



# MOON SHOTS PROGRAM<sup>®</sup>

**FISCAL YEAR 2019**  
ANNUAL REPORT

THE UNIVERSITY OF TEXAS  
**MDAnderson**  
~~Cancer~~ Center

Making Cancer History<sup>®</sup>

At The University of Texas MD Anderson Cancer Center, passionate teams of physicians and scientists with broad areas of expertise have united to focus on particular types of cancers in order to clinically impact disease. These teams — what we call Moon Shots® — work closely with cutting-edge research platforms to rapidly turn new scientific discoveries into clinical advances that can save patients' lives.

Together, they make up our Moon Shots Program®, and they are all driven by a common mission: to **end cancer**.

Now in its seventh year, the program's singular focus is well known. Thanks to the generous philanthropic support of the Moon Shots Program, our teams have been able to make impactful discoveries for patients, many of which you'll learn about from our Moon Shots researchers in this report.

Achievements such as these would not be possible without the Moon Shots Program and donors who support it. As you will read, this report emphasizes some of the notable ways that our unique approach to team science has enabled our success, such as:

- Funding facilitates the collection and banking of a large number of samples over long periods of times for extensive analysis.
- **Collaborations with Moon Shot platforms (as denoted throughout this report by red type)** allow us to rapidly profile patient samples to uncover treatment targets or identify paths of resistance.
- The platforms provide Moon Shot teams with access to unparalleled technical expertise and specialized equipment only available here.
- The unique infrastructure of the Moon Shots enables new discoveries to advance all the way from the lab to the clinic under one roof, improving efficiency and helping to benefit patients more quickly.
- Moon Shots support allows us to study whether lower treatment doses can be equally effective for patients, lowering costs and side effects.
- The program facilitates working directly with communities to establish initiatives that improve wellness, which lowers the risk of cancer and a variety of other chronic diseases.

- The Moon Shots Program studies individuals at high-risk of developing cancer, including researching personalized approaches to help individuals quit smoking and screening individuals with a genetic predisposition to developing cancer.
- The data generated through Moon Shots research are leveraged to obtain additional external grant funding and help with engaging strategic industry partnerships, generating substantial returns on the initial investments.
- The Moon Shots Program has built a strong foundation upon which future discoveries will be made and lives saved, positioning the program for future success.

These and other facets of the Moon Shots Program are unique to MD Anderson, enabling us to conduct innovative research not possible elsewhere. Cancer research and care can be incredibly complex. Its funding — and the subsequent impact — can be equally far-ranging and multifaceted. Every decision our investigators make and every data point they capture can bring us new answers as well as raise new questions. We are driven to learn from each of these to improve how we make decisions for the next patient. We hope our commitment to improving the lives of our patients shines through in the Fiscal Year 2019 Moon Shots Annual Report, and we are incredibly grateful for the support that makes the Moon Shots Program possible.





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*A conversation with Moon Shot co-leader, Michael Wang, M.D.*

## B-CELL LYMPHOMA MOON SHOT

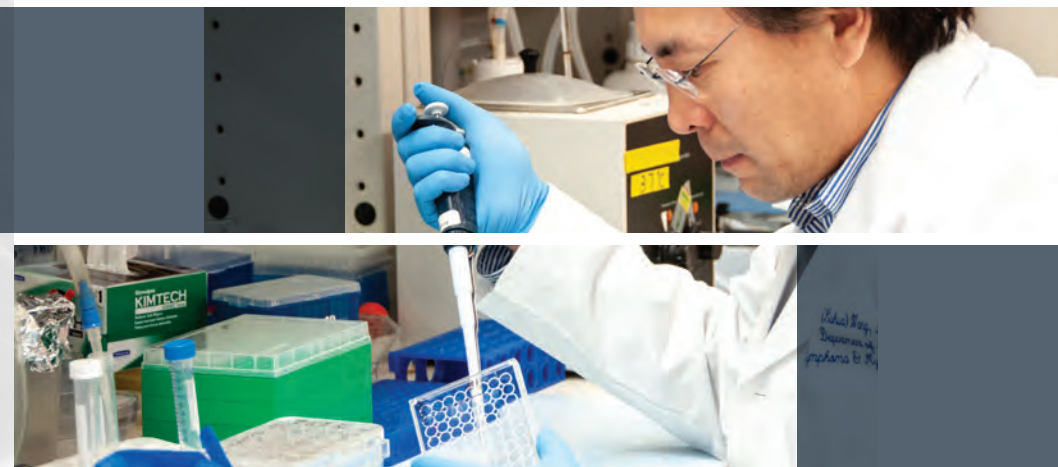
The B-Cell Lymphoma Moon Shot® is working toward the goal of doubling the cure rate for patients with B-cell lymphomas within five to 10 years — from about 30 to 60%. For many years, MD Anderson has been one of the largest referral centers for lymphomas in the world. We have championed many therapies currently in use for treating lymphomas, including the chemotherapies R-CHOP, R-ESHAP, R-MINE and R-HyperCVAD. Our department was instrumental in bringing forward rituximab, a monoclonal antibody, for the treatment of lymphomas.

MD Anderson has become a leader in some areas of lymphoma treatment, like diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL) treatment and cell therapy, but we have been less prolific in other correlational and translational therapies. The Moon Shot® has enabled us to turn our weaknesses into strengths.

Thanks to our generous donors, we've achieved clinical outcomes, pioneered scientific advances, and secured multiple grants.

In the past five years, our team's work has led to approvals for several drugs, most recently the FDA approval of ibrutinib and acalabrutinib in MCL and CD19 chimeric antigen receptor (CAR) T cells in DLBCL.

We have also developed chemotherapy-free treatment combinations. We have been able to unite several companies through the Moon Shot with window-of-opportunity clinical trials and were able to determine that chemotherapy-free targeted therapy was very effective and durable in patients



with fewer side effects. As part of the Moon Shot, we have designed the Window study for MCL, SMART studies for DLBCL, and we have championed combination targeted therapies for indolent lymphoma.

Additionally, we've found that a cellular pathway termed "oxidative phosphorylation" is mediating one of the major drug resistance mechanisms in MCL, and we want to counter that pathway to fight the resistance. We didn't have a drug corresponding to the pathway, but **through collaboration with the Institute for Applied Cancer Science and the Therapeutics Discovery platforms, we were able to use their oxidative phosphorylation inhibitor, IACS-10759.** It's now in clinical trials at MD Anderson for lymphomas. This would not be possible without the Moon Shot.

Finally, MD Anderson investigators led the pivotal trial for FDA approval of CD-19 CAR T-cell therapy in DLBCL, and we are now leading many studies, powered by continued Moon Shot support, to study mechanisms of resistance. And while CAR T-cell therapy is very effective, it comes with high toxicity, challenging logistics, and a significant price tag. **Therefore, we're working with the adoptive cell therapy (ACT) platform to use cord blood-derived natural killer (NK) cells to generate CAR-modified NK cells.** Novel stem cell transplantation strategies used in combination with CAR-modified NK cells are resulting in

promising clinical outcomes. Our initial results show that CD19 CAR NK cells are as effective and much less toxic than the available CAR T cells. They are immediately available "off the shelf", and hundreds of doses can be produced from one cord blood unit, making this approach markedly safer, less expensive, and more cost effective compared to commercially available CAR T cells. So far, they don't have the same toxic effects, and the efficacy is superb. The ACT platform is instrumental to our work. Based on the success of the CAR NK program, we are also developing an "off-the-shelf" universal T cell therapy platform termed "Infinite T cells". These Infinite T-cells would greatly reduce the cost of CAR T-cell therapy, and the platform has the potential to generate enough anti-CD19 CAR T-cells required for treatment of lymphoma patients all over the world within one month.

The Moon Shots Program® is truly helping us stay at the cutting edge of research and patient care. It brings together scientists in ways very few, if any, institutions are currently doing. The speed with which we can bring novel ideas from the lab to the clinic is unprecedented. And we have the capability to take drugs back to the lab to refine them or personalize them for our patients. And this is only possible because of donors to the Moon Shots Program. With their help, we are inspired to keep advancing oncology through this infrastructure.





Immunotherapy put Lori Shults' triple-negative breast cancer into complete remission after standard chemotherapy proved ineffective on the Breast Cancer Moon Shot's ARTEMIS trial.

*A conversation with Moon Shot co-leader, Stacy Moulder, M.D.*

## BREAST CANCER MOON SHOT

Triple-negative breast cancer (TNBC) makes up 15 to 20% of breast cancer diagnoses. The condition is often considered a single disease, when in reality, TNBC is a catch-all diagnosis of biologically different breast cancer subtypes that lack expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2).

In patients with localized disease, a neoadjuvant (pre-surgery) chemotherapy regimen of adriamycin (doxorubicin) and cyclophosphamide (AC), followed by a taxane-based regimen, results in a pathologic complete response (PCR) in 35 to 40% of patients and is associated with an excellent long-term prognosis. However, more than half of patients have a tumor that does not respond to chemotherapy. Approximately 50 to 60% of those patients will experience a recurrence of their cancers within two to three years.

Thanks to the Breast Cancer Moon Shot® and A Robust TNBC Evaluation Framework to Improve Survival (ARTEMIS) clinical trial, we are focusing on understanding why some TNBC patients do not respond to chemotherapy and seeking targeted therapies for these patients.

### **Personalizing triple-negative breast cancer treatment**

ARTEMIS is likely the first clinical trial attempting to identify chemotherapy-insensitive TNBCs during AC neoadjuvant therapy and then switching patients to an alternative regimen based on their molecular profiling.

Traditionally, neoadjuvant studies treat all enrolled patients with therapy that is not

specific to their TNBC subtype, resulting in up to half of patients with chemotherapy-sensitive disease receiving an unnecessary treatment, as well as the toxicities that come with it.

ARTEMIS is unique in that it is identifying the chemotherapy-insensitive population first, and then giving subtype-selected therapies.

### **Molecular profiling offers guidance**

The goal of ARTEMIS is to find out if treating chemotherapy-insensitive TNBC patients with therapy that has been selected based on subtyping will result in higher PCR rates and better long-term survival compared with standard chemotherapy. To answer this, patients in the study undergo biopsy before treatment, and immediately begin neoadjuvant chemotherapy while their TNBC subtype is determined through molecular testing.

We assess responses by imaging after two cycles and at completion of four cycles of chemotherapy. If a patient's disease is deemed chemotherapy-insensitive based on imaging during or after chemotherapy, we offer the patient the opportunity to participate in a non-randomized, single-arm therapeutic Phase II clinical trial selected based on their molecular profile.

**In addition to pretreatment biopsies, the APOLLO platform coordinates and oversees biopsy and sample collections after chemotherapy and surgical resection in order to provide material for translational research that aims to identify mechanisms of chemotherapy resistance.** This longitudinal collection strategy provides high-quality tumor specimens



“Once I realized I’d be getting what everyone else got, plus something extra if the conventional treatment didn’t work, I didn’t see a downside to it.”

LORI SHULTS

for genomic profiling, including **RNA sequencing and whole-exome sequencing, supported by the Cancer Genomics Laboratory**. Elucidating the immune response is also critical to understanding why certain individuals respond to chemotherapy while others do not. The Breast Cancer Moon Shot team performs comprehensive immune analysis to characterize and quantify the immune repertoire in responders versus non-responders to investigate how immune changes mediate a patient’s response to therapy.

We are looking at the chemotherapy-sensitive tumors and comparing them with the resistant tumors to determine if there are potential targets that haven’t been considered, based on the outcomes at each biopsy time point. Our goal is to translate these novel findings into the next-generation of targeted therapies for patients whose TNBC is not sensitive to chemotherapy.

#### **Unique design eliminates delay in treatment**

Because of the resources from the Moon Shots Program, as well as the trial’s unique design, patients who enroll in ARTEMIS typically undergo a biopsy within two to three days of consenting for the trial, and start chemotherapy immediately.

One of the most unique elements of this trial is that our patients don’t have to wait for the result of the molecular profiling to start treatment. The patient can start therapy, and by the time we need to make a decision after the first phase of treatment, we have that information to decide next steps.

If a patient’s tumor is chemotherapy-sensitive, she will continue with the AC chemotherapy, but if the tumor is chemotherapy-insensitive, the patient is offered the opportunity to participate in one of four non-randomized, single-arm therapeutic clinical trials linked to ARTEMIS. With the information found by the tumor analysis, we can offer patients the therapeutic trial best suited for their diseases.

We are guiding patients into clinical trials more thoughtfully, rather than treating everyone’s triple-negative disease the same.

#### **Working hand-in-hand with community physicians**

The ARTEMIS trial is an opportunity to partner with medical oncologists in the communities where patients live, providing them comfort and convenience.

After genomic profiling, patients return to their community medical oncologists to receive treatment. We know how important it is for patients to be in their home environment, where it is easier to receive chemotherapy.

However, for patients whose tumor doesn’t have a robust response to chemotherapy, MD Anderson offers a second opportunity for treatment with the portfolio of clinical trials linked to ARTEMIS.

Thanks to our donors, the infrastructure of the Moon Shots Program® helps make possible this patient-centric approach to clinical trials. It is giving our patients hope no matter their subtype.

*A conversation with  
platform co-leader,  
Ignacio Wistuba, M.D.*

## APOLLO

The Adaptive Patient-Oriented Longitudinal Learning and Optimization (APOLLO) platform focuses on assisting clinical and translational investigators at MD Anderson in the collection of patient specimens, including tissue, blood and other samples, on a longitudinal basis.

The longitudinal component of the collection is the key. Although it is a challenge, we have emphasized the importance of longitudinal tissue collection because it is key to understanding the progression of cancer.

Powered in part by philanthropic funding, the platform helps investigators in several ways. We have an Institutional Review Board-approved protocol that allows APOLLO to collect longitudinal samples for research purposes. We have also developed a workflow in collaboration with the Institutional Tissue Bank and different clinical settings to collect high-quality specimens in a timely fashion to be processed for future analysis.

Finally, we have developed a laboratory capable of performing real-time quality control assessment of specimens. This tells us what the quality of the material is going in as well as informs the power of the analysis we can run.

The principal feature that differentiates us from others is that APOLLO is a standardized and centralized sample collection and processing effort. We can offer our collaborating investigators the entire package so they don’t have to establish their own sample collection system.





It's important to note that APOLLO doesn't analyze any of the samples, but we work to enable high-quality downstream analysis. We collect quality samples, we process and perform quality control, and then we distribute to the different laboratories for analysis. Certain investigators or groups may have done things like this in the past, but this standardized and centralized effort is unique. It's key to promoting the work of the Moon Shots® here at MD Anderson.

We have a large number of clinical trials on immunotherapy and cell-based therapies — it's very exciting to collect tissues from patients on those trials in order to understand the potential mechanisms of sensitivity or resistance to these novel therapies. Our most exciting new project is with MD Anderson's rare tumor initiative.

This relatively new project is a priority area of research. Moon Shots leadership understood that we can make significant contributions to our patients by focusing on understanding these rare tumors. These cancers don't receive a lot of attention from biopharma companies or major clinical trials, but we see more than 5,000 cases of what we could consider rare tumors at MD Anderson. Therefore, we have the opportunity to make a real difference for these patients.

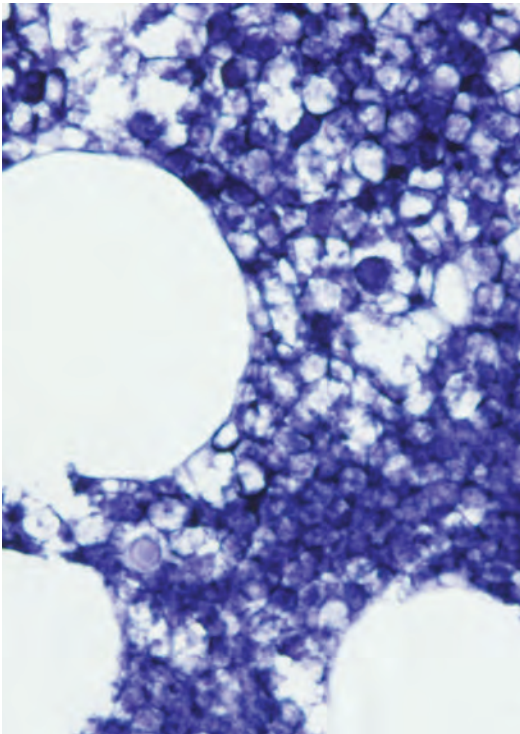
We are using the APOLLO platform to collect, process and distribute longitudinal samples from the rare tumor initiative for analysis. That project is going very well — we already have more than 400 specimens in the pipeline for analysis. We look forward to learning where this project takes us.

APOLLO is also assisting with several other new programs such as the brain metastasis clinic. We plan to collect and process samples from that clinic to understand how brain metastasis happens, how it progresses and how we can better treat these patients. We're also involved with MD Anderson's pre-malignancy effort, helping to understand how pre-neoplastic lesions evolve into invasive cancer. In the future, I see APOLLO as the main mechanism used to collect high-quality samples for research analysis from our patients, from early disease all the way to advanced, metastatic disease. Using this as the primary institutional resource, each investigator can receive help from APOLLO.

By standardizing the collection and processing of these samples and having high-quality material for analysis, the result will be standardized data across multiple diseases, across multiple tumor types, and on multiple forms of therapy. Investigators can then use those data to develop new hypotheses about the biology of the disease or design new cancer treatment approaches. When we get the critical mass of data out there from the analysis of these samples, investigators will see the benefit of our approach and more will partner with APOLLO.

*A conversation  
with Moon Shot  
co-leader, Varsha  
Gandhi, Ph.D.*

# CLL MOON SHOT



For many years, standard of care for patients with chronic lymphocytic leukemia (CLL) was a combination of chemotherapeutic agents, such as fludarabine and cyclophosphamide, as well as the monoclonal antibody rituximab, which targets CD20 on leukemia cells. This chemo-immunotherapy combination, known as FCR, was developed by faculty here at MD Anderson.

FCR therapy was the international standard of care when we launched the CLL Moon Shot®. For one subgroup of patients with CLL — those with mutations in the IGHV gene — FCR therapy results in disease-free survival for about 60% of patients. You can call that a cure. However, FCR doesn't work well for patients with unmutated IGHV and can be a harsh treatment, especially for elderly patients. Thus, with critical donor support, we set out to improve upon the standard of care to eventually bring cures to more patients.

Therefore, one of our flagship projects for the CLL Moon Shot is directed at advancing new targeted therapies for all CLL patients, particularly those with unmutated IGHV.

In general, patients with CLL are in good physical health and have productive, active lives, even when inflicted with this cancer. They do not want to disrupt that with trips to the hospital for treatment or suffer the debilitating side effects of chemotherapy drugs. Further, patients don't want to take on the risk of developing additional tumors that stems from receiving highly genotoxic chemotherapies.



Targeted therapies provide practical solutions to these issues. Almost all current targeted therapeutics for CLL are oral — eliminating the need for frequent hospital visits. They are well-tolerated, allowing patients to maintain active and productive lives. Although not fully established, the general belief is that targeted therapies should not result in long-term and undesirable adverse events. In general, quality of life is not compromised for patients with CLL on targeted therapies.

Since the launch of the Moon Shot®, several small-molecule targeted agents have been approved by the FDA for the treatment of CLL: ibrutinib, idelalisib, duvelisib, and venetoclax. Ibrutinib targets Bruton's tyrosine kinase (BTK), while idelalisib and duvelisib strike PI3-kinase (PI3K). These enzymes are pivotal in the B-cell receptor (BCR) pathway, which is responsible for proliferation, survival, and migration of CLL cells. Venetoclax neutralizes the Bcl-2 protein, a culprit that is accountable for the existence, maintenance and survival of CLL lymphocytes.

The advent of targeted therapies has given us tools to treat patients for whom standard treatments aren't effective, and we have focused our efforts to maximize the efficacy of these drugs, either alone or in mechanism-based combinations. Our aim is to increase the number of patients who achieve what we call "undetectable minimal residual disease (U-MRD)." This means we can't detect evidence of leukemic cells in the bone marrow following treatment, and we know that patients with U-MRD often go on to have long-term remissions and cures.

Because we can easily isolate CLL cells from the peripheral blood of patients, we have a unique opportunity to make preclinical discoveries in patient samples that we can translate to the clinic. We have taken advantage of that potential and profiled malignant lymphocytes from patients on ibrutinib. Through this work, based on molecular changes we observed in the Bcl-2 family of proteins following ibrutinib treatment,

we established that venetoclax is an optimal drug partner with ibrutinib.

Our clinical data provided additional justification for the combination of ibrutinib and venetoclax. These agents preferentially hit CLL cells in different niches and target distinct intracellular survival pathways. We therefore hypothesized that a sequential combination of ibrutinib and venetoclax would be highly effective.

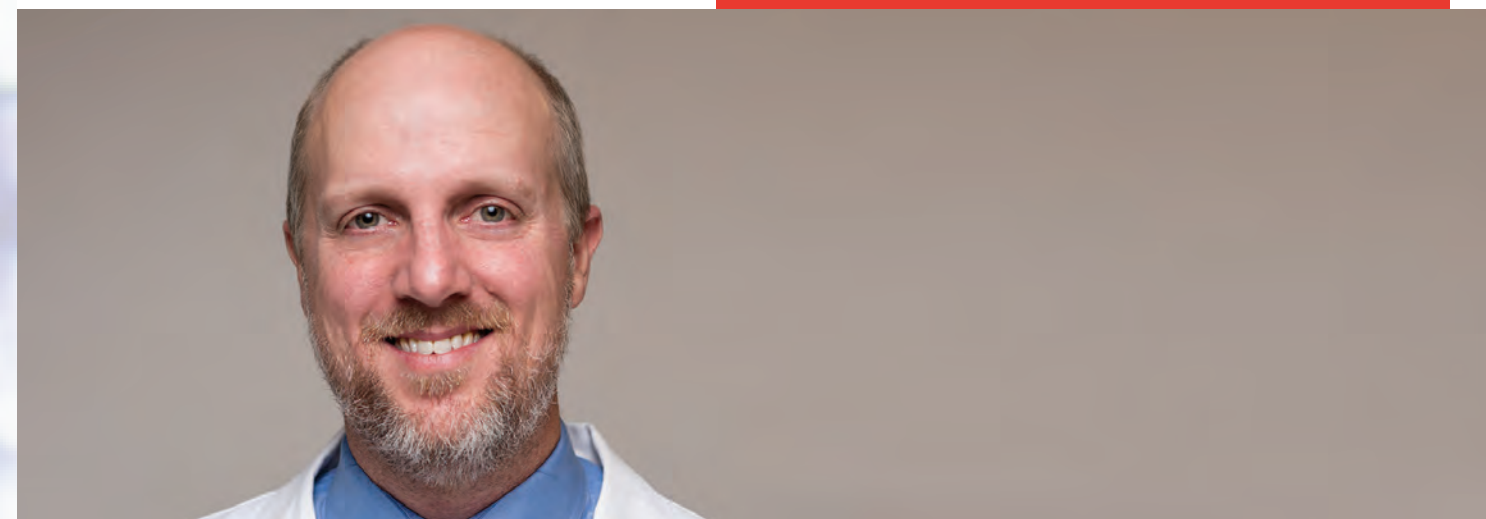
To test such a postulate, we designed a protocol where patients received three courses of ibrutinib, followed by venetoclax. At the one-year mark, around 90% of previously untreated patients achieved complete remission, and more than 60% had U-MRD. Complete remission rates and the U-MRD stage are further improving with time. This is a remarkable clinical outcome, as one year of treatment with ibrutinib or venetoclax alone mostly results in partial remissions and U-MRD standings are rare, if any.

**As a logical extension of this combination trial, we worked with the TRACTION platform to test the combination of a new and more selective BTK-inhibitor, acalabrutinib, with venetoclax in a mouse model of CLL.**

Currently, we are working on a new clinical protocol to combine these two agents.

With the unprecedented success of small-molecule targeted agents in CLL, grant revenues are not easily available for therapeutic approaches in this disease. Pharmaceutical companies are not attracted or enticed to a proposal where the investigator wants to test a reduced dose of the FDA-approved standard dose of their drug. Yet such studies are indispensable for optimal patient care and for future progress.

The CLL Moon Shot has been vital to our efforts to improve the standard of care for patients with CLL, and philanthropic funding has been instrumental in launching and completing our work in this area.



*A conversation with Moon Shot co-leader,  
Scott Kopetz, M.D., Ph.D.*

## COLORECTAL CANCER MOON SHOT

The Colorectal Cancer Moon Shot® continues to make significant advances toward eliminating the second leading cause of cancer deaths in the U.S. by intensively collaborating to improve prevention, early detection and treatment approaches for our patients.

Colorectal cancer screening by colonoscopy reduces mortality. However, this approach is costly, invasive and dependent on individual compliance. As a result, just two-thirds of individuals who might benefit from these screens undergo these critical procedures. Our Moon Shot® team has made ongoing advances in multiple blood-based diagnostic tests to non-invasively screen individuals for the presence of colorectal cancer. These tests rely on cancer related biomarkers that can detect and

monitor the progression of a patient's disease before, during and after treatment. This past year, our dedicated researchers further refined these tests and expanded their focus to include circulating tumor DNA as biomarkers of disease status. Our goal is to use blood samples to detect disease when potential lesions are so small they cannot be readily identified using diagnostic imaging approaches like magnetic resonance imaging (MRI). Leveraging work supported last year by the Moon Shot, we are implementing a circulating tumor DNA-guided study in colorectal cancer throughout the MD Anderson Network.

An interrelated central effort in the Moon Shot is understanding the molecular and biologic differences that separate colorectal cancer into



distinct groups. Support from the Colorectal Moon Shot helped identify four discrete molecular subtypes within the overall colorectal cancer disease spectrum. These distinct consensus molecular subtypes (CMS) can now be identified using clinical assays developed using Moon Shot funding.

Moon Shot support has also been leveraged to acquire government funding that enables further development and validation of our clinical assays. Applying this assay can be a critical first step to allow for testing targeted therapies. These data are being used to address the fundamental problem that a different treatment may be required for each separate subtype. Further work by the Moon Shot and others are confirming that CMS classification is associated with profound differences in the tumor-infiltrating immune cells and tumor microenvironment to identify additional targeting opportunities.

The final focus of our efforts is to activate patients' immune cells in a variety of ways, by creating novel combination treatment protocols, including vaccines and cellular therapies. While immunotherapies have offered improved treatment outcomes for some cancer types, these agents alone have not provided a satisfying responses for the majority of colorectal cancer patients. We are tailoring our treatment strategies to the genetic makeup of individual patient tumors. We are also optimizing targeting strategies that involve drug and immunotherapy delivery in conjunction with surgical resection of their tumors. This platform will determine whether this approach offers treatment benefits to patients and will guide future strategies by providing our researchers with specific information regarding how tumors respond to immunotherapies. For subtypes that are not responsive to checkpoint immunotherapy, we are developing personalized therapeutic vaccines designed to trigger an immune attack against established tumors. The trial improves upon earlier vaccine approaches by identifying tumor-specific neo-antigens that can be paired with receptors on the immune cells to enhance the immune response. We are also working toward engineering immune cell receptors to specifically and more effectively attack tumors. Chimeric antigen receptor T cell (CAR T-cell) therapy has been successful in other cancer types. We are beginning to examine its effectiveness in colorectal cancer and are excited by its potential.

The Moon Shots Program® has truly catalyzed our efforts to bring cures to patients suffering from colorectal cancers, beginning with helping to discover that they are indeed, not just one disease. The program brings together the best minds in oncology to determine the best course of action for each stage in the cancer care continuum. **Effectively engaging the Moon Shot platforms is bringing state-of-the-art scientific resources to our fingertips like never before, thereby significantly enhancing the pace at which we can bring research from the lab to the clinic, and then back to the lab for further refinement.** Finally, the Moon Shots Program helps us generate preliminary data for projects that otherwise might not be funded by other sources. We have leveraged these critical data to acquire external government and strategic alliance funding to accelerate our discoveries into clinical application for the benefit of our most important partners — our patients.

*A conversation with Moon Shot co-leader, Frederick Lang, M.D.*

# GLIOBLASTOMA MOON SHOT

Glioblastoma (GBM) is not among the most commonly diagnosed cancers in the U.S., but it can certainly be among the most devastating. Of the roughly 15,000 patients diagnosed annually, only 5 to 10% will survive five years. What is more problematic is the fact that the outlook has not changed a great deal in the past 30 years. If you look at data from 1980, the median survival was roughly 12 months. In 2019, the median survival was only 15 months after treatment with our current standard of care, which includes surgery, radiation, and chemotherapy.

Thanks to the generosity and foresight of our donors, our team is working to change those odds and save the lives of patients with a coordinated, multidisciplinary team of researchers and physicians committed to finding new vulnerabilities, testing new therapies and implementing better treatment approaches in the clinic.

Over the past year, the Glioblastoma Moon Shot® coalesced a critical mass of investigators — people who have traditionally been studying the disease

together with researchers from new disciplines that have not typically worked in this area.

With this in mind, we reorganized our Moon Shot® from a strategic point of view. Whereas before we were primarily focused only on therapeutic goals, we understand now that we needed significantly more early-stage discovery to provide more basic information about the cause of the disease so that we can ultimately find the “Achilles heel(s)” of glioblastoma and develop therapies around these discoveries. In the past, we have relied too often on drugs that were developed for other cancers, with the hope that they will work in glioblastoma. This approach has not been fruitful.

We want to identify new vulnerabilities in glioblastomas that can lead us to new treatments. To that end, we've partnered with an international research group called the GLASS Consortium to understand the changes in brain tumors over time at the genetic level. We're sequencing patient samples taken at different treatment points to understand how tumors respond and evolve over time.





Frederick Lang, Jr., M.D.  
Co-leader, Glioblastoma Moon Shot

We're also working to establish a tumor geographical atlas to better understand where particular cell types, like immune cells, reside in and around tumors. This work stemmed from our interesting finding that a particular type of immune cell is commonly found in glioblastomas (macrophages), while other types are not (T cells). This information will be extremely useful for learning how tumors develop and how they respond to various treatments. We are also identifying biomarkers from blood and spinal fluid that could be used to help us diagnose tumors more easily and monitor how well a particular treatment is working.

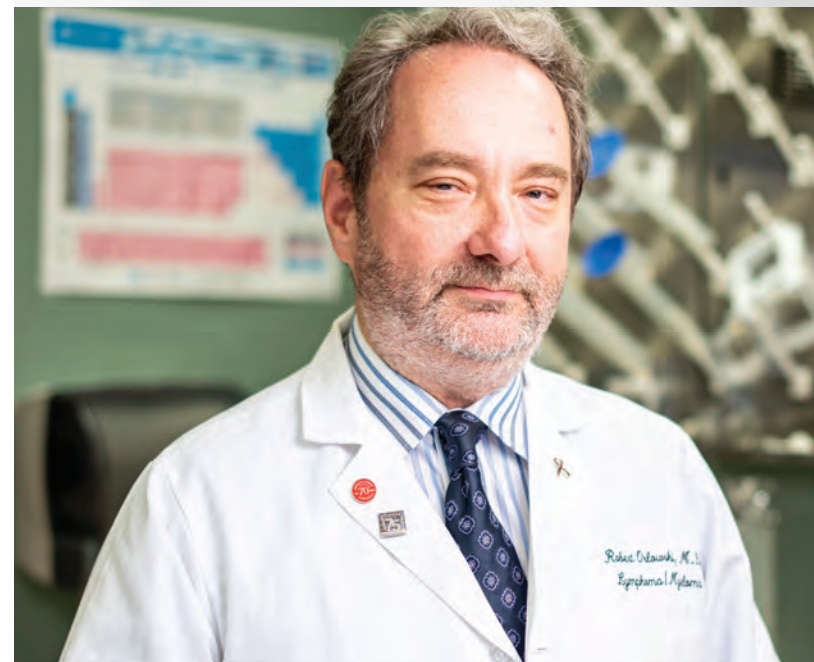
We focused on projects that have proven compelling in the preclinical setting and need the added effort from the Moon Shot to complete translational and regulatory studies so that we can begin testing approaches in the clinic for our patients. We've brought several new people to the team for these projects, and have explored exciting immunotherapy-based approaches.

Finally, the Glioblastoma Moon Shot is focused on implementing and executing various transformational clinical trials that are designed to bring important new options to our patients. We're conducting what we call "window of opportunity" trials, in which we treat patients with a therapeutic before surgery and then obtain tumor specimens during surgery in order

to understand the effect of the treatment on the tumor. We have been pioneers in these types of clinical trials, and we are currently testing several approaches with this trial design.

We also eagerly anticipate the results of Phase I clinical trial investigating mesenchymal stem cells as a delivery vehicle for oncolytic viruses. Not only is this a new agent, but this has the potential to open up endovascular neurosurgical oncology as a whole new field. Delivering therapies through the artery, and doing so in a selective manner, wasn't possible until recently. Because of new technology and new methods, we can thread a catheter into the blood vessels, specifically feeding the tumor, and infuse agents directly into that tumor. It gives us the opportunity to be much more selective in our treatments. We enrolled our first patient on this trial in April 2019, and we've just finished treating the third participant.

The Moon Shots Program® creates opportunities for more innovative thinking, as it funds exploratory projects that may not be able to secure funding from conventional sources. For federal grants, you have to have much more certainty in your research before you'll be funded. Donors to the Moon Shots Program give us a chance to be a bit more exploratory and innovative, which may be what it takes to find a cure for this deadly disease.



*A conversation with Moon Shot co-leader,  
Robert Orlowski, M.D., Ph.D.*

## HIGH-RISK MULTIPLE MYELOMA MOON SHOT

The High-Risk Multiple Myeloma Moon Shot® team is focused on two primary areas — advancing new treatments for patients with high-risk symptomatic disease and developing approaches to delay or prevent progression in patients with high-risk asymptomatic, or precursor, myeloma.

In patients already diagnosed with symptomatic myeloma, we can identify "high-risk" patients based on molecular features such as deletion of chromosome 17p or amplification of 1q21. Based on available data, we know these patients will survive only about three to four years, compared to survival of 10 to 15 years for those with "standard-risk" myeloma. Those high-risk patients respond well to our current therapies, but the duration of their response is very short, which is why we need new options.

**Our team is developing a variety of cell therapy approaches for patients with more advanced disease, leveraging the expertise found at MD Anderson and within the adoptive cell therapy platform.** We've shown in a Phase I study that we can expand natural killer (NK) cells derived from umbilical cord blood to safely treat patients with symptomatic disease. The preliminary data shows that this approach is safe, and there is evidence that they benefit patients with high-risk disease and keep them in remission longer.

Moving forward, we are planning to use engineered chimeric antigen receptor (CAR) NK cells that will be targeted to the cancer cells. We are developing the best approach for targeting multiple myeloma cells with a new generation of CAR NK cells and plan to launch the first-in-human Phase I study in patients. We hope these CAR NK approaches will have minimal toxicity and lots of clinical activity.



The other high-risk area we are targeting are those with precursor disease, such as smoldering myeloma or monoclonal gammopathy of undetermined significance (MGUS). Patients with high-risk smoldering myeloma have an estimated 50 to 70% chance of progressing to symptomatic myeloma within two to three years of diagnosis. We are working to understand why patients progress and develop treatments that will allow us to delay or prevent their progression to myeloma.

The hope is if we diagnose patients when they're in the asymptomatic phase, when the disease is less developed and their immune system is healthier, we might be able to find a sweet spot where we can cure patients and prevent symptomatic myeloma from appearing.

We are engaged in several clinical trials to investigate the use of immunotherapy to delay or prevent disease progression for patients with high-risk asymptomatic disease.

We have wrapped up a pilot trial investigating the use of pembrolizumab (anti-PD-1 antibody) in 13 intermediate- to high-risk smoldering myeloma patients, because expression of PD-L1, a related protein, was correlated with disease progression. This treatment was well-tolerated and even led to one complete response with remission ongoing for more than two years suggesting that it is possible to prevent disease progression with immunotherapy. Additionally, promising trial results with an anti-CD39 antibody called isatuximab prompted a Phase III trial.

One of the more exciting projects we're now working on is a vaccine study, which is personalized to the patient. We're sequencing DNA and RNA from the patient's myeloma cells to identify mutations most likely to be antigenic and cancer-specific, meaning that none of these mutations are present in normal cells. We then design a vaccine consisting of 10 peptides based on those findings. Each patient will receive a vaccine with a different set of peptides, specific to their cancer. Ten patients received their personalized vaccine and, in the next step, we will look at whether the vaccine induces anti-myeloma immunity and hopefully also clinical response.

With philanthropic support, the Moon Shots Program® has performed important exploratory work, utilizing the infrastructure of the platforms to look at important questions and gather preliminary data. For example, Moon Shots platforms allowed us to do RNA and DNA sequencing, bioinformatics analysis and immune profiling to help us understand why some patients progress to multiple myeloma from precursor diseases and others don't. This is a long-term project because it represents a small percentage of patients, so the work spans many years. But, with the support of the Moon Shot®, we have discovered some compelling things that have led to extramural funding. For example, we were awarded a Specialized Center for Research award from the Leukemia & Lymphoma Society based on our work, and three of the four projects there started off in the Moon Shot. It's been a great way to do important work that we can leverage for further outside funding.



*A conversation with platform  
scientific manager, Maggi Morgan*

## CANCER GENOMICS LABORATORY

Using next-generation sequencing, the Cancer Genomics Laboratory (CGL) 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.

One measure of the successful use of sequencing data is the contribution to science. To date, more than 10,000 samples have been sequenced across all 13 Moon Shots, resulting in more than 45 peer-reviewed publications.

The **HPV-Related Cancers Moon Shot®** is characterizing a rare HPV-related cancer with limited treatment options, especially for advanced disease. The team believes this to be the largest whole-exome analysis of this cancer, with the potential to uncover the involvement of multiple cancer genes contributing to tumor development.

The **Myelodysplastic Syndromes and Acute Myeloid Leukemia Moon Shot®** has a study on clonal hematopoiesis of indeterminate potential (CHIP), defined as a pre-malignant condition in which somatic mutations are found in one or more leukemia-associated genes. Work from this team and others have found that individuals with CHIP carry a higher risk of developing hematological malignancies and an increased risk of developing

therapy-related myeloid neoplasms (t-MNs); data from this work was published in June 2019.

The **Ovarian Cancer Moon Shot®** performed a comprehensive molecular analysis to better understand the diversity and the heterogeneity within high-grade serous ovarian cancer (HSGC) to help explain the high rates of drug resistance; this work is currently under review by a high-impact journal.

Within a few years, it is feasible that we will add liquid biopsies as a standard procedure to screen for early-stage cancers, monitor for responses to treatment and help explain why some cancers are resistant to therapies. Currently, the gold standard for getting high-quality sequencing data is to use freshly biopsied tumor tissue. However, there is added risk and discomfort for patients. **There has been a surge in research from the Prostate Cancer Moon Shot® team, for example, to use circulating tumor DNA, which has the potential to enable full-tumor genome characterization collected by minimally invasive means.**

The CGL is unique in that we interact with every Moon Shot, which epitomizes the multidisciplinary team effort embodied by the Moon Shots Program®. The data generated by our platform is used to advance the work of Moon Shot teams and facilitate more collaborations with additional platform teams. **For example, our collaboration with the Breast Cancer Moon Shot® provided valuable insights into therapeutic targets, which they are now pursuing with the TRAC-TION platform.** Very few, if any, cancer centers are advancing cancer therapy in this manner.



*A conversation with platform co-leader, Padmanee Sharma, M.D., Ph.D.*

# IMMUNOTHERAPY



Padmanee Sharma, M.D., Ph.D.  
James Allison, Ph.D.  
Co-leaders, Immunotherapy platform

Immunotherapy is a treatment that uses the body's own immune system to fight cancer.

One type of immunotherapy, called immune checkpoint inhibitors, provides lasting cures to a subset of patients with specific cancers, including Hodgkin's lymphoma, Merkel cell carcinoma, melanoma, bladder, kidney, head and neck, and non-small cell lung cancers.

Currently, not all patients benefit from immunotherapy, but through clinical trials, our experts are learning how to make this treatment more effective.

Within the immunotherapy platform, our goal is to make immunotherapy a standard treatment option for many more types of cancers and patients. Philanthropy is helping us expand the use of immunotherapy. We are currently working to:

- identify the patients most likely to benefit from current immunotherapies,
- investigate why immunotherapy works for some patients and types of cancers but not others, and
- develop new immunotherapies and powerful combinations of existing therapies.

We're testing tumor, blood, and bone marrow samples taken from patients treated on immunotherapy clinical trials to achieve these goals. The information we gather from analyzing these samples allows us to identify biomarkers that predict the likelihood that a patient will respond to currently available immunotherapies. This information can also guide our laboratory experiments aimed at finding new immunotherapy strategies.

Our platform's proximity to patients and our location within the world's largest cancer center enables us to bring cutting-edge immunotherapy trials and treatments into the clinic at a relatively quick pace, which is extremely difficult to achieve in an academic research center.

Success in our work requires collecting a large number of biological samples from patients. In addition, some of the state-of-the-art analyses we perform require fresh samples, so it's crucial that we have eligible patients nearby.

We also have a unique and multidisciplinary team of clinicians, physician-scientists, laboratory scientists and bioinformaticians — all of whom interact extremely closely. This collaborative effort provides real-time monitoring of

patients across many immunotherapy clinical trials for several cancer types.

These advantages allow us to seamlessly move immunotherapy discoveries from our research labs to our patients, and to test hypotheses generated from analyses of our patient samples back into the research lab for developing novel therapies. We view this process as being both "from bench to bedside" as well as the reverse, from the clinic back into the laboratory. This is only possible in a limited number of cancer centers.

Our platform leads path-changing studies that help uncover the complex biology of immunotherapies, in particular immune checkpoint inhibitors. Our accomplishments include:

- Discovering that the two primary immune checkpoint inhibitors used today, anti-PD-1 and anti-CTLA-4, affect the immune response in different ways.
- Conducting a clinical trial that led to the approval of anti-PD-1 therapy for the treatment of metastatic renal cell carcinoma, which is now the standard of care for these patients.
- Identifying how to predict whether a patient will respond to immunotherapy early during

treatment of metastatic melanoma, which is vital to delivering the right treatment to the right patient as quickly as possible.

- Providing preclinical data that supported the initiation of a clinical trial combining anti-CTLA-4 and anti-PD-1 therapy for the treatment of castrate-resistant prostate cancer, which was previously considered a bad target for immunotherapy.
- Providing immune monitoring data and expertise for a pilot randomized trial of perioperative anti-CTLA-4 and anti-PD-1 therapy for patients with resectable hepatocellular carcinoma, which had complete responders and, combined with platform data, led to a SPOR grant with two clinical trials in hepatocellular carcinoma.

Looking ahead, we would like to see immunotherapy applied earlier in treatment, in combination with traditional therapies, such as radiation, chemotherapy and targeted therapies. These sorts of combinations are already showing promise for eliminating cancer throughout the body and, with donor support, making immunotherapy available for more types of cancers.



*A conversation with platform leader,  
Samir Hanash, M.D., Ph.D.*

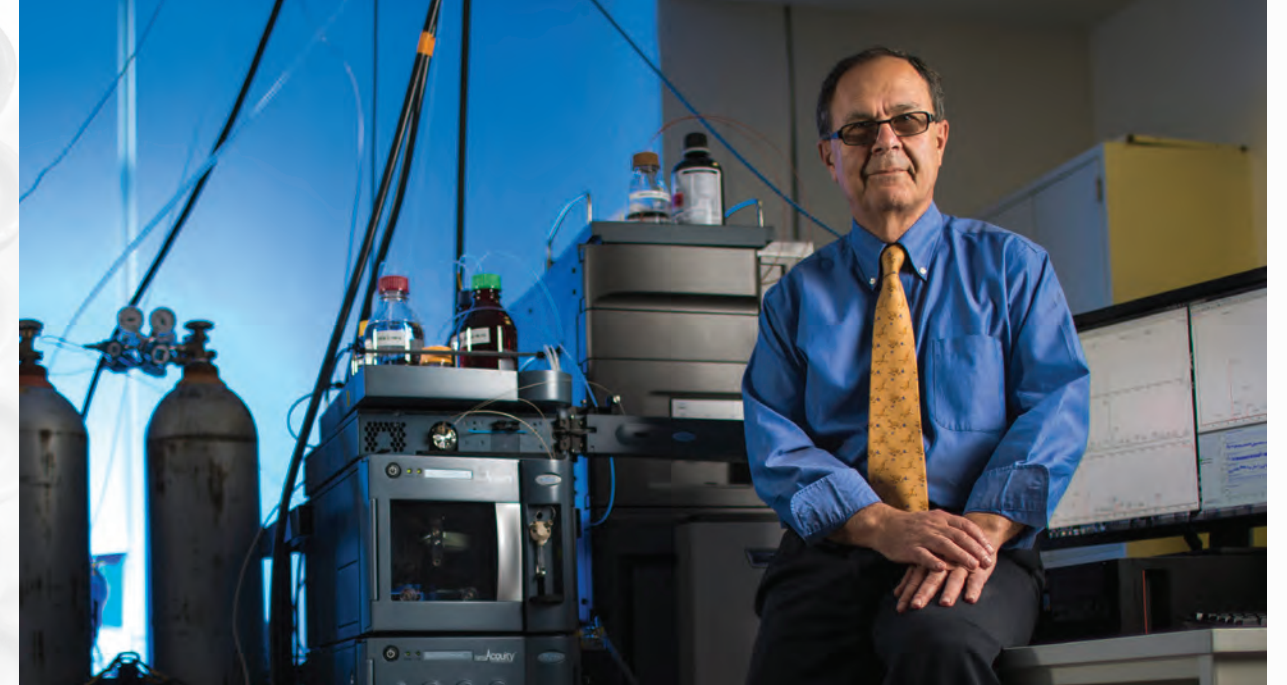
## PROTEOMICS

Proteins are the functional component encoded in the genome that are involved in virtually all aspects of cancer, from tumor development to progression and metastasis. Much emphasis in the cancer field has been on the genome and genetic mutations that lead to cancer. These mutations lead to changes in the downstream products of the cells, proteins and metabolites.

Although they are encoded in the genome, proteins and metabolites are highly dynamic. They are affected by many external factors and stimuli that may not be predicted directly at the genome level. This is why we believe it is so important to interrogate proteins and metabolites for their associations with altered states, such as cancer.

We rely heavily on mass spectrometers to dig deep into blood and tumor cells to find novel features that aid in diagnostics and treatment. From one drop of blood, we can get enough data to fill a laptop computer, and we use those data to develop early detection and treatment approaches that improve the lives of our patients.

The proteomics platform does in-depth analysis of biological fluids, tumor cells and tissues to find proteins and small molecules that can be used as therapeutic targets, early detection signals or biomarkers of cancer treatment



response for a number of disease types. In our work, we collaborate closely with several of the Moon Shot® teams to analyze a variety of cancer types including lung, colon, breast, ovarian, pancreatic, prostate, gastric, and leukemia.

With donor support, we've illuminated several features of cancer through the platform's work, such as how cancer cells transition from one state to another, a more metastatic state, and how we can better predict risk of developing lung cancer.

**As a result of platform discoveries, we launched a major trial with the Lung Cancer Moon Shot® to improve screening and early detection.** There are two components to the trial.

First, we aim to improve the interpretation of indeterminate nodules that are often found among patients that undergo computed tomography (CT) screening for lung cancer. In many cases, the CT scan is not able to provide a clear answer as to whether a nodule is cancerous or not. We hope that our blood test will be able to clarify those vague results without further invasive follow-up tests.

Secondly, we plan to determine the need for CT screening among subjects that currently do not

meet screening criteria based on their smoking histories. In fact, the majority of individuals that are destined to be diagnosed with lung cancer do not meet screening criteria. Therefore, if we can better determine cancer risk through a simple blood test, we could have substantial impact on lung cancer mortality.

We have obtained proof of principle through a blinded validation study that a blood test would outperform risk criteria based on smoking history. At present, we are doing additional validation with independent cohorts to further confirm the findings and ultimately obtain approval for the test from the Food and Drug Administration.

We are also advancing technologies which will allow us to study cancer-related proteins at higher and higher resolutions. We will continue to identify novel molecular features of cancer that contribute to improved risk assessment.

**We have active projects in this area at work with the Breast Cancer Moon Shot® and Pancreatic Cancer Moon Shot®.** Further, we are performing in-depth investigations of novel therapeutic targets we have identified to develop new immunotherapeutic approaches to treat a variety of cancers. We are excited to see these projects move forward to advances for our patients in the clinic.





## CANCER PREVENTION AND CONTROL

“I’ve been dealing with cancer my entire life. The idea that we can reduce people’s risk for cancer — that they may never have to endure chemotherapy or radiation — is pretty exciting to me.”

RUTH RECHIS, PH.D.  
DIRECTOR, BE WELL COMMUNITIES



The cancer prevention and control platform complements MD Anderson’s traditional efforts by working to advance public policies, educational programs and the delivery of community-based services at the population level in order to reduce cancer risk. Most importantly, we help MD Anderson address cancer risk factors where they concentrate — among underserved and less-connected sectors of the population.

### Be Well Communities

Be Well Communities™ is a place-based strategy for cancer prevention, meaning we work with specific communities to establish initiatives that improve wellness, which lowers the risk of cancer and a variety of other chronic diseases.

Ruth Rechis, Ph.D., is director of Be Well Communities. She was a young girl when her sister passed away from leukemia, so she’s familiar with the impact cancer can have on families. As a 25-year cancer survivor herself, she also knows the challenges of treatment and survivorship.

At just 15, she was diagnosed with Hodgkin’s lymphoma and went through six months of chemotherapy and radiation therapy. Although the treatments were successful, she now lives with a higher risk for breast cancer, cardiac issues and thyroid problems, and occasional skin cancers caused by the radiation.

Baytown, the third largest city in Harris County, was selected as the inaugural Be Well Community. The platform worked closely with the city to launch Be Well™ Baytown in November 2017. The initiative is led by MD Anderson and supported by ExxonMobil.

MD Anderson provides backbone support to more than 16 community partners in Baytown — individuals, schools, businesses,

government agencies and health care providers — to put evidence-based programs and solutions into effect. These programs target five areas known to increase cancer risk, including poor diets, low physical activity, tobacco use, excessive ultraviolet radiation exposure, and limited access to recommended preventive care and screenings.

Our goal is to take this gift of cancer prevention and put it into programs that will help people now and will be sustainable in the long term. These are programs, led by our partners, that are changing the culture of health within the communities where we work.

The Be Well Communities team draws upon the expertise of MD Anderson faculty as well as other programs within the platform, such as EndTobacco, to bring the best initiatives forward to the community.

Already in Baytown, Rechis notes evidence of behavior change, such as children eating healthier and being more physically active, and more produce being made available to Baytown residents. As programs expand and take root in Baytown, the platform is looking into launching similar initiatives elsewhere, tailored to the needs of that community.

### EndTobacco®

The EndTobacco program has a clear mission, evident in its name. As the leading cause of cancer and preventable deaths, tobacco use exacts a tremendous burden in the U.S. Through the leadership of Jennifer Cofer, director of EndTobacco, and with the generous support of our donors, the platform seeks to reduce youth smoking, limit exposure to secondhand smoke and increase cessation attempts among current smokers.

Cofer also is driven by a personal mission. Both her grandparents started smoking at age 13, so she grew up around cigarettes.



She battled personal health issues from secondhand smoke, but also became aware of the powerful addiction through her grandparents' struggle to quit smoking.

Motivated to make a difference for her grandparents and others, she chose to go into public health.

Public health gives Jennifer an opportunity to change the tobacco-control landscape, either through cessation, policy change, destigmatizing what smokers go through, or preventing kids from starting to smoke.

Unfortunately, both her grandparents succumbed to tobacco-related illnesses, but she was able to help them both successfully quit smoking.

Through EndTobacco, she and her team lead a variety of efforts to improve public policy, education, prevention and cessation services, both locally and nationally. They are implementing evidence-based actions in communities and across the state. These include partnering with universities adopting tobacco-free policies, and training health care providers to deliver best practices for tobacco-cessation treatment. For instance, EndTobacco coordinated with The University of Texas System to launch the Eliminate Tobacco Use initiative in 2016. Representatives from all 14 UT System institutions joined together to discuss best practices and policies, and by June 1, 2017, all 14 institutions were tobacco-free. The initiative continues to grow each year, and now includes additional universities across Texas and the nation.

EndTobacco also served as an educational resource to policy makers passing legislation to raise the minimum age for buying tobacco from 18 to 21, with the exception of those in the military. The program also established a program to train health care providers to deliver MD Anderson's state-of-the-art tobacco cessation approach to their patients.

These programs have the potential to save thousands of lives from tobacco-related disease, ultimately aligning perfectly with the goals of the platform and the Moon Shots Program® — to save lives through scientific discoveries.



Jennifer Cofer, MPH, CHES  
Director, EndTobacco Program



*A conversation with Moon Shot co-leader, Ann Klopp, M.D., Ph.D.*

# HPV-RELATED CANCERS MOON SHOT

One of the primary focuses of the HPV-Related Cancers Moon Shot® is on overcoming barriers to generating an effective immune response to HPV cancers. Because HPV cancers express unique antigens derived from viral proteins that tumor cells rely on to maintain their malignant state, these are theoretically the ideal targets for immunotherapy. Although checkpoint inhibitors have been approved for HPV-related cancers and have elicited improved outcomes in some cases, the rates of response have lagged behind expectations and immunotherapy fails in the vast majority of cases.

One of the important questions we want to answer is, "Why don't these work better?" With the help of donors, we are addressing a critical goal of the HPV-Related Cancers Moon Shot: to discover the mechanisms by which tumors evade immune response and to more effectively exploit the presence of these tumor-specific antigens.

To address this, we are looking at immune populations that recognize those HPV proteins. Using new technologies, we are studying the T-cell populations that recognize viral antigens in an effort to determine if they are absent, fail to infiltrate tumors, or are exhausted. Alternatively, we plan to investigate whether HPV-positive cancers are, in fact, failing to present these antigens in a way that the immune system can effectively recognize.

We are also working to determine why current immunotherapy isn't working. This knowledge will drive the next generation of trials. These may encompass new antibody approaches alone or in combination with therapeutic vaccines. Either way, a critical first step is our ongoing development of improved assays to

understand the immune response to HPV-positive cancers, which is our current focus.

Another way in which the Moon Shots Program has been critical to our efforts is through our access to serial analyses of HPV-positive cancers under treatment. In patients treated with radiation, we're learning that radiation works so well for HPV-positive cancers because it's increasing the number of activated T cells within the tumor. That's something we haven't been able to show before we were able to do these in-depth assays, using small samples of the tumors that we can acquire non-invasively. So now, we can see that the patients that respond well are the ones who are getting clonal T-cell expansion in their tumors. The question is, how can we get everyone to generate that response? That's where we are focusing our efforts as well — trying to understand the underlying mechanisms by which radiation is promoting these de novo anti-tumor T cell responses.

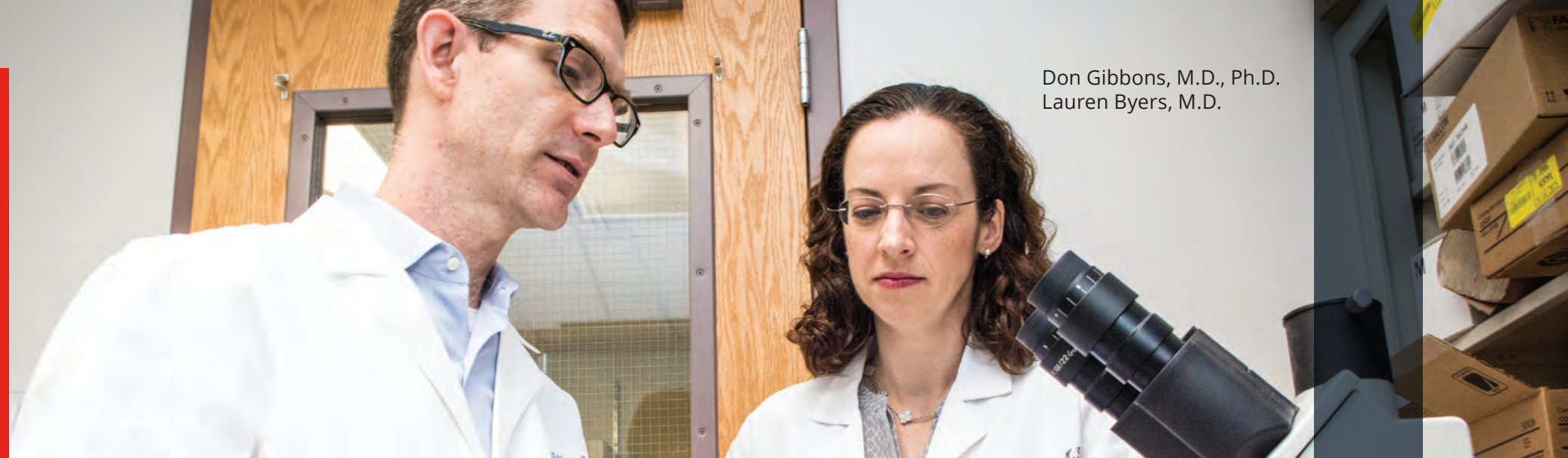
Lastly, our hope is to utilize a unique tissue banking and analysis resource we are building to understand the tumor microenvironment of both standard-of-care and immunotherapy patients, and how differences between patients' responses to subsequent therapies can be traced back to differences in either their tumors and/or their microenvironments.

The Moon Shots Program® has been incredibly helpful by providing funding for this type of comprehensive research. Moon Shots funding support has been critical to facilitate the collection and banking of the large number of samples required for this type of cross-site analysis. It supports our biological analyses and the necessary biostatistical resources to generate truly meaningful data that can help us treat patients more effectively.



*A conversation with Moon Shot co-leader,  
Don Gibbons, M.D., Ph.D.*

## LUNG CANCER MOON SHOT



Don Gibbons, M.D., Ph.D.  
Lauren Byers, M.D.

The Lung Cancer Moon Shot® team is committed to making new, patient-guided treatment options available for those that need them. To this end, and thanks to critical donor funding, the Genomic Marker-Guided Therapy Initiative (GEMINI) project collects clinical and molecular data profiles of all lung cancer patients treated at MD Anderson, regardless of the type of treatment they get or who their physician is. All of the patient information then goes into the GEMINI database.

The idea is to document the patient experience longitudinally over time and learn how they respond to their treatment. We then use the molecular data to learn from our patients and guide the most appropriate therapies. GEMINI has laboratory and clinical research components, both of which inform clinical trials based upon what we've learned.

There is a rapidly changing landscape in lung cancer, with almost two dozen new treatment indications in the last several years. With that, we are working to identify patterns and trends that tell us which of our patients are responding to which drugs. This allows us to rapidly identify subgroups that are more likely to respond or not respond well to standard therapies so we can bring new agents forward quickly, through strategic discovery efforts and clinical trials.

Originally, we wanted to slice up the pie and define all the molecular drivers of lung cancer. Of course, the pie has changed completely with the advent of immunotherapy. Now we're trying to do the same things with immunotherapy that we've done with targeted therapies. For the 20% of patients that respond to immunotherapy, why do they respond? For those that do not, why not? Can we identify molecular drivers or markers in the tumor microenvironment that differentiate these groups?

Overall we're using the GEMINI database in a variety of different ways. It's the central database for all patients on standard of care therapy as well as MD Anderson trials and even multicenter trials. We have an entire series of immunotherapy-based initiatives, like the ICON project, as well as NEOSTAR and LONESTAR trials, which use the GEMINI database to complement other study-specific data collected. It's always something central we can come back to, and continue learning the most we can to better treat our patients.

One of the best advancements we have made is with poziotinib, a previously failed EGFR drug that was resurrected by MD Anderson investigators. Our lab research indicated that it might be uniquely suited to attacking exon 20 non-small cell lung cancer. This really changed

the standard of care for a subset of lung cancer patients. We're hoping that in the next year, there will be an FDA approval.

We are also enthusiastic about many of our immunotherapy-based efforts. With the ICON project, we are working closely with the Translational Molecular Pathology Laboratory and others to perform immune profiling of early-stage patients who have had surgery. We have a large multidisciplinary team to deeply profile all of the tumors from these patients, and we're following those patients over time to match up their immune profiles with their responses to treatment.

From there, we have been able to launch the NEOSTAR, LONESTAR and other trials, using the infrastructure built through the Moon Shot. With these trials, we're learning if different immunotherapy treatments or combinations should be used to treat early-stage patients to potentially cure more patients before going to the operating room. This is the GEMINI effort around immunotherapy, and it has allowed us to bring these questions forward, rapidly translating new targeted and immune-based therapies into the clinic.

In addition to the internal collaborations made possible by the Moon Shots Program®, this voluminous database leads to preliminary data used in proposals for additional, external grant funding allowing us to really leverage the Moon Shots® support. The database has also been critical in engaging our industry partners. They see what we have in place with this database, and they know this data could help speed drug discovery or get the right drug to the right patients more quickly.



## 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 groups:

### **Institute for Applied Cancer Science (IACS)**

Developing impactful small-molecule therapies to effectively target tumor vulnerabilities.

### **ORBIT**

Advancing novel therapeutic antibodies that attack cancer cells or trigger immune responses.

### **TRACTION**

Conducting innovative translational biology to accelerate therapies into clinical trials.

### **Belfer Neurodegeneration Consortium**

Discovering therapies to treat neurological disorders and cancer-related cognitive conditions.

*A conversation with platform leader,  
Philip Jones, Ph.D.*

## IACS

Therapeutics Discovery has advanced a new small-molecule inhibitor of cancer metabolism to Phase I clinical trials. This new drug candidate marks the fourth novel therapeutic brought from concept to clinical trial by the division.

The drug candidate, IPN60090, targets glutaminase (GLS1), an important enzyme for metabolic energy production in the cell. **The small molecule, now being developed through a collaboration with the global biopharmaceutical company, Ipsen Biopharmaceuticals, was first discovered and developed by researchers in the IACS and TRACTION platforms.**

The first-in-human Phase I clinical trial in patients with advanced solid tumors began in March 2019 by enrolling and treating its first patient.

We are proud to see IPN60090 advance into clinical testing in partnership with Ipsen. This drug is the result of a significant collaborative effort to address unmet needs raised by our clinical colleagues, and it represents an innovative therapeutic opportunity for patients at MD Anderson.

**Much of the development of IPN60090 was made possible through collaborative relationships with researchers in the Lung Cancer Moon Shot® and Ovarian Cancer Moon Shot®.**

We announced a drug development partnership with Ipsen in 2018. Through the agreement, we

will progress IPN60090 through Phase I clinical development and Ipsen will be responsible for further global development and commercialization. This collaboration has expanded upon knowledge of the drug's mechanism of action and possible expansion to additional indications.

In addition to IPN60090, Therapeutics Discovery has several other therapies now in clinical trials. The first small molecule was IACS-10759, which is now in Phase I trials for patients with acute myeloid leukemia and a variety of solid tumors. **Two antibodies developed by the ORBIT platform also are now in clinical development and the Neurodegeneration Consortium is making rapid progress on the clinical development of new therapies for chemotherapy-induced peripheral neuropathy,** a common side effect for cancer patients who receive chemotherapy-based therapies.

In addition to these exciting clinical developments, Therapeutics Discovery is working in close collaboration with various Moon Shots® teams to advance several other novel therapies to clinical trial testing next year.

The robust pipeline and rapid development within Therapeutics Discovery speaks to the value of the group's unique model of drug discovery. We continue to strive each day to bring forward life-saving small-molecules, biologics and cellular therapies, inspired by the needs of our patients and made possible, in part, by our philanthropic partners.



*A conversation with platform leader,  
Dongxing Zha, Ph.D.*

## ORBIT

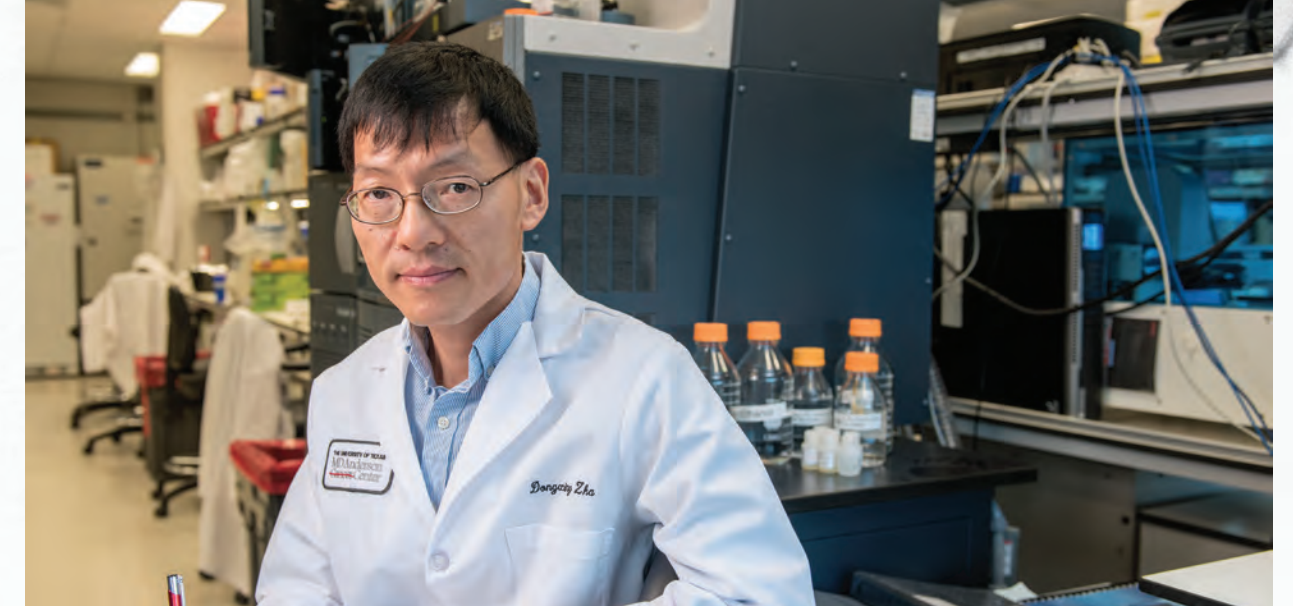
The Oncology Research for Biologics and Immunotherapy Translation (ORBIT) platform is an integrated group of drug development experts working to advance novel biologics and cell therapy that target cancer cells or stimulate an immune response. With donor support, and as part of the Therapeutics Discovery division, we work collaboratively with MD Anderson clinicians and researchers to avoid traditional barriers to biologics development and bring new therapeutics from concept to clinic, all under one roof.

**Working collaboratively with ORBIT and the Therapeutics Discovery division, leukemia researchers have advanced a first-in-class therapeutic antibody developed at MD Anderson into a Phase I clinical trial for patients with high-risk acute myeloid leukemia (AML), myelodysplastic syndromes (MDS) and myeloproliferative neoplasms.**

The antibody, known as h8F4, is a T-cell receptor (TCR)-like antibody that can kill leukemia cells by targeting PR1, a peptide found selectively on the surface of leukemia cells.

With support from Astellas Pharma Inc, the ORBIT platform advanced the clinical production, testing and development of h8F4.

We need new therapeutic options for AML to improve upon the standard chemotherapy treatment now available and bring lasting cures to more patients. While induction chemotherapy results in remission for roughly 70% of patients overall, many will experience



relapse and just 25% will be alive three-to-five years later.

The problem is that you cannot eliminate the leukemia stem cells that initiate the leukemia process. They are a rare population and are hard to eliminate with standard therapy. So we need something that has better outcomes, can help get rid of leukemia stem cells and is less toxic.

The PR1 peptide is normally found inside hematopoietic cells, the product of two protease enzymes. However, PR1 is selectively presented on the surface of leukemia cells by an immune-related protein called HLA-A2.

Recognizing the value of this as a leukemia target, researchers worked to develop h8F4, which binds PR1 in complex with HLA-A2 on the cell surface to induce death of the leukemia cells. In preclinical studies, h8F4 appeared to be effective at eliminating leukemia cells, particularly leukemia-initiating cells, in mouse xenograft models of human AML.

Based on preclinical data, ORBIT took responsibility for all aspects of drug development to advance h8F4 to the clinic. The platform completed all activities related to clinical drug chemistry, manufacturing and control, performed the necessary steps for Investigational New Drug (IND)-enabling studies, and completed safety, pharmacology and toxicology translational

studies. The ORBIT team also developed assays for pharmacokinetics and immunogenicity — the ability to provoke an immune response.

Through preclinical development and manufacturing work, the IND application was submitted and approved by the Food and Drug Administration. A Phase I clinical trial has opened and the first patient was treated in April 2019.

This is a great example of how a Moon Shots® platform can work together with MD Anderson clinicians that have been studying cancer biology for many years. We have a dedicated group that can complement our faculty's skill sets and enable the development of these products. We are really proud of this seamless collaboration to get this drug into the clinic.

ORBIT is now investigating alternative approaches to targeting PR1 in hematopoietic malignancies and other cancer types where it can be found. These include chimeric antigen receptor (CAR) approaches to target PR1 and overcome potential resistance to the h8F4 antibody.

Further, this approach broadens potential therapeutic targets by allowing researchers to go after proteins normally only found in the cell. We are now working to expand our pipeline of therapeutic antibodies for targets abnormally presented on the surface of cancer cells.





*A conversation with platform leader, Tim Heffernan, Ph.D.*

## TRACTION

The Translational Research to AdvanCe Therapeutics and Innovation in Oncology (TRACTION) platform supports the mission of MD Anderson by providing infrastructure, capabilities, and resources to evaluate translational hypotheses generated by investigators across the institution.

TRACTION is a core component of MD Anderson's Therapeutics Discovery division, a unique group of clinicians, researchers and drug discovery scientists working to develop innovative treatment options, inspired by the needs of patients and guided by the expertise of MD Anderson physicians. The platform functions as an industrialized translational research platform with the overarching goal of accelerating the translation of new knowledge into clinical impact.

Backed by philanthropic funding, our work covers a few major themes that aim to address several challenges we face in oncology drug discovery and development; namely the need for new targets, new mechanisms, new drugs, and better predictive platforms. We take a comprehensive approach that includes:

- Deploying disruptive technologies to identify and evaluate novel tumor dependencies.
- Performing fundamental mechanistic biology to explore new therapeutic or target hypotheses.
- Leveraging patient-centric translational platforms to identify which patients will most likely benefit from a given therapy.

Through our investment in patient-centric research, we have developed the infrastructure, platforms, and capabilities to enable collaborative translational research. By partnering with the drug discovery engines within Therapeutics Discovery, we aim to advance a portfolio of new medicines for our patients.

TRACTION is organized into cross-functional units that guide our research and development. Our Discovery and Innovation group employs technology platforms and advanced data analytics to evaluate new therapeutic concepts that fuel our early stage drug discovery pipeline. This group evaluates trends emerging from clinical data and seeks to understand the fundamental biological mechanisms of drug response, tumor heterogeneity and tumor evolution to uncover novel therapeutic concepts.

Our Target Biology group executes mechanistic studies on specific targets to advance our internal drug discovery and development portfolio from concept to IND filing. These studies inform on target biology, adaptive responses and mechanistic co-extinction, ultimately allowing us to formulate definitive hypotheses to guide clinical development.

Lastly, our Translational Biology team supports drug development by providing industry-scale disease modeling, translational biology, in vivo pharmacology and biomarker development capabilities. Through integration with disease site experts, this team curates a comprehensive, patient-centric toolbox of preclinical models for studies that guide clinical development and identify appropriate biomarkers of response.

TRACTION has established relationships across the institution in support of highly innovative

science aimed at addressing unmet clinical needs. Integration across MD Anderson is essential as our programs are enabled through symbiotic relationships that we have developed across basic, clinical and applied research disciplines, where we benefit from the expertise across MD Anderson to drive innovation around programs with the greatest probability of catalyzing transformative advances.

Over the last six years, we have collaborated with multiple Moon Shots® to generate pre-clinical data that have informed the design of several clinical trials, including novel and repurposed drugs as single-agent and combination therapies.

We have built on these successes to establish a number of exciting efforts ongoing with various Moon Shots teams. These programs span the drug discovery and development continuum, from target discovery through preclinical evaluation of new therapeutics. **Moon Shots collaborations have been critical to our success in advancing innovative therapeutic concepts within our own Therapeutics Discovery division, most notably, IACS-10759 and IPN-60090, two clinical programs developed in partnership with the Institute for Applied Cancer Science.**

**Most recently, we have partnered with the APOLLO platform, providing support to discover and develop new therapeutic concepts emerging from the rare tumor initiative.** A second area of interest is focused on enhancing our understanding of the biology of brain metastases to identify novel strategies that could be used in the new MD Anderson Brain Metastasis Clinic. Both of these initiatives rely on multidisciplinary teams that represent unique areas of strength at MD Anderson.



*A conversation with platform co-leader, Katy Rezvani, M.D., Ph.D.*

# ADOPTIVE CELL THERAPY

Natural killer (NK) cells distinguish between normal cells and abnormal cells, such as those that have become cancerous or infected by a virus. NK cells continuously patrol the body to look for these abnormal cells and destroy them.

The adoptive cell therapy (ACT) platform uses the inherent ability of NK cells to recognize cancer and build on that by giving them the ability to seek and destroy cancer cells that have made themselves invisible. It's akin to arming a fighter jet with a heat-seeking missile. The platform has pioneered the use of chimeric antigen receptor (CAR)-modified NK cells for treating cancer. We isolate NK cells from umbilical cord blood and genetically engineer them to introduce a CAR, which recognizes a target on the surface of cancer cells. These CAR NK cells are then manufactured and given to patients.

CAR NK cells are administered to a patient in two phases. First, we give conditioning chemotherapy for three days to prepare the patient's body for the cell infusion. After two days, we infuse the CAR NK cells in just the same manner that we would give a blood transfusion. Then, we wait for the cells to do their job.

Perhaps the biggest advantage of CAR NK cells is that they do not cause graft-versus-host disease (GVHD), a devastating condition caused by donor T cells attacking healthy cells in the recipient. Because NK cells don't cause GVHD, they can be given from a donor to a recipient without any requirement for matching. That means from one donor you can make multiple doses of CAR NK cells to treat multiple patients.

In fact, we have shown that we can manufacture hundreds of doses of CAR NK cells from a single unit of cord blood. Ultimately, our plan is to freeze and store these CAR NK cells in a cell bank so that when a patient comes to the clinic, we can take those CAR NK cells immediately from the bank to treat the patients, making this a truly off-the-shelf-product. So, the time from diagnosis to treatment is significantly shorter.

So far, we've treated a small number of patients and, thus far, we have not observed any long-term side effects, nor does it appear to be impacting our patients' quality of life.



The ACT platform is working in collaboration with several Moon Shots® to translate the cell therapies that we have developed in the research lab to the clinic. **For instance, the CAR against CD19, which is what's currently in the clinic for the treatment of patients with CLL, non-Hodgkin's lymphoma and ALL, was initially developed in collaboration with the CLL Moon Shot® and the B-Cell Lymphoma Moon Shot®, together with the support and expertise from the ACT platform.**

This support enabled us to translate preclinical work to develop the procedure for CD19 CAR NK cells in the GMP facility, which allowed us then to take them into the Phase I/II clinical study we're now conducting.

In the lab, we are continuously striving to innovate. For us, going after CD19 was a proof of principle. We wanted to show that the CD19 CAR NK cells are going to be at least as effective as CD19 CAR T cells in terms of efficacy. We've shown that they are as effective and that the safety profile is even better than what we have observed with CAR T cells. Obviously, with the added advantage that the cells can now be generated as an off-the-shelf product.

We are very interested in targeting other types of cancer in collaboration with multiple Moon Shot teams and other investigators at MD Anderson. We've now developed CARs against 10 different types of cancer that we are testing and validating pre-clinically, with the ultimate goal of translating these to the clinic.

The Moon Shots Program supported the CAR NK concept from birth. Early on, we couldn't get grant funding from any of the funding agencies because they believed that this approach was too risky and unlikely to work. The Moon Shots Program supported it from its preclinical development all the way to the current clinical trials. In fact, we recently reached a licensing and research agreement between MD Anderson and Takeda, who will now collaborate to bring this innovative cell therapy forward.

Without the Moon Shots Program® and the philanthropic support that catalyzes it, we certainly would not have been able to develop this therapy for our patients.



*A conversation with Moon Shot researcher, Simona Colla, Ph.D.*

# MDS and AML MOON SHOT

The incidence of myelodysplastic syndromes (MDS) in the U.S. is between 15,000 and 45,000 new cases diagnosed every year. Associated with aging, the majority of cases occur in people 65 years and older. Therefore, we expect the incidence to increase dramatically in the coming years because our population is living longer and many more people will be in this age group.

The situation is a bit different for acute myeloid leukemia (AML). It also occurs more frequently in older people, but young people may be diagnosed with it as well. Each year in the U.S., about 13,000 new cases are diagnosed and there are about 10,000 deaths.

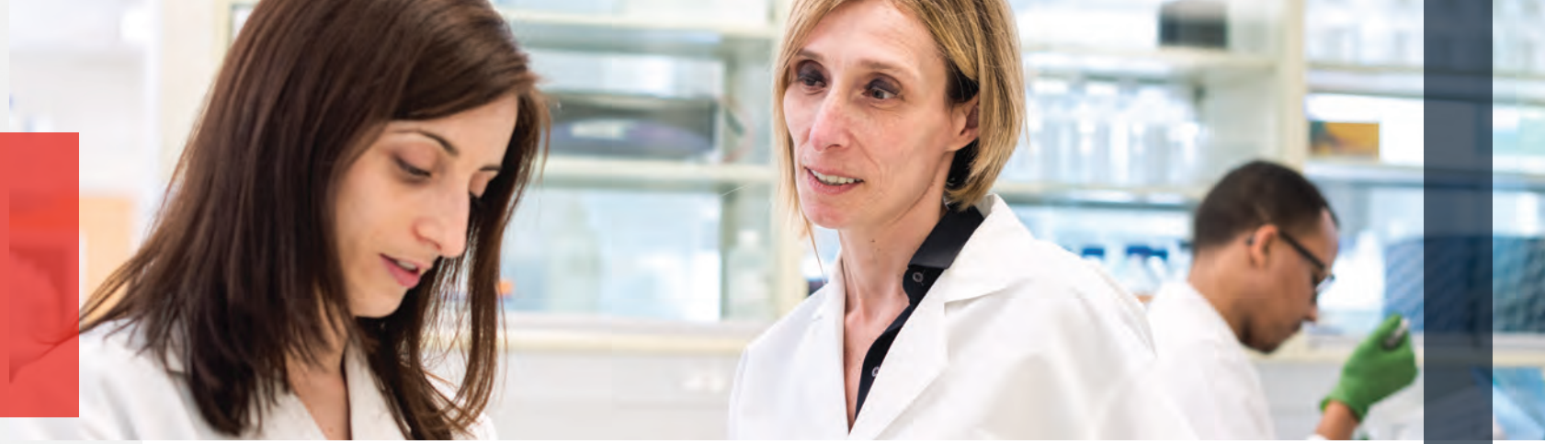
The goal of the MDS and AML Moon Shot is to understand the underlying biology of these diseases in order to find new treatment options to improve patient outcomes and ultimately cure these diseases. This immense effort is possible, in part, because of our generous donors.

Currently, the only curative treatment for MDS and AML is stem cell transplantation. Unfortunately, many patients are unable to receive stem cell transplants because suitable donors are unavailable or there is a risk of serious side effects, such as viral infections or graft versus host disease. Members of our team are working to expand the population of MDS and AML patients who can receive stem cell transplants while also conducting research into ways to reduce or eliminate possible side effects, decrease the risk of relapse and improve patient outcomes.

Many patients with MDS become cytopenic, meaning their bone marrow cannot produce

mature blood cells, so these patients have a very low number of neutrophils, platelets and red blood cells, and a large number of immature blood cells known as blasts. They are often dependent on blood transfusions to survive, particularly in the early stages of treatment. The standard of care for MDS is therapy with hypomethylating agents (HMAs). If a patient responds to HMAs and their body begins producing mature blood cells again, they might not need continued transfusions. However, the majority of patients eventually stop responding to treatment. When that happens, patients may die from their cytopenias or they may progress to AML. When HMA treatment fails or patients progress from MDS to AML, there are few available treatment options. Therefore, there is an urgent need for the development of new standard of care treatments, in addition to treatments for patients for whom HMA therapy has failed.

Our team of researchers and physician-scientists discovered that treatment with HMAs does not necessarily eliminate all of the cancer stem cells in the bone marrow that give rise to the disease. The therapy works downstream, on the more mature cell populations in the bone marrow, but not on the stem cells that originate the disease. If you have the stem cells that give rise to disease remaining after treatment, these cells will eventually become resistant, acquire new genetic alterations and expand, leading to treatment failure and relapse. We therefore need to understand what the mechanisms are that drive HMA treatment failure and are responsible for disease progression. To this end, we performed in-depth molecular profiling to identify these cells, often working with as few



as 500 cells from each patient's bone marrow. Through genomic and genetic analyses, we are beginning to understand the characteristics of the cells that make them resistant to HMAs. With this understanding, we are beginning to develop new strategies to target and eliminate these specific disease-generating cells, with the goal of preventing treatment resistance and relapse.

We recently discovered that there are two subgroups of MDS, each with a distinct stem cell population harboring specific alterations. We have identified potential vulnerabilities for each subgroup of MDS, and are now trying to target these vulnerabilities with specific drugs.

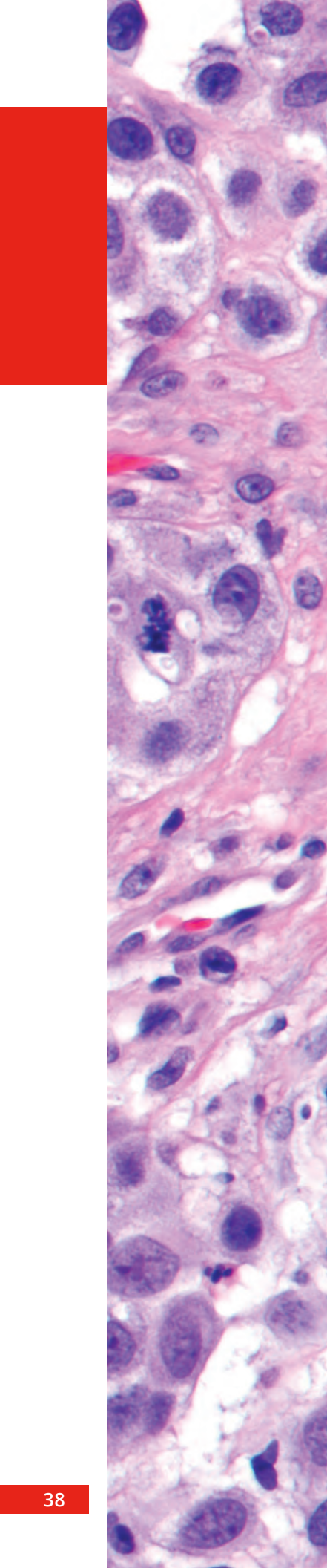
We are currently designing pre-clinical research studies to test targeted treatments based on the molecular characteristics we identified through our genetic profiling efforts. We want to target the cells of origin for MDS and AML in order to prevent the diseases from relapsing or progressing following treatment. Since we have identified distinct subgroups of patients with MDS, we are also developing multiple strategies

to target MDS stem cells, based upon patients' unique characteristics.

Since MDS and AML are tremendously heterogeneous diseases, we need to analyze a large number of samples throughout the course of the diseases in order to gain a true understanding of their underlying biologies. MD Anderson has the largest MDS and AML clinic of its type in the world. This large, diverse patient population, in addition to our library of thousands of archived samples, provides us with the ability to undertake large-scale analyses to understand the origins of this devastating disease.

**MD Anderson and the Moon Shots Program® also provide us with the top talent and unparalleled resources, including opportunities to collaborate with researchers across platforms, such as the Cancer Genomics Laboratory and adoptive cell therapy.** These collaborations allow us to rapidly sequence and analyze genetic mutations in our patient samples, and to generate high-quality manufactured products for our stem cell transplantation clinical trials. We are grateful for the opportunities such collaborations provide.





*A conversation with Moon Shot researcher,  
Rodabe Amaria, M.D.*

# MELANOMA MOON SHOT

Melanoma is one of the most genetically-mutated tumor types, making the cancer aggressive and its treatment challenging. To further complicate matters, the nature of these abnormalities can be diverse, can differ from patient to patient and can influence how a patient responds to treatment. The Melanoma Moon Shot® team is developing clinical trials to exploit the weaknesses of these tumors. We are honing in on a treatment strategy that is changing the standard of care for many melanoma patients.

Neoadjuvant therapy (treatment before surgery) has proven effective for several cancer types and is increasingly common as a treatment approach. However, we have not widely studied this form of treatment for melanoma. This is beginning to change with the emergence of effective treatment options.

We look forward to a number of clinical trials that represent the most impactful projects performed by the Melanoma Moon Shot this past year, focusing on high-risk stage 3 melanoma. A pair of targeted therapies given before and after surgery for melanoma produced at least a six-fold increase in time to progression compared to standard-of-care surgery for patients with stage 3 disease. Early results of this study, comparing surgery to pre- and post-surgical treatment with the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib, were so strikingly positive that the trial was halted and changed to a single-arm using the combination. This shows the vast potential of this treatment strategy.

Melanoma Moon Shot investigators are also responsible for a larger push towards further investigation of neoadjuvant treatment regimens. In fact, an international consortium — the International Neoadjuvant Melanoma Consortium, co-led by Melanoma Moon Shot investigators, has published a series of best-practice recommendations for conducting clinical trials for neoadjuvant therapies in patients with locally advanced melanoma. The recommendations



cover clinical trial design, including patient inclusion criteria, treatment duration, statistical endpoints, surgical considerations, and biospecimen collection and analysis. These guidelines are intended to align the field with standard practices that will maximize the impact of neoadjuvant trials by pooling study data and more rapidly bringing effective therapies to patients with earlier stage disease.

The advantage of a neoadjuvant approach in this setting is that it enables an interval evaluation of the tumor cells after therapy to determine the extent to which those tumor cells responded to the therapy in real time and predict which patients are likely to experience durable responses going forward. It also provides us the tissue resources to determine why tumors may not respond to therapy and thus tailor therapies going forward as we learn more about resistance.

We are also excited to explore immune checkpoint blockade, a therapy pioneered by immunotherapy platform co-leader James Allison, Ph.D., in the neoadjuvant setting. This immunotherapy has been effective against metastatic melanoma and in reducing the risk of relapse after surgery for high-risk stage 3 disease. However, there is evidence in preclinical models that neoadjuvant checkpoint blockade treatment may be superior to giving these agents in the adjuvant setting (after surgery). The challenge is to translate preclinical findings and create the most high-impact clinical trials to

learn as much as possible and refine the therapeutic regimens our patients desperately need.

And we are doing just that. One recent example of a high-impact neoadjuvant study with immense potential is a Phase II trial of nivolumab plus the CTLA-4 checkpoint inhibitor, ipilimumab. Each drug blocks a separate off switch on T cells, freeing the immune system to attack cancer. This is the first randomized neoadjuvant clinical trial of immune checkpoint blockade for melanoma patients.

Results of the Phase II study were extremely promising. With the checkpoint blockade combination, 73% of patients had their tumors shrink, 45% had no evidence of disease at surgery (pathological complete response) while 73% had grade 3 side effects, causing dose delays in 64% and delaying surgery for some. The results show the need to optimize therapeutic regimens to reduce toxicity, but the patient responses demonstrate the feasibility of this approach.

With a standardized set of best practices for neoadjuvant melanoma trials, the Melanoma Moon Shot team has helped establish an ideal setting to study biomarkers of response and mechanisms of resistance, setting the stage with a data-rich trial platform to keep the field moving forward and bring more effective treatments to patients as early as possible in their diseases. We are thrilled to initiate more innovative combination treatment approaches in the future, and we are grateful for the funding from our donors that power the Moon Shot®.



*A conversation with Moon Shot co-leader, Shannon Westin, M.D.*

## OVARIAN CANCER MOON SHOT

Ovarian cancer is the most lethal gynecologic malignancy. Although survival times continue to improve, the mortality rates for this disease remain unacceptably high, and the cure rates have not increased. With help from our philanthropic partners, the Ovarian Cancer Moon Shot® is working on innovative treatment strategies that will yield lasting results and cures for more patients.

For patients with a new diagnosis of ovarian cancer, treatment generally will include a combination of surgery, chemotherapy, and perhaps immunotherapy. However, the sequence in which patients should receive those therapies has been highly variable. We know that the one-size-fits-all treatment paradigm does not work. We have developed an effective approach for determining which patients should have surgery versus chemotherapy first.

Despite aggressive therapy upfront, most patients unfortunately develop relapse of their cancer. Therefore, we are implementing new approaches for “maintenance” therapy, which are aimed at increasing survival times and preventing recurrence. These include testing new immune therapies.

The other issue is identifying the appropriate treatment when patients recur. Targeted therapies such as PARP inhibitors and bevacizumab have shown substantial promise and some of these drugs have been granted FDA approval based on work done by our Moon Shot® investigators. Unfortunately, the cancers eventually become resistant to these drugs and one of our major projects involves work to understand, overcome, and prevent such resistance. We have completed several clinical trials that address this problem and more are planned.

Specifically, with regard to PARP inhibitors, we have examined human tumor material before and after treatment to identify additional drug combinations. This information, coupled with laboratory models, has led to promising clinical trials. We established the Combinatorial Adaptive Resistance Treatment (CART) program, which allows us to test tissue from patients, and then further test possible combinations in the lab.



We start with early phase trials to make sure we can target these pathways safely and then push that out into larger trials.

One of the most exciting projects within the Moon Shot involves a very large Phase IB trial, investigating the combination of a PARP inhibitor with two agents targeting the PI3K pathway. We saw great success with regard to sustained responses. For example, we have a patient who has been on treatment for almost four years now. This was a woman who had multiple cancer recurrences, and multiple lines of prior therapy. Now, she has been able to function very well and is providing support to other patients. Also from that particular trial, we were able to build our next trial, a PARP and MEK inhibitor in appropriately selected patients.

Similarly, we have been able to develop new combinations for targeting the blood supply (anti-angiogenesis) to cancer. Work done by our Moon Shot® investigators led to the development of a new therapy which has shown remarkable effectiveness for patients with relapsed disease and is now being moved into large scale clinical trials. Intraperitoneal immune checkpoint inhibitor is a previously unexplored area of clinical investigation that has many attractive features. Immune checkpoint

inhibitor administration could potentially improve the immune-related side effects of these drugs by resulting in more cancer-specific and less off-target immune activation. In addition to higher local (peritoneal) and lower drug concentration levels in the blood, other potential advantages include better effects on the tumor in the abdominal cavity. The pelvic and peri-aortic retroperitoneal lymph nodes are the draining lymph organs for the peritoneal cavity, and as such, are the expected site for enhanced immune cell activation following immune checkpoint blockade.

Another exciting and innovative feature of this immunotherapy clinical trial is the opportunity to obtain samples from near the tumor (ascites) which will allow us to understand how this treatment works. All patients undergo placement of a port in the abdomen, which allows both infusion of the immune drugs and aspiration of peritoneal fluid. These strategies will lead to the next generation of combination immune therapy trials.

We could not carry out this work without the Moon Shots Program® and its benefactors. We look forward to further expanding the work to improve outcomes for women with ovarian cancer.





*A conversation with Moon Shot researcher, Eugene Koay, M.D., Ph.D.*

## PANCREATIC CANCER MOON SHOT

Pancreatic cancer is a very aggressive malignancy that might appear to be confined to the pancreas, but has often already metastasized upon diagnosis. This spread may be microscopic in nature, such that it is undetectable on CT or MRI scans in the liver or elsewhere. Among our many efforts, the Pancreatic Cancer Moon Shot® is working to improve the use of therapies before surgery to treat metastatic cancers and improve outcomes for our patients.

Surgeries for pancreatic cancer are generally highly morbid. Most of the time, patients require a procedure called a Whipple surgery, which can have devastating effects. And if a patient has metastatic disease at the time of surgery, this life-altering operation may actually be of no use.

To address this, oncologists have adopted a therapies protocol known as neoadjuvant therapy. The idea with neoadjuvant, or

pre-surgical, therapy is to give some chemotherapy to try to kill off those individual cells that we suspect are there and to shrink the tumor. Then, we are able to identify patients who respond well to treatment, and can properly treat the ones we think have a cancer confined to the pancreas and should benefit from surgery.

MD Anderson surgeons, medical oncologists and radiation oncologists were among the first to push this concept forward in pancreatic cancer. That's been our approach to treating the disease for about two decades, and it seems that more and more practices are beginning to adopt this concept. There are clinical trials now also showing promise with the neoadjuvant approach.

Most experimental trials for pancreatic cancer are done for patients with late-stage, metastatic disease as opposed to the early stage,

pre-operative space. There just aren't as many patients diagnosed with earlier-stage disease, so it's hard to do conduct those trials.

The platform trial structure of our Moon Shot® is a Phase II randomized study that allows us to gain some efficiencies over the typical trial design. Patients on the trial will be randomized to either a control arm, which is standard neoadjuvant therapy followed by surgery and/or radiation, or an experimental arm, which is standard neoadjuvant therapy plus the treatment we are investigating.

On the platform trial, you can add experimental arms over time while maintaining the same control arm. This way, you don't have to replicate the control arm each time you test a new experimental therapy. In a traditional approach, five experimental therapies would require five distinct control arms. With the platform trial, we have a single control group that can be expanded and adapted over time as needed, or as standard of care changes.

Also, because we are removing the tumors at the time of surgery, we can analyze the pathological response rate at that time. This is the primary endpoint of our trial, rather than progression-free or overall survival. For those endpoints, you must follow the patient until the cancer comes back, which requires much more time. With pathological response as our primary endpoint, we can eliminate trials which are failures and replace them with new candidates or combinations.

By looking at the tumor under the microscope and gauging how the cancer cells have died off after neoadjuvant therapy, we get an early readout of outcome to allow us to accelerate research and translate our findings to patients faster. We've shown that pathological response rate is a good predictor of overall survival in pancreatic cancer, so that's why we chose this as our endpoint.

With neoadjuvant therapy, our intent is to be able to take the patient to surgery, remove the entire tumor from the pancreas and then analyze it. This allows us to study biomarkers, protein levels, gene expression, mutations and a number of different things happening at the microscopic scale to understand how the drug is actually working.

Our hope is that by doing this, we can gain some insight that we can apply to the vast majority of patients with metastatic cancer. For example, we may find biomarker signatures that help us eventually select a particular therapy for a particular patient who will most benefit from that drug.

We feel this platform trial will establish a basis to investigate new therapies for this deadly disease and finally make significant strides forward in our goal to improve outcomes for pancreatic cancer. Thanks to our donors, the Moon Shots Program® has been instrumental in supporting our aim to make an enduring impact for patients at MD Anderson, our network, and beyond.



*A conversation with Moon Shot researcher, Ana Aparicio, M.D.*

# PROSTATE CANCER MOON SHOT

Prostate cancer is the most common cancer diagnosed in American men, and the second leading cause of cancer death in men. While hormone-based therapies are effective for many men, there remain an estimated 20% of patients who will not benefit and have significantly worse outcomes.

These patients have a subtype of prostate cancer known as aggressive variant prostate cancer (AVPC), which does not respond to therapies that block androgen receptor (AR) signaling.

Developing a better understanding of AVPC and identifying new therapeutics options is a major focus of the Prostate Cancer Moon Shot®.

Most prostate cancers are driven by androgens, and these typically respond very well to hormonal therapies, which are the backbone of prostate cancer therapy. However, AVPCs do not respond well to hormonal therapies. They also grow and spread more rapidly, often to places prostate cancer doesn't typically spread. Because of this, and because patients have fewer treatment options, their prognosis is much worse than that of the typical prostate cancers.

Unlike other cancers, with prostate cancer, we don't have biomarkers that can classify it into its different subsets. With prostate cancer, even though we can see in the clinic that it is a heterogeneous disease, we call it one name and we treat it like it is one disease.

The problem with this is that if you have a therapy that might greatly benefit one of those subsets, but not the others, and you test it in everyone, you dilute its effect and most of the time, you end up with a negative clinical trial. But even if your clinical trial is positive, you are now going to subject many people that are unlikely to benefit to potentially toxic treatments. Therefore, a big effort of our Moon Shot® has been to try to classify the disease into its therapeutically relevant subsets so that we can make progress more efficiently.

With the support of the Moon Shot, we developed a molecular signature for the AVPC and found that men whose tumors had this signature benefitted greatly from the use of platinum-based chemotherapy. We're working to get this molecular signature into a CLIA-certified assay so that we can use it to select patients for clinical trials and to help guide patients' treatment. In parallel, we have devoted a major effort to define biologically relevant subtypes of AVPC and, in a major new development, identified robust transcriptional signatures that enable the definition of two forms of AVPC: mesenchymal and stem-like prostate cancer and neuroendocrine prostate cancer. We are now focused on trying to dissect the heterogeneity within these aggressive variants. Our overall goal is to define these different subsets molecularly and work to identify therapeutic vulnerabilities within each.



**We look forward to working with the Therapeutics Discovery teams to develop new medicines based on what we learn so that we have more effective treatment options for our patients with AVPC.** This will be an important step in helping us to develop a therapeutic plan for our patients. There's a distinction to be made — there is drug development and then there is therapy development, which is about how you combine or sequence treatments, which may not all be drugs.

For example, one of our questions is whether the primary tumor of a patient presenting with de novo metastatic disease, should be treated. For patients with AVPC, we think that treating the primary tumor may help to control the cancer down the line, whereas we don't believe this is beneficial to patients with typical prostate cancer. We're actually conducting a Phase III trial to help us answer that question.

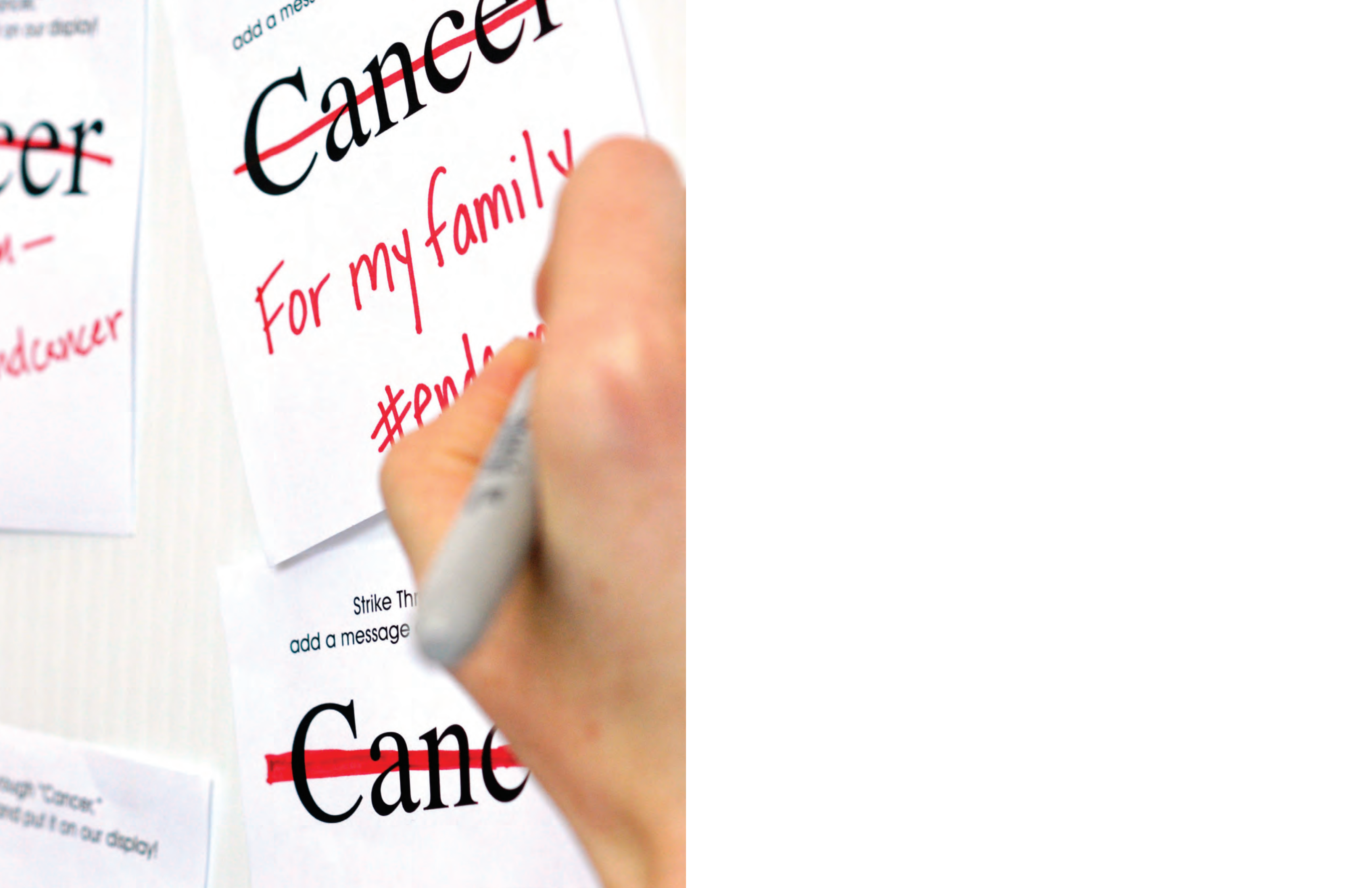
So it's not all about drugs. It is about optimally integrating the therapies that are available or are in development, in an effort to control the disease definitively. To this end, we need to understand what our treatments do to the biology of the tumor. Each of these treatments we're giving to our patients is changing the biology of their tumors, so understanding what the best sequences and combinations of those treatments are, will be key to improving outcomes.

One avenue that we have recently opened up is understanding the particular immunological features of AVPC. **We are collaborating with the immunotherapy platform to define the immune profile of these aggressive variants and see how we can harness the immune system to address this subset.** Exciting new results indicate that myeloid suppressor cells that are abundant in AVPC reduce the efficacy of immunotherapy in this form of the disease. And we are designing clinical trials to assess the efficacy of compounds that reverse immunosuppression.

The Moon Shots Program has been key because it's provided a strong framework to ask the right questions and put together the right investigators. There are lots of questions related to AVPC, and the biggest value has been our ability to build a framework in which everyone is contributing their piece of the puzzle. It fosters collaboration within our team of investigators, which is key. We can't do it alone.

We've also received support to conduct a number of the correlative and preclinical studies that helped us arrive at the definition of the AVPC molecular signature. It's hard to get extramural funding for this type of research, but you need this information to generate hypotheses that lead you to the next step. We so appreciate our generous donors, who help make this possible.





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