicolaou, Ph.D., and his colleagues at Rice University published the first total synthesis of halichondrin B using a well-known process called “the Rice Lab’s reverse approach.” Published in the *Journal of the American Chemical Society* on **June 9, 2021**, this simplified process can be used to make chemical variants of halichondrin B like eribulin, which is used to treat breast cancer and liposarcoma. Rice University recruited Dr. Nicolaou with the help of CPRIT’s $6 million Recruitment of Established Investigators Grant (R1226), awarded on August 2, 2012.

- Working with a team of researchers from the Lineberger Comprehensive Cancer Center at the University of North Carolina, CPRIT award recipient Bellicum Pharmaceuticals Inc. developed a safety switch that can reduce severe side effects of T cell immunotherapy. Chimeric antigen receptor T cell therapy (CAR-T therapy) uses modified T cells that can cause life threatening toxicities in certain patients. The researchers engineered T cells with a safety switch called inducible caspase-9 (IC9), which can be activated in patients who develop toxic side effects by administering a drug called rimiducid. Published in the **June 10, 2021**, issue of *Blood*, the findings suggest that IC9 is safe and effective against refractory B-cell acute lymphoblastic leukemia, a difficult to treat, fast-moving cancer that often occurs in children and adolescents. In 2011, Bellicum Pharmaceuticals Inc. received a $5.7 million CPRIT Product Development Research award (RP110508) to develop the T cell therapy safety switch CaspaCIDe. Bellicum also received a $16.9 million CPRIT Product Development Research award (DP160057) in 2016 to develop T cell therapy for acute myeloid leukemia (AML).

- The journal *Neuro-Oncology* published an abstract on **June 1, 2021,** which shows positive safety and efficacy data for CT-179, a promising OLIG2 inhibitor drug developed by CPRIT award winner Curtana Pharmaceuticals Inc., an Austin-based biopharmaceutical company. CT-179 prolonged event-free survival in an animal model of medulloblastoma as a single agent and showed increased efficacy when combined with palbociclib, a CDK4/6 inhibitor marketed by Pfizer. Curtana received a $7.5 million CPRIT Product Development Research award (DP140034) in 2014 for developing novel small molecule precision targeting treatments for brain cancers in children and adults.

- Researchers from Baylor College of Medicine and the Texas Children's Cancer Center studied molecular clock restoration as a potential method to improve treatment for neuroblastoma tumors. Their findings, published in *Nature Communications* on **June 18, 2021**, suggest that normalizing the molecular clocks in a patient's cells can suppress cancer growth and improve cancer's response to chemotherapy. The researchers reached this hypothesis by studying patients with amplified MYCN genes, which can cause neuroblastoma to spread. They discovered that BMAL1 and the receptor that activates it, RORα, were suppressed. Testing two restorative approaches—genetic overexpression and synthetic reactivation of RORα—the researchers successfully restored BMAL1, the gene that drives the molecular clock cycle. "We know metabolic processes are really important in how tumors develop resistance to chemotherapy," said Eveline Barbieri, M.D., Ph.D., assistant professor of pediatrics at Baylor College of Medicine. "In the future, if we can develop therapeutics that restore the molecular clock in a clinical setting, we may be able to use them in combination with standard chemotherapy to avoid treatment resistance." In 2016, Baylor College of Medicine received a $5 million Core Facilities Support award from CPRIT (RP170005) for the study of gene mutations, like BMAL1, which cause cancer progression.

- CPRIT Scholar Omid Veiseh, Ph.D., assistant professor of bioengineering at Rice University, discovered adverse effects of textured breast implants. During the six-year study, published in *Nature Biomedical Engineering* on **June 21, 2021**, patients who were exposed to textured-surface implants developed large cell lymphoma (BIA-ALCL), while patients who were exposed to smooth-surface implants did not develop large cell lymphoma. The researchers conducted three individual trials—one in rabbits, one in mice, and one in humans—and, in each trial, observed the same immune responses in their patients: the rougher the implant surface, the more irritated the surrounding tissue became. Chronic inflammation can eventually lead to cancer, and this could explain why textured implants cause lymphoma. Understanding that rougher implants cause a greater inflammatory T cell response can help scientists and doctors design safer implant materials. Many Texas-based bioengineers contributed to this study, including researchers from Rice University, Baylor College of Medicine, and The University of Texas MD Anderson Cancer Center. In 2017, Rice University recruited Dr. Veiseh from the Massachusetts Institute of Technology with support from CPRIT's $2 million Recruitment of First-Time, Tenure-Track Faculty grant (RR160047).

- CPRIT Scholar K.C. Nicolaou, Ph.D., professor of chemistry at Rice University, teamed up with AbbVie Inc. to create antibody-drug conjugates (ADCs) that target cancer cells using what Dr. Nicolaou calls the significant bystander effect. Recorded in the *Proceedings of the National Academy of Sciences* on **June 22, 2021**, this research builds on prior multidrug-resistant cancer studies. Dr. Nicolaou's unique ADC drug kills cancer cells indirectly, destroying non-targeted cancer cells that neighbor targeted

cells. In this way, "[t]he bystander effect is expected to improve the efficacy of the ADC drug," said Dr. Nicolaou. In August of 2012, CPRIT awarded a $6 million Recruitment of Established Investigators Grant (R1226), which helped Rice University recruit Dr. Nicolaou from The Scripps Research Institute.

- Han Xiao, Ph.D., a CPRIT Scholar and assistant professor of chemistry at Rice University, co-developed an antibody conjugate called BonTarg to treat cancers that metastasize to the bone—an event that occurs in roughly 70% of breast cancer survivors who experience metastases. Dr. Xiao and his colleagues (a team of scientists from Baylor College of Medicine led by Xiang Zhang, Ph.D., and Dr. Xiao's team at Rice labs) published their findings in *Science Advances* on **June 23, 2021**. The researchers relied on pClick technology, a novel strategy developed by Dr. Xiao that uses antibodies to deliver cancer inhibitors into bone tumors without harsh chemicals, enzymes, or ultraviolet lights. Using pClick, the researchers coupled alendronate, a compound used to treat osteoporosis, with trastuzumab, an antibody that targets the HER2 gene in breast cancer. BonTarg substantially increased the concentration of the trastuzumab antibody delivered within the tumor sites, a result with promising potential for treating other metastasis-prone cancer tumors. In 2017, Rice University recruited Dr. Xiao from Stanford University with the help of CPRIT's $2 million First-Time, Tenure-Track Faculty grant (RR170014).

- On **June 23, 2021**, Tvardi Therapeutics, a biotech startup founded by Ron DePinho, M.D., professor of cancer biology at The University of Texas MD Anderson Cancer Center, raised $74 million in series B financing for its clinical programs, including future clinical trials on the company's oral, small-molecule inhibitor signal transducer and activator of transcription 3 (STAT3) to treat various cancers. In support of the work of Dr. DePinho and the researchers at Tvardi, CPRIT granted a $900,000 Individual Investigator Academic Research award (RP140612) in 2014 for targeting collateral genomic deletions in various cancer types.

- A team of researchers led by Carlos Arteaga, M.D., professor of internal medicine at The University of Texas Southwestern Medical Center, discovered an important relationship between two genes common in breast cancer patients—human epidermal growth factor receptors, HER2 and HER3. Using computer modeling to study this relationship, the UT Southwestern researchers discovered that HER2 and HER3 share a tight protein bond which reduces the effectiveness of HER2 inhibiting drugs in patients with both HER2 and HER3 gene mutations. This research, published in *Cancer Cell* on **June 24, 2021**, is significant for carriers of both genes. "Patients that carry both HER2 and HER3 mutations are likely not going to be good candidates for treatments by HER2 inhibitors themselves," said Ariella B. Hanker, Ph.D., assistant professor of internal medicine at UT Southwestern. "By also inhibiting the action of HER3, we can make some headway against these tumors." In awarding a $6 million Recruitment of Established Investigators Grant (RR170061), CPRIT helped UT Southwestern recruit Dr. Arteaga from Vanderbilt University School of Medicine in 2017.

- Announced on **June 29, 2021**, engineers from Rice University are joining a nation-wide effort to develop implantable devices that regulate sleep. The Defense Advanced Research Projects Agency (DARPA) is funding this $33 million project, which could help military personnel, first responders, and international travelers who must constantly adjust their sleep cycles. Designed to function as a molecular pharmacy, these grain-sized devices will use the same peptide molecules that control the

body's circadian rhythm to relieve adverse effects of traveling including jetlag, fatigue, and gastrointestinal problems. CPRIT Scholars Omid Veiseh, Ph.D., assistant professor of bioengineering, and Jacob Robinson, Ph.D., associate professor of electrical and computer engineering at Rice University are directing two key components of the DARPA project: creating engineered cells that produce therapeutic biomolecules and creating wireless bioelectronic implants that store engineered cells and regulate drug production. Their efforts will allow scientists to deliver peptides into the bloodstream with ultra-accurate precision, a capability with endless possibilities, said Dr. Veiseh, including chronic disease management. Each device will be powered by a low-grade magnetic field that is generated by the device itself. The magnetic field will also control how a device communicates. This magnetoelectric technology will include advanced device security. For instance, as a safety feature, communication with the devices will require close contact, and each device will include a built-in deactivation protocol, allowing users to permanently destroy the engineered cells. In 2017, with support from CPRIT's $2 million Recruitment of First-Time, Tenure-Track Faculty grant (RR160047), awarded on May 18, 2016, Rice University recruited Dr. Veiseh from the Massachusetts Institute of Technology.

- Announced on **July 9, 2021**, in a Phase 1 clinical study, Molecular Templates Inc., an Austin-based biopharmaceutical company, dosed its first subject with MT-6402, a third generation of engineered toxin bodies (ETBs) designed to treat patients with PD-L1 positive solid tumors. Patients who are confirmed carriers of PD-L1 expressing tumors or who have confirmed PD-L1 expression in the tumor microenvironment will be eligible to screen for enrollment in the Phase 1 Study. "The PD-1/PD-L1 axis is central to many tumors and targeting that axis with a new mechanism of action has an opportunity to provide meaningful benefit to patients," said Eric Poma, Ph.D., CEO and CSO of Molecular Templates. In 2011, CPRIT awarded Molecular Templates a $10.6 million Product Development Research grant (CC121020) to develop its proprietary targeting biologics, ETBs, to treat lymphoma.

- Announced on **July 12, 2021**, the Houston-based biotech company Hummingbird Biosciences entered into a multi-year strategic research agreement with The University of Texas MD Anderson Cancer Center to study and test HMBD-002, Hummingbird's VISTA antagonist antibody. Hummingbird received a $13.1 million CPRIT Product Development Research award (DP190027) in February of 2019 to develop HMBD-002-V4 to treat patients who are resistant to cancer immuno-oncology drugs.

- A recent study marks the first use of the MassSpec Pen in pancreatic cancer surgery on human patients. Researchers from the University of Texas at Austin and Baylor College of Medicine recorded their findings from the 18 pancreatic surgeries in the **July 13, 2021**, issue of the *Proceedings of the National Academy of Sciences*. Study co-author Livia Eberlin, Ph.D., a CPRIT investigator and an assistant professor of chemistry at UT Austin, led the team who developed the MassSpec Pen technology. This state-of-the-art diagnostic tool detects cancerous tissue at a much faster rate than frozen section analysis, the current gold standard method for finding and removing cancerous tissue. Since 2016, Dr. Eberlin has received three academic research awards (RP160776, RP170427, RP180381) to advance the MassSpec Pen's diagnostic capabilities. To date, the pen has been tested in more than 150 human surgeries.

- Researchers from The University of Texas Southwestern Medical Center investigated the safety profiles of stereotactic ablative radiation (SABR), an ultra-precise high-dose radiation treatment for kidney cancer. SABR delivers high radiation to tumor vein extensions to stop renal cell carcinoma from traveling through the bloodstream to other vital organs. During clinical trials, the UT Southwestern scientists administered five doses of SABR to six patients, then they conducted a follow up on each patient two years later. As recorded in the **July 15, 2021,** issue of the *International Journal of Radiation Oncology, Biology, and Physics*, no patient treated with SABR experienced serious complications. In 2018, CPRIT awarded a $6 million Multi-Investigator Academic Research award (RP180725) in support of the UT Southwestern Medical Center's work on SABR.

- While studying STING immune proteins, researchers from The University of Texas Southwestern Medical Center discovered that a protein called cGAS is linked to a rare neurodegenerative condition called Neimann-Pick disease type C. Their findings, published in the online journal *Nature* on **July 21, 2021**, could lead to new precision targeting therapies for the disease, which currently has no effective treatments. In February of 2018, study co-author Nan Yan, Ph.D., professor of immunology and microbiology at UT Southwestern, received a $900,000 Individual Academic Research award (RP180288) to design immunotherapy drugs that restore immune response inside of cancer cells.

- The Houston-based biotech company Hummingbird Biosciences Inc. announced **August 2, 2021**, that the United Kingdom Medicines and Healthcare Products Regulatory Agency approved its application to start clinical trials to test HMBD-001, a novel antibody that inhibits HER3-mutated tumors, in human patients with advanced solid cancers. Hummingbird received a $13 million CPRIT Product Development Research award (DP190027) in February of 2019 to develop an antibody therapy for treatment resistant cancers.

- In a collaborative study on stem cells in mammals, researchers from Baylor College of Medicine discovered a possible link between ageing and cryptic transcription—a genomic phenomenon that disrupts normal cell function. The study, published in *Nature Aging* on **August 2, 2021**, suggests that if we knew how to control cryptic transcription, we could slow down the cellular aging process. "In previous work, we showed that cryptic transcription in yeasts and worms is not only a marker of aging but also a cause," said study corresponding author Weiwei Dang, Ph.D., assistant professor of molecular and human genetics at Baylor College of Medicine. "Reducing the amount of this aberrant transcription in these organisms prolonged their lifespan." Baylor College of Medicine recruited Dr. Weiwei Dang to Houston from the University of Pennsylvania in 2012 with the help of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty grant (R1306).

- Researchers at Baylor College of Medicine developed algorithms to detect early-stage schizophrenia. During the study, available in the **August 3, 2021**, issue of *Translational Psychiatry*, the team used bioinformatics to analyze epigenetic markers, which turn genes on and off, in patients diagnosed with schizophrenia. Study co-author and CPRIT investigator Robert Waterland, Ph.D., professor of pediatrics-nutrition, and his colleagues built an algorithmic model that correctly identified 85% of patients with schizophrenia (using a control group of patients without a history of schizophrenia). To build this highly accurate model, Dr. Waterland's team used a set of specific genomic regions that consistently appear within different types of tissue inside a given person; the team discovered this set of genomes in a prior study. Dr. Waterland received a $1 million Individual Investigator Academic

Research award (RP170295) in November of 2016 to develop effective epigenetic biomarkers to identify individuals at high risk for cancer.

- Researchers from The University of Texas MD Anderson Cancer Center discovered that the long noncoding RNA *HULC* directly regulates phenylalanine metabolism. Published in *Science* on **August 6, 2021**, this finding can possibly lead to new treatments for phenylketonuria—a rare, hereditary metabolic disorder. With the help of a $2 million CPRIT Recruitment of First-Time, Tenure-Track Faculty grant (R1218) the MD Anderson Cancer Center recruited study author Liuqing Yang, Ph.D., assistant professor of molecular and cellular oncology, from the University of California in San Diego in August of 2012. Dr. Yang also received a $900,000 CPRIT Individual Investigator Academic Research award (RP200423) in February of 2020 to research mechanisms responsible for immune-resistant liver cancers.

- A team of investigators led by C. Patrick Reynolds, M.D., Ph.D., director of the Texas Tech University Health Sciences Center School of Medicine Cancer Center, published findings in the August 18 edition of *Science Translational Medicine* showing that neuroblastoma develops resistance to chemotherapy by adopting an alternative lengthening of telomeres (ALT) mechanism to continue replicating. Telomeres are repetitive sequences of non-coding DNA at the end of a chromosome that protect the chromosome from damage.

  Using patient-derived cell lines, Dr. Reynolds' team determined that this telomere dysfunction promotes organic activation of an enzyme, ATM kinase, which, in turn, promotes resistance to chemotherapy. They found that a clinical-stage small-molecule inhibitor of the ATM kinase, under development by AstraZeneca, reversed chemotherapy resistance in patient-derived xenografts, suggesting a potential strategy to target ALT neuroblastoma chemoresistance. The findings are important because neuroblastoma patients with this phenotype do not respond well to treatment. Scientists also report the ALT mechanism in many other types of cancers; it is likely what makes those cancers resistant to chemotherapy.

  Dr. Reynolds explains that understanding how ALT works and how to target it will shape future clinical trials that may benefit patients with tumors that depend on the ALT mechanism. An individual investigator research award in childhood cancers (RP170510) supported Dr. Reynolds' research.

- The U.S. Food and Drug Administration approved belzutifan, a leading-edge pharmaceutical, as a treatment for cancer associated with von Hippel-Lindau disease (such cancers include renal cell carcinoma, central nervous system hemangioblastomas, and pancreatic neuroendocrine tumors). Researchers from The University of Texas Southwestern Medical Center, including several CPRIT grantees, are responsible for the developmental breakthroughs that led to the FDA's **August 13** approval of belzutifan. Steven McKnight, Ph.D., professor of biochemistry, discovered the key protein (HIF-2α) that led to belzutifan's creation with support from a $650,000 CPRIT Multi-Investigator Academic Research award granted in 2011 (RP110708-AC). Fellow CPRIT investigators Richard Bruick, Ph.D., and Kevin Gardner, Ph.D., identified multiple molecules that inhibit HIF-2α's activity with the help of two CPRIT academic research awards, granted in 2010 (RP100846) and in 2012 (RP130513). Many of these molecules were tested in clinical trials by the biopharmaceutical

company Peloton Therapeutics Inc., which received support from a $3.2 million CPRIT Product Develop award granted in June of 2010 (R1009).

- CPRIT Scholar and biochemist Omid Veiseh, Ph.D., and bioengineer Jordan Miller, Ph.D., from Rice University are creating insulin-producing implants for patients with Type 1 diabetes. Rice University recruited Dr. Veiseh from the Massachusetts Institute of Technology in May of 2016 with the help of a $2 million CPRIT First-Time, Tenure-Track Faculty grant (RR160047).

- Researchers from Baylor College of Medicine discovered a protein inhibitor that can help stop the spread of SARS-CoV-2—the virus that causes COVID-19. Using DNA-Encoded Chemistry Technology, the researchers were able to test billions of molecules to find one that inhibits a critical component of the virus's replication process. With this technology, they studied 1,000-times more compounds than possible if using traditional methods. Their findings, available in the **September 7, 2021**, issue of *Proceedings of the National Academy of Sciences*, show that the compound, CDD-1713, is a potent inhibitor of the key viral protein, $M^{pro}$. Baylor College of Medicine received a $6 million CPRIT Core Facility Support Award (RP160805) in May of 2016 to develop the DNA-Encoded Chemistry Technology that made this discovery possible.