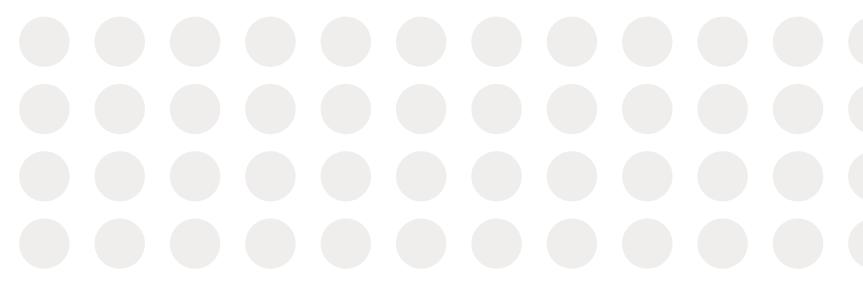


MDAnderson Cancer Center

Making Cancer History®



Cancer does not stop during a pandemic, and neither has the Moon Shots Program® at The University of Texas MD Anderson Cancer Center.

From the earliest stages of the COVID-19 pandemic, MD Anderson has remained committed to ensuring the health and safety of our patients, our workforce and our community. We implemented a proactive, multi-faceted approach that has successfully allowed us to prevent unnecessary exposures to, and spread of, COVID-19 on our campuses.

The need for innovative translational and basic research remains. In Fiscal Year 2020, the scientific community was forced to adapt to new ways of working. However, the interconnected, collaborative infrastructure of the Moon Shots Program enabled our teams to continue making meaningful progress. Thanks to carefully coordinated safety protocols, we continued to advance all 13 of our Moon Shots®, with the benefit of our research platforms that help our teams bring novel concepts from the bench to the bedside for our patients. Remote monitoring and virtual visits allowed us to care for patients and continue important clinical studies while minimizing in-person visits and potential exposures.

As you read through this report, you will see that, despite the pandemic's challenges, our Moon Shots teams continue to leverage a scientific organization unique to cancer centers worldwide to advance life-saving treatment options for our patients.

We are bringing improved treatments to our patients, including cellular, targeted, combination and immunotherapies, and we are learning more about how to overcome resistance to these therapies in many cancers.

We are uncovering more accurate biomarkers, such as circulating tumor DNA, to detect cancers early in their progression, when they are most treatable, and to better portend disease relapse.

We are stratifying cancers into subsets with specific vulnerabilities, which allows us to further personalize treatments for patients.

And we are exploring the body's microbiome to boost treatment response in patients.

Philanthropy seeds ideas that cannot be funded through other mechanisms. The essential nature of donor support has been particularly prescient throughout this global health crisis, providing for programs in a contracted funding environment for the scientific community worldwide.

We hope this report fosters a sense of pride in the impact brought about by your generosity. Thank you for what you are making possible for our patients.

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B-CELL LYMPHOMA

MOON SHOT

Program Leaders: Richard Champlin, M.D. Christopher Flowers, M.D. Michael Wang, M.D.

Lymphoma is the most common hematological malignancy, and B-cell lymphoma accounts for 85% of all lymphomas. In the United States, there are 700,000 patients currently living with this disease, and nearly 80,000 new lymphoma cases are diagnosed each year. Approximately 21,000 people succumb to lymphoma annually.

If not cured by frontline therapy, B-cell lymphoma becomes progressively more resistant to therapies, and most relapsed patients die from progressive disease. The overall cure rate for B-cell lymphoma was estimated at only about 30% when the B-cell Lymphoma Moon Shot® launched. The goal of the program is to use clinical, translational and basic science approaches to double the cure rate of our patients with B-cell lymphoma in the next five to 10 years.

The Moon Shot has created an innovative and collaborative environment that encourages a multi-modal approach and utilizes state-of-the-art technologies through the platforms. The program has allowed its members to think big, inspiring the development of new ideas and strategies with its support. Furthermore, our interactions and collaborations with the Moon Shot platforms will continue to support and accelerate our individual discoveries. The therapies, scientific discoveries and assays developed by our team will help overcome therapeutic resistance and improve outcomes of patients with B-cell lymphoma.

To overcome resistance mechanisms, we are developing precision medicines, stem cell transplantation strategies and cellular therapies, such as chimeric antigen receptor (CAR) T-cell and CAR natural killer (NK)-cell therapies. Moreover, we have now focused on the resistance mechanisms related to relapse or a non-response to different cellular therapies and are developing alternative therapies to thwart resistance. We are investigating the role of different components in the microenvironment and discovering new targets and novel therapies or treatment combinations to be tested in clinical trials.

Looking ahead, we are focusing on a number of projects that give us the best opportunity to push B-cell lymphoma treatment forward and improve patient outcomes. These include:

- + Developing an innovative genetically engineered CAR NK-cell strategy to treat non-Hodgkin lymphoma patients that have failed prior CD19 CAR T-cell therapy.
- + Formulating a novel CAR T-cell therapy with specificity for B-cell lymphoma and no expression in other tissues.
- + Prioritizing strategies to make CAR T-cell therapeutics more effective and inexpensive while improving patient outcomes.

- + Characterizing the diffuse large B-cell lymphoma epigenome in order to identify novel therapeutic strategies.
- Elucidating the mechanisms of response and resistance to diffuse large B-cell lymphoma treatment to identify patients most likely to benefit from potential therapeutic combinations.
- + Exploring the mechanisms of resistance to Bruton's tyrosine kinase inhibitor therapy in mantle cell lymphoma, and development of strategies to overcome this resistance.
- + Establishing patient-tumor derived mouse models to determine the mechanism of action of an MDM2 inhibitor against post-transplant lymphoproliferative disorders.

These innovative projects are moving the needle and will improve the standard of care for patients with B-cell lymphoma, and we are incredibly appreciative of the generous donors who make these advancements possible.

BREAST CANCER ::: MOON SHOT

The bold goal of the Breast Cancer Moon Shot® is to create a precision medicine program for the neoadjuvant, or pre-surgical, treatment of triple-negative breast cancer (TNBC), a catch-all diagnosis of biologically different breast cancer subtypes that lack expression of estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2. TNBCs account for 15 to 20% of breast cancer diagnoses and the five-year survival rate for patients treated with neoadjuvant therapy is 66%.

The most critical unmet clinical need for patients with localized TNBC is preventing both the overtreatment of patients that will respond well to neoadjuvant chemotherapy and the undertreatment of cancers that are chemo-resistant. To accomplish this, we are developing a molecular predictor that combines ultrasound imaging with gene expression profiling to identify patients who have chemo-sensitive TNBC, thereby eliminating unnecessary exposure and toxicities from additional therapies to these patients. For those patients identified to have chemo-insensitive TNBC, our molecular profiling strategy selects the most appropriate therapies based on the specific tumor characteristics from each patient. Our projects offer unique contributions to advance clinical care in TNBC and will enable us to optimize neoadjuvant therapy in TNBC.

In order to use precision medicine to improve cure rates in TNBC, the first step is to develop a clinical trial platform that advances therapy in the localized setting, where there is the greatest chance for cure. One of our top initiatives is designed to improve outcomes in patients undergoing neoadjuvant therapy using a personalized therapeutic strategy developed by achieving the following goals:

- + Identifying clinical and molecular predictors of disease response
- + Escalating therapy in TNBC patients who are not responding to chemotherapy by targeting specific mechanisms of disease resistance
- + De-escalating therapy in select TNBC patients likely to achieve pathologic complete response with either less chemotherapy or a targeted drug

In TNBC, the tumor immune microenvironment plays an important role in prognosis and response to neoadjuvant therapy. Immune cells in the tumor, known as stromal tumor-infiltrating lymphocytes (sTILs), are a reproducible biomarker and multiple studies have confirmed their predictive value in TNBC. Immunotherapy also is emerging as a therapeutic strategy in TNBC, though it is important to note that the

introduction of checkpoint inhibitors targeting PD-1 or PD-L1 have not resulted in the same positive outcomes that have so profoundly impacted other cancers, such as lung cancer and melanoma. To support our overarching goal of using precision medicine to improve cure rates in TNBC, we designed an initiative to comprehensively evaluate and utilize the host immune response by achieving the following goals:

- + Identifying predictors of response to neoadjuvant therapy in sTIL-high TNBC
- + Enhancing immune-profiling of the immune landscape in TNBC
- + Assessing longitudinal immune response
- + Determining the role of the gut microbiome in TNBC response to neoadjuvant therapy
- + Evaluating the role of ancestry and how it affects the immune response to TNBC

We are on track to develop a precision medicine platform by FY22. And we could not have advanced our programs to this point without the support of donors to this Moon Shot. We cannot overstate the importance of philanthropy to our program and how grateful our clinicians, scientists and of course, our patients are for these generous gifts.





Chronic lymphocytic leukemia (CLL) is the most prevalent adult leukemia in the United States. A disease of older adults, management in the age of chemoimmunotherapy was limited by advanced age, comorbidities, poor fitness and therapeutic toxicity. As the treatment paradigm continues to shift away from chemoimmunotherapy towards targeted therapies and monoclonal antibodies, successful long-term management has significantly improved.

Program Leaders: Nitin Jain, M.B.B.S Varsha Gandhi, Ph.D. William Wierda, M.D., Ph.D.

Thanks to novel agents and combinations, patients of all ages and fitness — and even those with relapsed/refractory disease — may have extended periods of disease control and may even achieve undetectable minimal residual disease status, which allows extended treatment-free interval. The curative potential of these novel agents and combinations will be clarified years from now when follow up has matured and outcomes are known.

However, despite remarkable progress in the field, some patients with CLL experience relapse of their disease or disease resistant to targeted therapies, including ibrutinib and venetoclax. Further, some patients develop Richter's transformation, an aggressive B-cell lymphoma with limited treatment options and unfavorable outcomes. Moreover, we lack understanding of the immune dysfunction inherent in patients with CLL. Interrogation of immune function would support our efforts to prevent other infections and second primary malignancies — both frequent causes of death in patients with CLL, including those who have achieved remission with undetectable minimal residual disease.

The CLL Moon Shot® has evolved its focus over the past 7 years. Our aim is to end reliance on chemotherapy as standard of care for CLL and to double the cure rate from 35% to 70%. The introduction of targeted therapy — particularly Bruton's tyrosine kinase and BCL2 inhibitors — resulted in dramatic, durable responses, allowing us to move away from FCR

(fludarabine + cyclophosphamide + rituximab) chemoimmunotherapy for the majority of patients with CLL. Further, we are seeing remarkable success with our novel CD19 chimeric antigen receptor (CAR) natural killer (NK)-cell therapy platform with most treated patients experiencing durable partial or complete remission. These findings contribute to our excitement that a cure may be on the horizon. We are developing our program focused on inducing deep, durable remissions in patients with high-risk features and/or relapsed/refractory disease, including Richter's transformation. Additionally, we are identifying and reducing the risk of Richter's transformation and second primary malignancies, while preventing infections and complications through the reconstitution of the immune system of patients with CLL.

Looking ahead, we believe we can end reliance on chemotherapy as standard of care for CLL and to double the cure rate through the following strategies:

- + Targeting CLL pathophysiology
- + Targeting immunosuppression
- + Harnessing innate immunity to target CLL using CAR-NK cells
- + Focusing on Richter's transformation therapeutics and second primary malignancies

We are, indeed, incredibly grateful for the generosity of donors to the CLL Moon Shot. Philanthropy plays a large part in our ability to translate innovative research into effective therapies for our patients.

COLORECTAL CANCER MOON SHOT

Program Leaders:

Scott Kopetz, M.D., Ph.D. Eduardo Vilar-Sanchez, M.D., Ph.D. Nancy You, M.D.

In 2020, colorectal cancer (CRC) was diagnosed in nearly 150,000 individuals in the United States, ending the lives of more than 50,000 patients, making it the second most frequently diagnosed and third most deadly cancer. Although the overall incidence of CRC in the United States has declined, it is rising at an alarming rate in young people and certain ethnic populations.

To address critical needs in this field, we initiated the Colorectal Cancer Moon Shot®, which resulted in numerous preclinical and clinical advances. We helped to define the colorectal cancer consensus molecular subtypes (CMS), the four primary disease subtypes now commonly embraced by the medical community. We also developed a CLIA-based CMS assay — a test used to determine the molecular subtype of CRC to identify the best course of treatment. The test developed by the CRC Moon Shot team had less than 1% sample failure due to analytical factors, indicating that it can reliably be applied even to small community center-based laboratories.

About 25 to 30% of patients with stage III colon cancer will relapse within five years due to minimal residual disease (MRD), occurring when a small number of cancer cells persist during treatment and after remission. **To enable** the molecular detection of MRD, we also developed a blood based non-invasive **CRC-specific test** — **CRC23.** A circulating tumor DNA (ctDNA) test, CRC23 is being used to detect specific mutations that are now being validated in 1,000 patients (MiRDA trial) across 10 U.S. sites. We have demonstrated that ctDNA can serve as a marker of minimal residual disease following tumor resection. We also developed a personalized neo-antigen vaccine pipeline, and we aim to prevent disease progression in these patients by using:

- + Personalized vaccines in combination with an anti-PD-1 immune checkpoint inhibitors and CD40 agonist
- + Cord blood-derived natural killer (NK) cells and chimeric antigen receptor (CAR) NK cells.
- + Animal models of MRD, established in collaboration with the TRACTION platform, to better understand MRD and to develop new, targeted treatment approaches.

Lynch syndrome is the most common hereditary cause of colorectal cancer, seen mostly in those younger than 50. We seek to prevent the development of CRC in those with Lynch syndrome. To this end, our preclinical examination of Lynch syndrome genetically engineered mice and patient-derived organoids taken from Lynch syndrome patients showed efficient prevention of colorectal cancer with naproxen.

We are completing preclinical studies to open a Phase I clinical trial testing a prophylactic common neo-antigen vaccine (with and without naproxen) for Lynch syndrome.

While hereditary CRC accounts for some young onset colorectal cancer, three out of every four patients have no family history of CRC. We are making efforts to molecularly and clinically identify and characterize the differences between young-onset and lateonset colorectal cancer. These studies also examine the associated microbiome and immune infiltrates.

While anti-PD-1/PD-L1 checkpoint blockade produces durable, often curative clinical benefit in responders, approximately half of patients eligible for these immunotherapies do not respond. Recent in vivo data demonstrated that fecal microbiome transplant from PD-1responsive and non-responsive cancer patients into mice was directly correlated with anti-PD-1 responses. We are investigating differences in microbiome compositions between CRC patients who did and did not respond. We plan to open a Phase II single-arm, openlabel study to evaluate treatment with immune checkpoint inhibitors plus fecal microbiome transplants in patients who do not respond to initial immunotherapy.

These comprehensive efforts are designed to maximize immediate impact for our patients and to strengthen the colorectal cancer scientific program, and they are made possible, in part, by our generous donors. We are incredibly grateful for your support.

GLIOBLASTOMA MOON SHOT Program Leaders: Amy Heimberger, M.D. Frederick Lang, Jr., M.D. John de Groot M.D.

The overarching goals of the Glioblastoma Moon Shot® are to answer the unmet clinical needs of patients with glioblastoma (GBM) — to decipher the biological underpinnings of this disease and to use those findings to develop and rapidly translate new therapeutic approaches that will dramatically improve the survival and quality-of-life of patients.

Since its inception in 2015, the Moon Shot has made significant progress in achieving these goals. We have developed a data-gathering infrastructure through our Prospective Assessment of Correlative and Tissue Biomarkers (PROACTIVE) Database, which has accumulated longitudinal clinical data on more than 2,800 brain tumor patients, including more than 1,350 GBM cases. We also have taken a leadership role in the international Glioma Longitudinal Analysis of Serial Samples (GLASS) Consortium, which has yielded exciting preliminary data around treatment-induced genomic changes in GBM over time and has demonstrated the power of our approach and the need for more extensive and diverse testing. These results were published in the prestigious journal, *Nature*, in 2019. We also have begun deciphering the immunological underpinnings of GBM, including the predominance of macrophages/microglia in GBM, laying the groundwork for exploration into the full repertoire and functional states of immune populations.

Another major success of the Glioblastoma Moon Shot is the preclinical development and clinical translation of multiple home-grown agents that we have tested in unique "window-of-opportunity" trials, including Delta-24-RGD (an oncolytic adenovirus), WP1066 (a STAT-3 inhibitor) and CMV-targeted T cells. We developed all of these from the bench to the bedside through

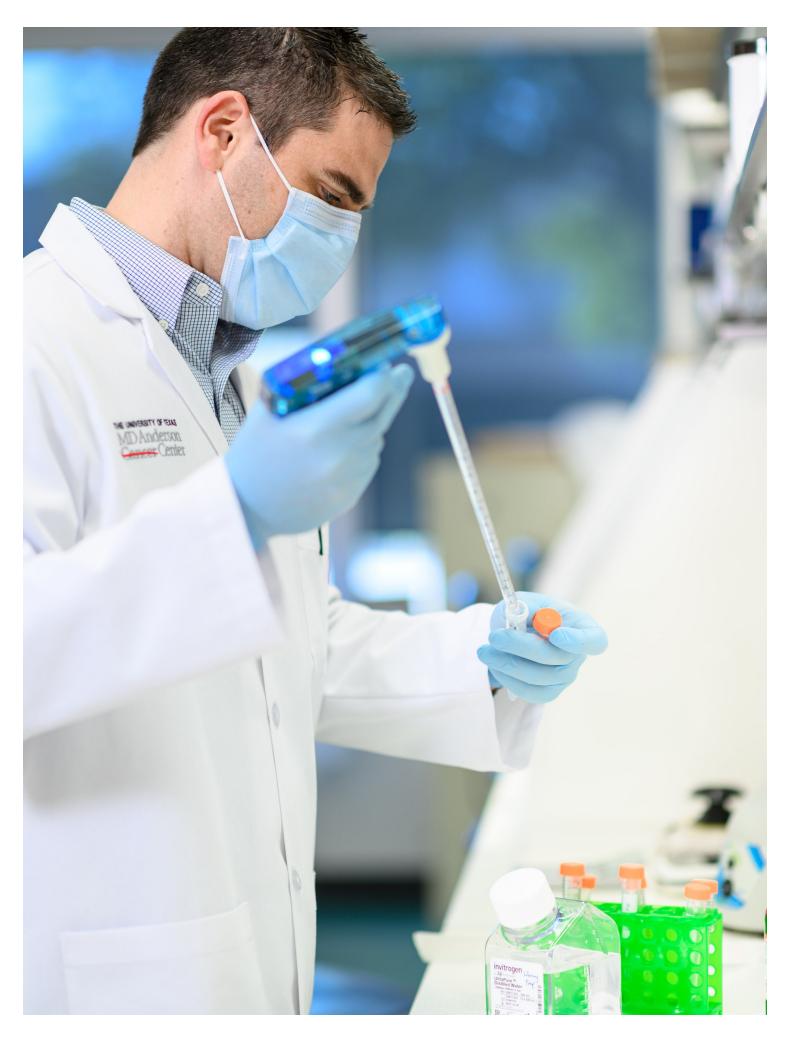
the unique infrastructure of the Moon Shots
Program, with the hope that continued progress
may lead to one or several of these agents
becoming FDA-approved in the near future.
We also have developed a robust pipeline
of new strategies and therapies, including
natural killer (NK) cells, tumor-infiltrating
lymphocytes and mesenchymal stem cells
loaded with oncolytic viruses, of which we are
the first to deliver intra-arterially to patients
with GBMs.

Our achievements and future success are built upon multidisciplinary, integrated and highly translational teams that draw upon the wealth of expertise both inside and outside of MD Anderson. We have leveraged the multitude of Moon Shot platforms to understand the complex biology that drives GBM and rapidly translate the most novel therapeutics to patients. We think that this approach will lead to a clear understanding of the biological drivers of GBM oncogenesis and to new FDA-approved therapeutics that will dramatically extend the survival of patients with GBM, including mitigating therapeutic toxicities.

To decipher the biological underpinnings and biomarkers of GBM, we are building upon

our past biospecimen successes through the creation of a unique central nervous system (CNS) Tumor AnaLYsis STream (CATALYST), a cross-functional, holistic biospecimen analysis **pipeline.** This pipeline provides a streamlined workflow and comprehensive analysis of tumor specimens as well as cerebrospinal fluid, blood and stool (microbiome) from all patients undergoing surgical resection. CATALYST will lead to a comprehensive catalogue of primary and recurrent GBMs, as well as other gliomas, metastases and rare brain tumors, for comparison. This compendium of tumors will enable longitudinal, comprehensive analyses of tumor specimens and matched blood, cerebrospinal fluid, and stool. These data will help us uncover novel biological drivers of GBM, enhancing GLASS consortium-related efforts and creating new collaborations, while also creating a pool of controls for matched window-ofopportunity clinical trials of new therapeutics.

We are excited about the prospects of these innovative strategies to improve the clinical care of patients with glioblastoma, and we are incredibly appreciative of the philanthropic support that helps make this work possible.





HPV-RELATED CANCERS M

MOON SHOT

Program Leaders: Maura Gillison, M.D., Ph.D. Ann Klopp, M.D., Ph.D. Jeff Myers, M.D., Ph.D. Michael Curran, Ph.D.

In 2012, 4.5% of all cancers worldwide were attributable to high-risk human papillomavirus (HPV) infection, including 640,000 cases of cervical, vaginal, vulvar, anal, penile and oropharyngeal (head and neck) cancers. Despite cervical cancer screening programs in high-income countries and highly effective HPV vaccines, the burden of HPV-caused cancers continues to rise. Due to population growth, the projected global estimate for cervical cancer cases in 2030 is 770,000. Thirty thousand new cases of HPV-positive oropharyngeal cancer are anticipated each year by 2030.

HPV remains a major cause of cancer morbidity and mortality worldwide. Public health initiatives at MD Anderson are appropriately focused on increasing access to HPV vaccination. These efforts will be essential to reversing ongoing incidence trends and to decreasing morbidity and mortality attributable to HPV-related cancers. Our team strives to leverage our unique resources to reduce morbidity and mortality for all patients diagnosed with HPV-related cancers.

The HPV-Related Cancers Moon Shot® is a comprehensive, multi-disciplinary program designed to address several unmet clinical needs for patients diagnosed with all HPV-positive cancers. The program integrates clinicians and scientists dedicated to HPV-related cancers across MD Anderson, and, importantly, aims to bring new, talented investigators together with the

necessary resources to improve outcomes for patients with these diseases. We have partnered with platforms and industry collaborators to translate our findings quickly into clinical trials. This Moon Shot is moving the needle for patients with HPV-related cancers through the following approaches:

- + Targeting HPV oncogenic drivers necessary for the malignant phenotype (HPV E5, E6 and E7)
- + Identifying tumor-intrinsic and -extrinsic barriers to innate and adaptive cell-mediated immune responses to guide rational selection of combination therapies to improve cancer control across HPV-positive cancers
- + Identifying secondary host genetic alterations shared across and unique to each cancer site at diagnosis and first failure for development of biomarkers and targeted therapeutics.

Our CBP/p300 priority project investigates approaches to target the unique susceptibilities created by the HPV E6/E7 protein functions. No therapeutics have ever been successfully developed in this space. To this end, we are performing exciting research into antigenicity (the property of being able to induce an immune response) and the tumor microenvironment to identify and overcome

barriers to productive immune infiltration across HPV cancers. These efforts are geared towards developing strategies to understand the function of the HPV reactive T-cell population, especially markers of activation and exhaustion, which may ultimately be used to develop combination immunotherapy approaches or to adapt standard therapies, including radiation.

Our efforts in the microbiome space are addressing the relevance of the diversity of the microbiome across the HPV-positive disease sites to develop specific microbiome interventions.

Finally, we have ongoing work in the arena of biomarker discovery, in which we are building an infrastructure to support uniform, prospective collection of annotated clinical data and biospecimens to provide a rich resource for future hypothesis-driven research.

The HPV-Related Cancers Moon Shot sees these efforts, aided by generous gifts from donors, as the best opportunities to improve therapeutic options for patients suffering from HPV-related cancers.

HIGH-RISK MULTIPLE MYELOMA MOON SHOT MOON SHOT Hi is also essential to under of multiple myeloma to go vulnerabilities. The disease having well-defined precumen occional gammopathy significance (MGUS) and so while we have defined far likelihood of progression.

Program Leaders:Robert Orlowski, M.D., Ph.D.
Eric Davis, M.D.
Elisabet Manasanch, M.D.

Multiple myeloma (MM) is the second most commonly diagnosed hematologic malignancy. Estimates indicated that MM was diagnosed in more than 32,000 new patients in the United States in 2020. Novel drugs have more than doubled the median overall survival in this disease, but until 2012, most of this improvement had been in patients with standard risk disease defined by clinical and molecular criteria. Unfortunately, without a curative therapy, virtually all patients will develop and succumb to relapsed/refractory MM. Due to the disease's high rates of morbidity, mortality and lack of effective therapies, it is essential that we continue to advance new and effective treatment options for our patients.

It is also essential to understand the progression of multiple myeloma to grasp its therapeutic vulnerabilities. The disease is distinctive for having well-defined precursor states, including monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM. While we have defined factors predicting the likelihood of progression to symptomatic disease, even high-risk patients in precursor states are currently not routinely treated. This indicates that high-risk MGUS, as well as smoldering and symptomatic MM, represent important and urgent areas of unmet medical need for the development of novel, more effective therapies. To this end, the following are the goals of the High-Risk Multiple Myeloma Moon Shot®:

- + To double the time from precursor states to symptomatic MM within the next three to five years, and
- + To double the progression-free survival and/or decrease mortality of high-risk MM patients by 50% within the next two to three years.

We are doing this by applying novel immunotherapeutic approaches to prevent disease progression and to deepen minimal residual disease (MRD), an important predictor of progression-free survival in MM.

Our team is focusing on the mechanisms underlying progression from precursor states to active MM to develop a reliable model to predict disease progression. This will aid in the implementation of novel immunotherapy

strategies to prevent progression from MGUS and smoldering MM to symptomatic disease.

We also are working to evaluate the efficacy of immunotherapies such as monoclonal antibodies and personalized vaccines in high-risk smoldering MM to prevent disease progression. Our program uses adoptive cord blood-derived natural killer (CB-NK) cell therapy approaches to eradicate MM cells, and ultimately, neoplastic stem cells. We have validated the use of CB-NK cells with anti-MM activity (pioneered at MD Anderson) in high-risk patients undergoing autologous (from the patient) stem cell transplantation and are now developing approaches to target immune cells to specific MM antigens to enhance their anti-myeloma activity.

Finally, a new addition to the Moon Shot involves exploiting the prominent role of heat shock protein (HSP)-70 in innate and adaptive immunity by targeting the protein with a home-grown antibody to enhance tumor antigen presentation to dendritic immune cells and provide proof of pre-clinical concept in myeloma prior to clinical translation.

The clinical advancements we have made, and seek to make looking ahead, are driven in part by the generosity of donors to the Moon Shot, for whom we are extremely grateful. Philanthropy helps drive our advancements, catalyzing our work so that we can provide better outcomes for our patients.



Program Leaders: John Heymach, M.D., Ph.D. Ara Vaporciyan, M.D. Don Gibbons, M.D., Ph.D.

Despite the significant improvements in targeted and immune therapies and recent FDA approvals of new therapeutic agents, lung cancer remains the leading cause of cancer mortality, accounting for more annual deaths than colon, pancreatic and breast cancers combined. The Lung Cancer Moon Shot® seeks to improve these grim statistics.

The Moon Shot is a comprehensive, multi-disciplinary initiative aimed at dramatically impacting the burden caused by lung cancer through integrated approaches that change the way we prevent, detect and treat lung cancer. We are doing this through the following efforts:

- + Identifying personalized, biomarker-driven strategies to help individuals quit smoking, reducing their likelihood of developing lung cancer
- + Performing deep molecular profiling on all MD Anderson lung cancer patients to identify new targetable mutations and subgroups of patients likely to benefit from novel therapeutic regimens

There are four main focuses of the Lung Cancer Moon Shot. The goal of our Lung Cancer Therapeutics Pipeline project is to work with colleagues across the institution to identify, develop and test new targets and therapeutics for the treatment of lung cancer. We will emphasize our efforts in patients who come to us with drug refractory or resistant disease in both the small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) populations.

Testing new therapeutics for genomically-defined sub-groups of SCLC and NSCLC builds from our discoveries over the past five years, where the Moon Shot was essential in creating an infrastructure to support these efforts. We are also developing innovative adoptive T-cell therapies for NSCLC patients for whom immune checkpoint blockade therapies have not been effective. And finally, we are identifying surface targets of molecularly-defined subsets of SCLC to develop novel antibody-based therapies.

A critical initiative of the Moon Shot involves identifying molecular and imaging markers that predict outcomes for novel immunotherapeutic approaches in lung cancer patients. With a growing portfolio of clinical trials assessing the benefits of immunotherapy, we have a massive collection of data to answer questions about how and why patients respond differently to treatment. In order to better understand the mechanisms in patients along the cancer continuum (early-stage to late-stage disease), we are investigating biomarkers of immunotherapy response and resistance. examining radiomics (extracting and quantifying patterns from radiographic images into mineable data), and using this data as a predictor of treatment response and exploring treatment combinations to improve immune-based treatment regimens.

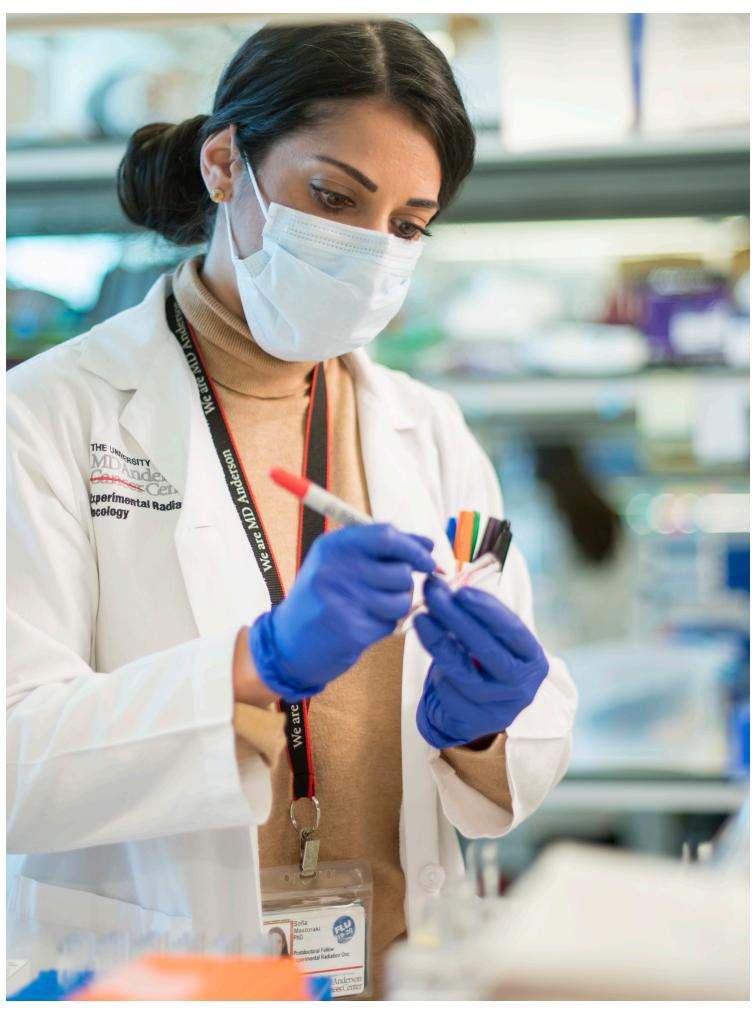
The parallel preclinical and clinical structure and organization of this project serves as a driver for our bidirectional investigation and rapid development of strategies into the metastatic and early-stage treatment settings. This work advances our other initiatives by feeding our clinical data sets and facilitating therapeutic agent development.

The GEMINI project uses our existing database of lung cancer patients to build and benchmark an institutional data integration initiative. This project is establishing a comprehensive and user-friendly data hub that makes molecular biomarker data available to physicians in real-time so treatment decisions and clinical trial matching can be applied to each individual patient as efficiently as possible. Although initially built and tested for the management of lung cancer patients, the efforts will provide an infrastructure that can be used by clinicians/researchers for any tumor types across the institution.

The cancer prevention PISCES project is developing personalized approaches to enhance smoking cessation. Improving cessation outcomes requires continued research aimed at refining our treatment algorithms toward better personalized treatment approaches and the broad dissemination of our most effective treatments. We do this by training health care providers in the delivery of advanced counseling techniques and pharmacotherapies. After having conducted clinical trials to develop a biomarker panel capable of predicting optimal cessation strategies, our primary focus is to definitively test these biomarkers in a randomized clinical trial that has the potential to change the standard of care for tobacco cessation across the United States.

These projects are at the forefront of lung cancer prevention, detection and treatment. We are proud to be innovators in this space and graciously thank the generous donors who have contributed to our program.





MDS and AML MOON SHOT

Program Leaders:Guillermo Garcia-Manero, M.D.
Hagop Kantarjian, M.D.

While myelodyspastic syndromes (MDS) are relatively rare, they represent the second most frequent referral to the department of Leukemia at MD Anderson, only behind acute myeloid leukemia (AML). Every year, up to 45,000 people are diagnosed with MDS and an additional 13,000 are diagnosed with AML. MDS and AML also can develop because of treatment for other types of cancer, and approximately 10% of patients with AML have treatment-related disease. About one-half of patients with MDS and AML die of complications of their disease.

The current standard of care for MDS is treatment with hypomethylating agents (HMAs), including azacitidine and decitabine. However, most patients either fail to respond to treatment or develop resistance to the drugs. We critically need new therapies to treat MDS in the frontline or at failure/relapse. Stem cell therapy is the only definitive cure for MDS or AML, but not all patients are candidates for the treatment and many experience serious side effects and relapse. We desperately need to improve upon stem cell therapy technology to expand the population of patients who are eligible for, and can benefit from, the treatment and to reduce or eliminate adverse events, such as graft-versus-host disease and relapse.

The MDS and AML Moon Shot® is creating novel methodologies and technologies that improve patient outcomes. Our current and near-term priorities center on the following areas:

Targeting anti-apoptotic pathways in MDS at the time of progression

Our ongoing research into the bone marrow stem cells that lead to the development and progression of MDS uncovered the existence of two distinct populations of MDS patients. This work will be published in *Nature*. We hypothesize that response to chemotherapeutic agents will be different for patients from each of these two populations. This past year, we learned that inhibition of the BCL2-mediated survival pathway decreased tumor burden in patientderived xenograft models. These results support the idea that targeting BCL2 with venetoclax elicits a durable response in only one of the two MDS types, potentially uncovering a means of improving patient stratification in clinical trials of this drug. Additionally, we hypothesize that MCL1 inhibitors may have a clinical benefit to patients in this MDS population and are testing this in an on-going clinical trial.

Developing next-generation cellular therapies in MDS and AML

Cellular therapies, including chimerica antigen receptor (CAR) T-cell therapy, use cells from a patient's own blood to fight their cancers. Our team is leading the way in developing the next generation of cellular therapies utilizing natural killer (NK) cells to circumvent transplant complications such as graft-versus-host disease. The team is developing an off-the-shelf CAR NK cellular therapy for patients with AML utilizing NK cells from healthy donors engineered to specifically target MDS and AML cells. NK cells are intrinsically sensitive to glucocorticosteroids, drugs commonly used to reduce inflammation; therefore the CAR NK cells will be engineered to

be resistant to glucocorticosteroids and improve treatment efficacy. This approach will increase accessibility to stem cell transplantation, reduce the time between diagnosis and treatment and reduce the cost of cellular therapies.

Targeting minimal residual disease and stemlike cells in high-risk AML

Minimal residual disease refers to leukemic cells that remain behind following ablative therapies and stem cell transplantation. These leukemic cells then have the potential to rebound and lead to treatment failure and disease relapse. Therefore, identifying minimal residual disease is a priority for improving treatment efficacy and patient outcomes. Using cutting-edge genetic analysis technology and biostatistical and computational analysis, our team is searching for novel means of identifying and pharmacologically targeting minimal residual disease in patients with high-risk AML.

Delineating the history of genetic and phenotypic evolution of clonal hematopoiesis and leukemia progression

MDS is a tremendously heterogeneous disease. Through the course of disease development and progression, MDS patients acquire a number of different genetic mutations in their bone marrow stem cells. In this project, we are studying the sequence in which MDS patients acquire these mutations and which mutations become the most clinically relevant over time. This will yield important insights into the biological mechanisms of MDS development and progression and may give our researchers additional targets for therapeutic development.

These exciting, innovative projects are an amalgamation of various funding sources, one of the most prominent of which is philanthropy. We are grateful that donors are helping us improve the standard of care for MDS and AML.

MELANOMA MOON SHOT

Program Leaders: Jeffrey Gershenwald, M.D. Michael Davies, M.D., Ph.D.

Jennifer Wargo, M.D. Hussein Tawbi, M.D., Ph.D.

Melanoma, the deadliest form of skin cancer, is an aggressive yet often preventable disease. It is largely caused by exposure to ultraviolet radiation, the sun and indoor tanning devices. The inception of the Melanoma Moon Shot® occurred during unprecedented developments of new therapies for melanoma, and we are committed to taking full advantage of this progress for our patients.

Our team recognized the clear opportunities to reduce the impact and burden of melanoma through improved primary and secondary prevention initiatives. In 2013, Texas became the fourth state to prohibit indoor tanning for youth under the age of 18. Since then, 21 states and the District of Columbia now have such legislation — many as a direct result of our leadership and partnership with the Cancer Prevention and Control platform and the American Cancer Society - Cancer Action Network — to educate key stakeholders on the dangers of indoor tanning. Tanning bed use before age 18 increases risk of melanoma by 85%, and starting between ages 18 and 24 increases risk by 91%. Melanoma is now one of the most frequently occurring cancers in young adults ages 20 to 30 and is the main case of cancer death in women ages 25 to 30.

When diagnosed early, melanoma is highly treatable. However, despite evidence that early-stage melanoma diagnosis is associated with favorable outcomes, there are no broadly available, effective screening strategies for this disease. Our team has developed a dermoscopy curriculum to educate dermatology residents on its use for early diagnosis and detection of cutaneous melanoma. These strategies demonstrate our team's commitment to markedly reducing the impact and burden of cutaneous melanoma through preventative measures.

Of all skin cancers, melanoma is the most likely to metastasize. The management and outcomes for patients with stage IV metastatic melanoma have been revolutionized with the approval of 10 targeted therapy and immune checkpoint blockade (ICB) immunotherapy regimens for melanoma since 2011. Single agent anti-PD-1 ICB achieves responses in about 40% of stage IV patients, but most of them still fail to respond, while others progress after initial response. Combined treatment with anti-PD-1 and anti-CTLA4 therapies achieves higher response rates (about 55%), particularly in patients with brain metastases, but frequently incurs high-grade toxicities with only modestly improved overall survival compared to anti-PD-1 alone.

Although our team has made several contributions to the field in understanding predictors of response to ICB therapy, there remain many opportunities to translate these findings into more effective treatments for patients. As there are no effective immunotherapy regimens for patients that have progressed on anti-PD-1 and anti-CTLA4, nor for patients that have progressed on targeted treatment regimens, we need to understand and overcome resistance to combined anti-PD-1 plus targeted therapy, a combination treatment that is likely to be approved soon.

Melanoma spreading to the central nervous system remains a prevalent problem in stage IV patients and is frequently the initial — and sometimes only — site of systemic treatment failure. While both ICB and targeted treatments have improved outcomes in these patients, we need more effective strategies to overcome central nervous system metastases once they have failed approved therapies. Our team is currently focusing on predicting and treating central nervous system metastases to further reduce deaths from melanoma.

Leptomeningeal disease, when melanoma cells invade the cerebrospinal fluid, is a major challenge, as it portends a survival of less than eight weeks on average and has very few treatment options or laboratory models amenable to preclinical research. We have led the development of intrathecal immunotherapy, which encompasses injection into cerebrospinal fluid, as a novel strategy for these patients, with proof-of-principle long-term survival in subsets of patients to build upon.

Treatments approved for stage IV disease are being applied in earlier settings, with ICB and targeted therapies now FDA approved as adjuvant therapy for stage III disease. However, there are no approved systemic therapies, beyond high-dose Interferon-α2b, for patients with stage II disease. Patients with resected high-risk primary cutaneous (stage II) and stage III melanoma vastly outnumber (almost by a three times) patients with stage IV metastatic melanoma. While this population represents the largest group of melanoma patients, they have varied outcomes that are difficult to predict. We must identify risk-informed strategies for adjuvant treatment in clinically localized and particularly "high-risk" patients with stage II disease to better individualize prognosis and disease management. This is an important area for our Moon Shot.

The Melanoma Moon Shot is focusing its efforts on areas with potential for the most wide-spread impact on patients worldwide. We are proud and grateful to receive support from generous donors every year, as they keep our programs functioning and inspire us to work every day to improve the lives of our patients.

OVARIAN CANCER MOON SHOT

Program Leaders: Anil Sood, M.D. Amir Jazaeri, M.D. Shannon Westin, M.D.

For women with advanced-stage, high-grade serous ovarian cancer (HGSOC), the most common type of ovarian cancer, the five-year survival rate is just 39%. We desperately need to improve upon current detection, prevention and treatment paradigms. The Ovarian Cancer Moon Shot® is focused on improving outcomes for patients with HGSOC and other subtypes of ovarian cancer (e.g., low-grade serous ovarian cancer [LGSOC] and clear cell) where emerging scientific knowledge and our unique resources provide profound opportunities for clinical impact.

Our program has made significant accomplishments since its inception. Much of this work has been carried out through extensive engagement of Moon Shot platforms for deep interrogation of each sample from our therapeutic trials, with an emphasis on longitudinal changes and integration of DNA, RNA and proteomic data. These studies have provided insights into how adaptive and other resistance mechanisms limit therapy efficacy and provide rationale for development of new combination treatments to overcome these resistance mechanisms.

Our current research projects focus on areas of significant potential clinical impact:

Overcoming adaptive resistance to PARP inhibitors and anti-VEGF drugs

Approximately 70-80% of patients with ovarian cancer will enter remission after surgery and platinum-based chemotherapy, but the majority of those patients will unfortunately develop recurrence. PARP inhibitors and anti-VEGF therapies have helped to improve outcomes, but many patients either will not respond or develop resistance. In this project, we are looking closely at the biology of the disease to understand how therapy resistance develops so that we can develop rational treatment combinations that overcome resistance. We are leveraging our innovative clinical trials infrastructure to enable these studies and evaluate novel therapeutics that may benefit our patients. This project is important because most women with ovarian cancer will receive treatment with one or both of these agents during their disease continuum.

Developing more effective immunotherapy approaches

Unlike some malignancies, immunotherapy has had modest success in ovarian cancer. This is likely due to the immune-suppressive environment created by the tumor, which prevents the immune system from eliminating the disease. Our Moon Shot aims to develop rational combination immunotherapy approaches based on translational science

incorporated into ongoing trials. We are performing comprehensive studies on samples from patients participating on our clinical trials to learn how cancers adapt and progress in response to immunotherapy treatment. Our findings will help us identify the patients most likely to respond and the molecular pathways responsible for treatment resistance, which we can target with combination therapies.

Targeting LGSOC with innovative therapies aimed at hormonal and important signaling pathways

Our Moon Shot team sees the largest number of patients with LGSOC in the country, positioning us to leverage the unique molecular landscape of these tumors to develop novel therapies. LGSOC is a subtype that accounts for roughly 10% of all ovarian cancers, and it is more likely to be resistant to available chemotherapies. Fortunately, there are frequent genetic mutations that may be effectively targeted with novel treatments. We are performing in-depth studies of LGSOC to identify the best treatment targets and evaluate novel therapies to better treat these patients.

The Ovarian Cancer Moon Shot is tightly integrated with the SPORE, pharmaceutical alliances, the National Cancer Institute and various foundations, and, of course, philanthropy. We are incredibly grateful for the support we receive from generous donors year after year.



PANCREATIC CANCER MOON SHOT

Program Leaders: Anirban Maitra, M.B.B.S. Robert A. Wolff, M.D. Matthew Katz, M.D.

The overarching goal of the Pancreatic Cancer Moon Shot® is to enhance the survival rates for pancreatic ductal adenocarcinoma (PDAC) patients through innovative studies with a clear line of impact to the clinic.

The five-year survival rate for early-stage cancers is close to 90%; in contrast, the five-year survival rate of PDAC across all stages is only 10%. It is estimated that by diagnosing half of patients with early-stage disease, compared to the current 15%, we could more than double the five-year survival rate of pancreatic cancer patients. **To that end, we are generating biomarkers that facilitate early diagnosis of PDAC in high-risk cohorts.** We continue to enroll and monitor individuals at risk for developing PDAC through the Moon Shot-supported Pancreatic Cancer High-Risk Clinic, and accrue longitudinal specimens (blood, saliva, and microbiome) on these high-risk patient cohorts. We also are validating a biomarker panel indicative of risk of either harboring or developing early-stage PDAC.

More than 90% of PDAC cases have activating KRAS mutations, but we have been largely unsuccessful at inhibiting mutant KRAS therapeutically.

We seek to change this trend by using systemic delivery of iExosomes, a Moon Shot-supported technology developed through our Adoptive Cell Therapy platform designed to specifically target oncogenic KRASG12D using a biological process in which RNA molecules inhibit gene expression or translation. In all preclinical models, iExosomes as a single targeted agent significantly enhanced overall survival, showing consistent, robust anti-tumor response and specific target engagement. The FDA has approved a Phase I clinical trial employing exosomes to deliver siRNA specific to oncogenic KRASG12D, and we have translated researchgrade iExosomes to a clinical grade product. With this, we are commencing the first clinical trial in metastatic PDAC patients using iExosomes.

PDAC-targeted adoptive cell therapies represent our home-grown efforts at circumventing profound resistance to immune checkpoint inhibitor immunotherapy. We are deploying two adoptive cell therapy approaches to improve the effectiveness of immunotherapy in pancreatic cancer treatment. First, we have established methods to reliably expand autologous (taken from the same individual)

tumor infiltrating lymphocytes (TILs) from metastatic PDAC tissue, leading to a strategic alliance with Iovance Biotherapeutics and the first-in-nation TIL trial specifically for PDAC. We will build upon this success to develop the next generation of TILs that can bypass TGF-betainduced immune suppression in the PDAC tumor microenvironment. Second, the availability of natural killer (NK) cells from multiple sources and their proven safety profile in the allogeneic (taken from a donor) setting positions them as attractive contenders for "off-the-shelf" adoptive cell therapy. New to our Moon Shot this year, we are planning preclinical studies of cord bloodderived NK cells to bypass immune checkpoint resistance.

The Pancreatic Cancer Moon Shot is in a fantastic position to exploit the vulnerabilities of one of the deadliest cancers. We are excited about the upcoming innovative trials that we anticipate will impact our ability to offer effective treatment options to our pancreatic cancer patients. These advancements are made possible, in part, by our philanthropic partners. Thank you for your support.

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PROSTATE CANCER MOON SHOT

Program Leaders: Christopher Logothetis, M.D. Filippo Giancotti, M.D., Ph.D. Padmanee Sharma, M.D., Ph.D.

The Prostate Cancer Moon Shot® is building on our progress in developing discovery platforms capable of monitoring prostate cancer progression at a biological level. Our goal is to link our understanding of biology within defined subsets of prostate cancer to identify novel single-agent or combination therapies.

Treatment options for prostate cancer have not advanced at a similar pace as those for other common solid tumors. Although patients with "non-lethal" cancer may eventually succumb from age-related co-morbidities, those progressing to metastatic castration-resistant prostate cancer do not live longer if treated with complete androgen receptor blockade. **These considerations have led the Prostate Cancer Moon Shot to focus on the most troublesome subsets of prostate cancer.** We are focused on two broad, clinically defined phenotypes: those that exhibit androgen receptor (AR)-independence and those with AR therapy-resistance progression in bone. These broad groupings are composed of biologically heterogeneous subsets. The overarching goal of the Prostate Cancer Moon Shot is to develop therapies specific to each subset and integrate the observations to develop an effective marker-informed treatment strategy.

For patients whose tumors do not respond well to hormonal therapies (i.e. AR-independent prostate cancers), we are exploring two avenues of research. First, we have defined AR-independent tumors based on their clinical behavior and appearance on biopsies and termed them aggressive variant prostate cancers (AVPCs). We defined a molecular

signature for these tumors that can help identify more effective treatments for it. Second, we evaluated the molecular characteristics of hundreds of advanced prostate tumors and identified three subgroups that go from those that are responsive to hormones, through a transition subgroup, to an androgen receptor-independent subgroup. We are combining the findings from both approaches to identify new biomarkers and therapy targets.

It is critically important that we monitor biological responses to therapy in order to anticipate the emergence of treatment resistance. This is made all the more difficult in prostate cancer because of the complexity in sampling bone metastases safely. We are exploring the evolution of castration-resistant circulating biomarkers (e.g., plasma-free DNA and circulating tumor cells) to anticipate and monitor the progression of prostate cancer under the **influence of therapy.** We initially linked our findings in circulation to contemporaneously collected tumor tissue and observed parallels in known driver pathways. The observations lend confidence to our discovery and monitoring initiative, which will be used to biologically

monitor prostate cancer longitudinally. This program will be developed so it can eventually be used to apply specifically timed therapies prompted by the emergence of molecular resistance.

Prostate cancer is among the cancers known as immunologically "cold" and refractory to immune checkpoint therapy. We hypothesize, based on experimental and clinical observations, that combined immune checkpoint therapy would overcome the resistance to monotherapy in some patients. Initial clinical observations favored the concept and their findings led to an ongoing multi-institutional study.

The identification of the TGF-beta pathway as a driver of resistance and candidate therapy target prompted an investigation to determine the efficacy of TGF-beta inhibitors in men with castration-resistant prostate cancer.

These exciting advancements are made possible, in part, through philanthropy, for which we remain grateful. Donor support continues to help drive our progress toward better therapeutic options for our patients.

PLATFORMS

The research platforms of the Moon Shots Program® are key to the entire initiative and unique to the effort. They give the Moon Shots Program the unique capability to go from discovery all the way to interventions and treatments that impact patients' lives. They provide the Moon Shots with the technology needed to advance science and medicine, with expert staffing and resources. Through these platforms, the Moon Shots have direct access to several important capabilities and areas of expertise that are not typically available to academic researchers, including:

- + Drug development
- + Prevention and outreach
- + Cancer genetics and proteomics
- + Immunology
- + Preclinical cancer modeling
- + Storage, processing and access to massive amounts of medical and scientific information

APOLLO

Imagine being able to capture all the information relevant to a single patient during the course of his or her treatment: physical and biochemical information as determined by genetic makeup, clinical data, research data arising from the patient's tissues and blood samples, etc. Add the ability to track all these relevant data for each patient over a period of time — in a systematic, standardized way that will lead to deeper insight and to improved patient care. This is exactly the mission of APOLLO, a clinical framework aimed at assuring quality data by providing a structure that accelerates research-driven patient care. APOLLO integrates all clinical care and research data from other platforms, such as the Cancer Genomics Laboratory, Proteomics

and Immunotherapy, to enable analytical studies on this information, with the goal to accelerate better patient outcomes. Every patient will ultimately contribute to, and potentially benefit from, this standardized approach.

APOLLO's expertise uses data to guide the collection, processing and analysis of ontreatment, pre- and post-treatment biopsies to inform and optimize therapeutic decisions.

Cancer Genomics Laboratory

Using next-generation sequencing, the Cancer Genomics Laboratory provides a powerful systematic mutation discovery vehicle for virtually every Moon Shot across MD Anderson. By sequencing the DNA in a tumor before and after treatment, researchers hope to learn how cancer adapts to treatment and potentially becomes resistant to it. We utilize this methodology to uncover the underlying molecular abnormalities that drive the growth and spread of cancer. As a result, we provide valuable data that may uncover new avenues for targeted treatments.

Cancer Prevention and Control

More than 50 percent of cancer cases are preventable by applying knowledge we already have. The cancer prevention and control platform develops and implements evidence-based, community-focused programs in prevention, screening, early detection and survivorship. The goal is to achieve a measurable reduction in the cancer burden, especially in the underserved who experience a disproportionate share of cancer and cancer risk factors (e.g., tobacco, obesity, unhealthy diets, physical inactivity, excessive ultraviolet exposure, failure to undergo recommended cancer screenings). The platform's cancer control interventions span the following categories:

- + Policy interventions
- + Education public and professional programs
- + Services at the community level, beyond MD Anderson's walls

The platform evaluates and develops new cancer control policies and education initiatives. It

also designs and implements community and professional education programs and develops community-based clinical service delivery by working with other groups and foundations.

Proteomics

The proteomics platform sifts through thousands of cancer-related proteins to find those useful for diagnosis, imaging or as targets for various types of treatment — from immunotherapy to the use of antibodies or small molecules. The platform employs varied technologies from advanced mass spectrometry to probe tissues, cells and biological fluids to chip-based technologies that allow detection of proteins and their specific alterations associated with tumor development. The depth of analyses undertaken by this platform to find the right biomarkers that could lead to the next diagnostic, preventative or therapeutic agent for a cancer type is immense: analysis of a tissue specimen or cancer cells from a single patient can generate terabytes of data. The proteomics platform is fully engaged with several projects offering vast arrays of biospecimen resources for many of the Moon Shots.

Immunotherapy

Immunotherapy, which aims to unleash the power of the immune system by specifically enhancing the anti-tumor activity of immune cells, is proving to be the "breakthrough of the century." Immune-based treatments work by modulating the expression of key molecules that regulate the function of immune cells and has already proven to be highly effective in treating cancers, such as melanoma. It has the potential to be successful in the treatment of many other types of cancer. This platform is working with the different Moon Shots to bring the most advanced immunotherapies for specific tumor types to the clinics. Integrating cutting-edge basic immunology with new clinical trials through indepth analyses of animal models and patient tumor samples, the platform is guiding the development of immunotherapies for treating all types of cancer. Recent achievements include collaboration with Bristol-Myers Squibb to conduct clinical trials testing several new immunotherapy drugs as potential

treatments for acute myeloid leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, myelodysplastic syndrome and myelofibrosis.

Adoptive Cell Therapy

One approach to immunotherapy involves engineering patients' own immune cells (such as T cells) to recognize and attack their own tumors. The adoptive cell therapy platform was established to innovate, develop and implement novel cell-based immunotherapies, including customized T cells to attack cancer. The platform speeds up the production of clinical-grade cells and uses them to test efficacy and hypotheses through clinical trials for both children and adults.

The platform supports the Moon Shots and other MD Anderson programs by providing enabling technologies; regulatory, educational and clinical expertise; process development; and manufacturing infrastructure for novel cellular immunotherapies.

Translational Research Accelerator

Every industry is grappling with enormous volumes of data — both structured and unstructured — which are leading to new, more efficient ways to conduct business. The Translational Research Accelerator integrates all information systems to improve patient outcomes with efficient, secure use of research and clinical data.

This platform is breaking up research and information silos by gathering data related to questions across tumor types. It is increasing efficiency of data use and building a strong foundation of secure and accurate patient information that is accessible and responsive to analyses. It is also proving invaluable in maintaining the historical accuracy of existing databases that have developed over time in various departments/clinics. It is "putting data to work" by bringing together the vast amounts of information generated across the clinical, research and scientific domains and showing a longitudinal perspective of patients.

Therapeutics Discovery

The Therapeutics Discovery Division at MD Anderson is a drug-discovery engine developed to eliminate the bottlenecks that hamper traditional drug development. Comprising more than 100 dedicated cancer researchers, doctors, drug developers and scientific experts, the division develops small molecule drugs, biologics and cellular therapies, inspired by the needs of MD Anderson cancer patients and guided by the expertise of the center's clinicians. To create life-saving transformational medicines quickly, safely and effectively, Therapeutics Discovery works with unparalleled proximity to patients and an unmatched wealth of clinical experience.

The Therapeutics Discovery division consists of the following platforms:

Institute for Applied Cancer Science (IACS)

IACS applies scientific knowledge of what drives tumor formation and progression to develop new, small-molecule cancer drugs to address high unmet medical needs. Leveraging the world-class translational and clinical research expertise that is recognized as a hallmark of MD Anderson and working in collaboration with its physicians — IACS aligns its drug discovery research directly with clinical need: bringing new therapeutics to patients through novel clinical trials. New therapies are needed for those patients whose tumors cannot be effectively treated with existing standard-of-care agents. IACS is advancing new small-molecule therapeutics into the clinic against protein targets that are not being aggressively pursued by biopharmaceutical companies. It is also collaborating with TRACTION to develop comprehensive biomarkers to maximize the therapeutic potential of each drug used on its own and in combination with other drugs.

Oncology Research for Biologics and Immunotherapy Translation (ORBIT)

Monoclonal antibody-based therapy has become one of the most effective strategies for treating cancer patients. ORBIT focuses on the rapid discovery and development of new monoclonal antibodies (mAbs), targeted biologic drugs for cancer. These special, laboratory-designed

antibodies are capable of attaching to specific proteins on the surface of cancer cells, thus making them easy targets for the body's own immune system.

ORBIT is establishing an industry-standard timeline for preclinical development of mAbs at MD Anderson and working with several Moon Shots on promising leads. It offers core capabilities, including target identification and validation of preclinical data, biomarker development, pharmacology, antibody discovery and production, etc. The goal is to identify and validate novel tumor-specific antigens and to deliver innovative biological therapies for a number of cancers.

Translational Research to Advance Therapeutics and Innovation in Oncology (TRACTION)

Potential drugs in the making must go through a series of preclinical tests before they can be submitted for the FDA approval process. TRACTION accelerates the development and evaluation of novel drugs to improve the probability of success in the clinic. The platform addresses the problem of failures in drug development by testing the impact and tolerability of single drugs or combinations of drugs in preclinical models, such as cell lines and mouse models that bear human tumors — replicating how patient tumors would respond to certain drugs. TRACTION functions as an industrialized pharmacology unit by offering core services, including:

- + Translational biology: focusing on discovery and development of biomarkers to guide new drug development and boost understanding of drug action mechanisms.
- + In vivo pharmacology: studies to observe the way drugs are absorbed into cells/systems and their interaction and/or changes on absorption, and to check drug efficacy.
- + Systems pharmacology and functional genomics: utilizing systems biology approaches to predict mechanisms of drug resistance and using functional genomics to inform target identification.
- + Model development: annotating diverse patient-derived mouse models.

Your support today drives the breakthroughs of tomorrow.

On behalf of our patients, thank you.

For more updates, visit: cancermoonshots.org



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