MOON SHOTS PROGRAM® REPORT

FISCAL YEAR 2021

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

YOU ARE THE CATALYST

Launched in 2012, the Moon Shots Program® is a comprehensive effort to significantly reduce deaths and transform cancer care. Moon Shot teams pursue innovative projects prioritized for greatest patient impact. Specialized platforms provide infrastructure, systems and strategy. And all of this is driven by philanthropy. We are proud to present the Fiscal Year 2021 Moon Shots Program Report, which describes how each Moon Shot team is moving the needle for our patients over the course of the last year, with your help.

Through your generous support, patients at MD Anderson are receiving improved treatments, such as cellular therapies, targeted drugs, combination regimens and immunotherapies.

Philanthropy is driving our ability to detect cancer earlier, when it is much easier to treat, by helping to fund research into biomarkers, like circulating tumor DNA. This focus also helps us better predict when patients may relapse, so that we can be prepared with a plan.

We know that many cancers do not consist of just one type of mutated cell, but many subtypes. And donors like you provide the funding that allows us to establish and refine these definitions, which allows our doctors an opportunity to attack these subtypes based on their particular weaknesses.

Your incredible giving has aided in our understanding that the makeup of the bacteria in a patient's gut — the microbiome — can either increase or decrease the effectiveness of cancer treatments.

You are the catalyst for our ability to treat our patients with the most advanced therapeutic plans available anywhere. Your visionary investment contributes to our ability to attack cancer as a unified force, with a genuine team-science mentality that accelerates research efforts, so that we can get them to patients as quickly as possible. The support of our donors has seeded many of the leading-edge advancements that make MD Anderson the first place people think of when they learn they have cancer.

On behalf of everyone in the Moon Shots Program, from the lab assistants who may become future leaders in oncology, to the program leaders who have dedicated their lives to peeling back the layers of the cancer conundrum, we extend to you our most heartfelt gratitude for all that you have done for our patients and community.


Falcon
Graduated Pipet Tips

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B-CELL LYMPHOMA

MOON SHOT

Cellular Therapies

The Moon Shot® envisions developing and improving patient-specific treatment strategies by enhancing immune cells through cellular therapy — specifically, we are pursuing next-generation engineered NK cells for lymphoma patients after CD19 CAR T cell therapy failure, and we are improving efficacy and affordability of CAR T cell therapy for B-cell lymphomas.

In collaboration with the adoptive cell therapy platform, we are developing cord blood-derived natural killer (NK) cells to generate CAR-modified NK cells. These laboratory-engineered NK cells with enhanced anti-tumor activity can then be infused into the patients. They are immediately available "off the shelf," making this approach remarkably safer, and more cost-effective than standard CAR T cell therapy. The preclinical data validate that CD19 CAR NK cells are as effective and much less toxic than the available CAR T cells. We are currently evaluating the potential of this approach in a Phase I/II clinical trial. Additionally, our team has devised and published a strategy to generate fourth-generation "armored" CAR engineering of cord blood-derived NK cells to boost their functions. The efficacy of this approach is currently under investigation.

> The goal of the B-cell Lymphoma Moon Shot is to use clinical, translational and basic science approaches to double the cure rate of patients with B-cell lymphoma.

We are also developing novel, off-the-shelf, "infinite T cells" to improve the efficacy and affordability of CAR T cell therapy for lymphoma patients. Infinite T cells have the potential to revolutionize the field of adoptive T cell therapy for lymphomas as well as other hematological and solid tumor malignancies and infectious diseases.

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

Lymphoma is the most common hematological malignancy, and B-cell lymphoma accounts for 85% of all lymphomas. In the U.S., there are 700,000 patients currently living with this disease, and nearly 80,000 new lymphoma cases are diagnosed each year. Approximately 21,000 lymphoma-related deaths occur annually. If not cured by frontline therapy, B-cell lymphoma becomes progressively more resistant to therapies, and most relapsed patients die from progressive disease. The goal of the B-cell Lymphoma Moon Shot® is to use clinical, translational and basic science approaches to double the cure rate of patients with B-cell lymphoma.

This approach would reduce the cost of CAR T cell therapy, giving us the ability to rapidly generate cells that retain their function long term.

Tailoring Treatments

The Moon Shot is supporting another key initiative of our B-cell lymphoma scientists — epigenetic targeting of B-cell lymphoma and the development of a patient-derived xenograft repository. The goal is to supplement the preclinical studies that will directly translate into clinical trials by providing the model for testing novel therapeutic strategies to tailor/develop personalized interventions.

Targeting the same goal, albeit, with a unique perspective, our Moon Shot experts are exploring the gut microbiome landscape — composed of bacteria, both good and bad, that live and coexist inside of humans — to understand its impact in response to CAR T cell therapy and ways to manipulate it to improve treatment outcomes tailored to individual patients. We are rolling out a multicenter study to investigate and validate microbiome configurations and effectors in CD19 CAR T cell therapy efficacy and toxicity.

Concurrently, we are working to prevent resistance through targeted therapy, specifically through improving the efficacy of pirtobrutinib, to overcome resistance in mantle cell lymphoma. Recently, MD Anderson led the first and only pirtobrutinib trial in mantle cell lymphoma patients. Our team is taking it to the next level to study the mechanisms of action and resistance, and develop novel therapeutic strategies aimed at improving patient outcomes.

The therapies, scientific discoveries and assays developed by our team will help overcome therapeutic resistance and improve outcomes of patients with B-cell lymphoma. We are incredibly grateful to each of our donors, whose generosity continues to catalyze the work we do for our patients.

BREAST CANCER

Program Leaders: Junjie Chen, Ph.D., Kelly Hunt, M.D., Debu Tripathy, M.D., Maia Rauch, M.D., Ph.D., Clinton Yam, M.D.

The bold goal of the Breast Cancer Moon Shot® is to create a precision medicine program for the neoadjuvant, or pre-surgical, treatment of triple-negative breast cancer (TNBC). TNBC is a heterogeneous subtype of breast cancer that lacks expression of estrogen receptor (ER), progesterone receptor and human epidermal growth factor receptor 2 (HER2). TNBCs account for approximately one out of every five breast cancer diagnoses. About 40% of TNBC patients undergoing neoadjuvant therapy have an excellent response and favorable long-term prognosis. However, patients who are not free of invasive disease at the time of surgery have dismal long-term outcomes.

Leveraging Patient Data

Pathologic complete response after neoadjuvant therapy in TNBC is associated with improved survival, thus the timely prediction of response provides a unique opportunity to personalize therapy and identify patients with chemotherapy-resistant disease who may benefit from novel therapies in a clinical trial. To accomplish this, we are developing a response prediction algorithm that integrates key data from quantitative MRI, pathology, molecular profiling and the immune microenvironment to understand the key drivers of response and resistance to therapy. Our researchers have incorporated the latest in artificial intelligence and deep-learning technology into this project with the primary aim of identifying early responders to chemotherapy while also making clear the factors that contribute to therapy resistance. This approach will help us to achieve the following goals:

- Identifying clinical, imaging, and molecular predictors of disease response and resistance

- Escalating therapy in TNBC patients who are not responding to chemotherapy by targeting underlying mechanisms of disease resistance with novel therapies
- De-escalating therapy in select TNBC patients likely to achieve pathologic complete response

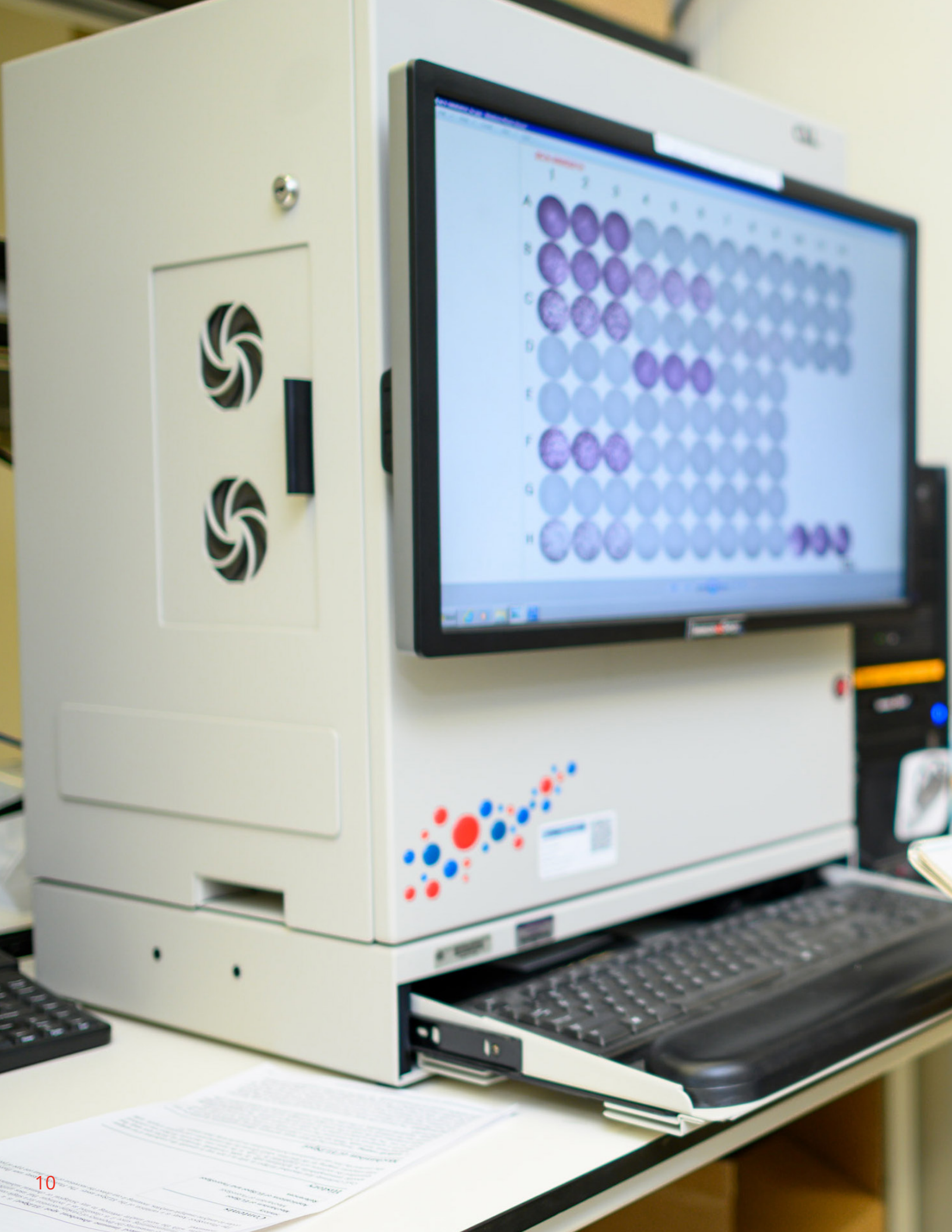
Opportunities for Immunotherapy

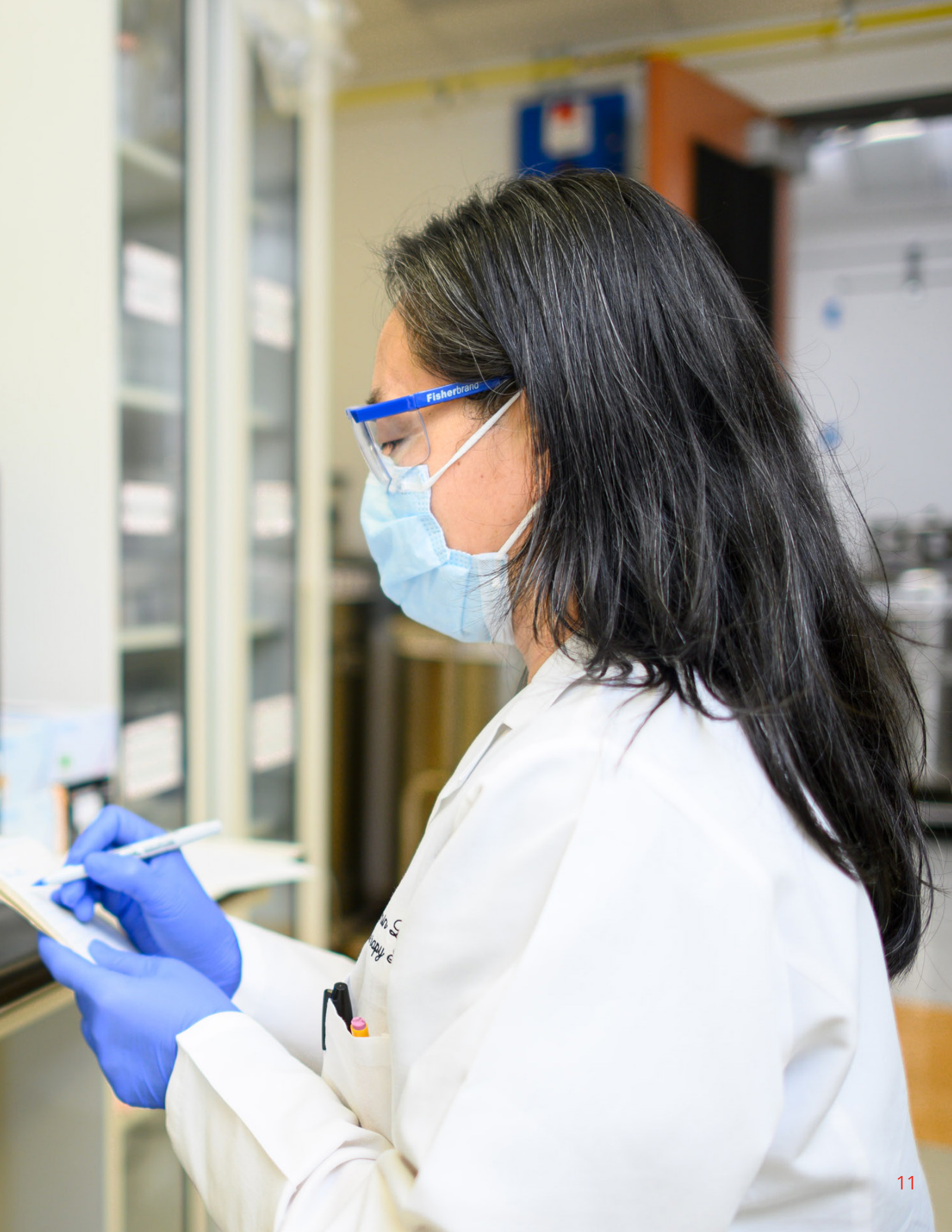
In TNBC, the tumor immune microenvironment plays a key role in prognosis and response to neoadjuvant therapy. Immune cells in the tumor, known as stromal tumor-infiltrating lymphocytes (sTILs), are a reproducible biomarker, and multiple studies have confirmed that high levels of sTILs are associated with improved outcome and increased response to therapy. Immunotherapy has recently emerged as a therapeutic strategy in the neoadjuvant setting of TNBC, though it is important to note that the introduction of checkpoint inhibitors targeting PD-1 or PD-L1 have not resulted in the same positive outcomes that have so profoundly impacted other cancers, such as lung cancer and melanoma. Since not all TNBC patients will be eligible for, or benefit from, the addition of immunotherapy, we designed an initiative to comprehensively evaluate the host immune response to select patients with a high likelihood of benefit to immunotherapy, while also elucidating the mechanisms by which resistance to immunotherapy develops in certain patients. This endeavor supports our overarching goal of using precision medicine to improve cure rates in TNBC by achieving the following goals:

> We could not have advanced our programs to this point without the support of donors to this Moon Shot.

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

The Breast Cancer Moon Shot team is evaluating current projects and developing strategies for future research that will contribute to meaningful impact for patients. Your support has advanced our programs to a point not possible without philanthropy. Our clinicians, scientists, and, of course, our patients are grateful for your catalyzing gifts.

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CHRONIC LYMPHOCYTIC LEUKEMIA

Since its inception, the Chronic Lymphocytic Leukemia Moon Shot® has led and/or participated in paradigm-shifting studies that have improved therapeutic options and outcomes for patients living with CLL, the most prevalent adult leukemia in the U.S. Chemoimmunotherapy regimens, whose effectiveness was limited by advanced age, comorbidities, poor fitness and therapeutic toxicity, have been replaced by targeted therapies and monoclonal antibodies. These latest therapies provide extended periods of disease control in patients of all ages and fitness, even those with relapsed/refractory disease. Moreover, we are observing deep, durable remissions as evidenced by undetectable minimal residual disease (MRD) status, enabling sustained treatment-free intervals.

Despite these advances, we must do more to help our patients.

We are working on strategies to help patients with 17pdel and/or with mutated TP53, as they are considered a high-risk group for poor clinical outcomes, who are difficult to treat, progress rapidly after therapy, and have markedly shorter survival.

Developing Predictability

Up to 8% of untreated CLL patients and 16% of treated patients experience transformation of their disease into a highly aggressive, high-grade lymphoma known as Richter's Transformation. The overall survival of patients with Richter's Transformation is poor and there are currently no standard effective treatments available. We have a better chance of treating Richter's Transformation if we know it will develop in patients. To this end, we have identified a genetic marker of risk: the microRNA signature. We are leveraging the data generated through the Moon Shot® to secure peer-reviewed National Institutes of Health funding and have since graduated this specific project.

These latest therapies provide extended periods of disease control in patients of all ages and fitness, even those with relapsed/refractory disease.

MOON SHOT

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

Over the past year, we have made strides in understanding CLL biology. Our investigators have established a comprehensive immune cell biobank, a precious patient resource that enables us to interrogate the patient immune system before, during and after treatment, including relapse. Such knowledge is allowing investigators to better understand immune dysfunction and features of immunosuppression inherent in patients with CLL at all stages of disease. Our biobank is a critical component of our efforts to maximize the benefit of current and future targeted therapies.

Unleashing the Immune System

We are taking the knowledge we gain from our patients and leveraging the data through exciting projects that are helping us to better understand the pathophysiology of the disease. Across multiple projects, we have studied next-generation reversible and irreversible BTK-inhibitors (acalabrutinib, zanubrutinib) and BCL-2 inhibitors (venetoclax), expanding our insight of how these novel agents work in patients with CLL. Specifically, we are gaining understanding of modulation of the immune system so that we may better harness our innate response to disease. Secondly, we are confirming the synergy of these targeted agents to maximize and potentially limit duration of treatment. To this end, the combination of ibrutinib plus venetoclax is yielding undetectable MRD in patients with CLL. Through analysis of the clinical, molecular and tumor microenvironment, we are identifying distinct characteristics associated with poorer outcomes, which enable us to target this subset of patients sooner.

Biomarkers Lead to Early Interventions

Finally, we know that early identification of disease leads to earlier interventions and improved outcomes. To this end, we are leveraging the infrastructure of the Moon Shots Program through a collaboration with the Melanoma Moon Shot® and the department of Translational Molecular Pathology, whose Immunoprofiling Laboratory designs, validates and analyzes cancer immune-related markers in clinical samples. We are developing a screening tool to identify a subclinical pre-cursor of CLL in patients with melanoma previously undiagnosed with CLL. We hope to anticipate the onset of CLL using this test. In Fiscal Year 2022, we anticipate translating this screening tool to patients with renal cell carcinoma to reduce the risk of second primary malignancies for patients with CLL.

We extend to donors our sincere and heartfelt gratitude for their support as we work toward the day when CLL will be a completely curable disease in all cases.

COLORECTAL CANCER

MOON SHOT

The overall incidence of colorectal cancer in the U.S. has declined due to preventive colonoscopy screenings; there are now more than 1.5 million survivors of the disease. Even though the overall death rate continues to decline, deaths from colorectal cancer among people younger than 55 have increased 1% per year over the recent decades.

To address critical needs in this field, we initiated the Colorectal Cancer Moon Shot®, which has resulted in numerous preclinical and clinical advances. We helped to define the colorectal cancer consensus molecular subtypes (CMS); the four primary disease subtypes now commonly recognized by the medical community as necessary to stratify patients into subgroups with distinct therapeutic strategies. We also developed a CMS assay — a test that can determine the molecular subtype of colorectal cancer for each patient and potentially identify the best course of treatment. The test developed by the Moon Shot® team had less than 1% sample failure due to analytical factors, indicating that it can reliably be used even by small community center-based laboratories.

The CMS unlocked a new way of thinking about colorectal cancer and how we treat it. Our team is combating the disease on multiple fronts:

- We are crafting personalized therapeutic vaccines in combination with an anti-PD-1 immune checkpoint inhibitor and CD40 agonist.
- We are leveraging cord blood-derived natural killer (NK) cells and chimeric antigen receptor (CAR) NK cells.
- We are developing preclinical models of minimal residual disease, established in collaboration with the TRACTION platform, to better understand its biology and to develop new, targeted treatment approaches.

Finding All the Cancer

We are prioritizing our ability to find and eliminate as many cancer cells as possible. About 25 to 30% of patients with stage III colon cancer will relapse within five years due to minimal residual disease (MRD), occurring when a small number of cancer cells persist during treatment and after remission. To enable the molecular detection of MRD, we developed a blood-based non-invasive colorectal cancer-specific test — CRC23. This circulating tumor DNA (ctDNA) test is being used to detect specific mutations. It is now being validated in the plasma of 1,000 or more patients within our Colorectal Cancer Moon Shot/CPRIT-funded trial based at MD Anderson that also involves more

than 10 other research sites in the U.S. We have demonstrated that ctDNA can serve as a marker of minimal residual disease following tumor resection. Our ctDNA efforts span multiple projects and are aimed at intervening when disease burden is low and more curable.

Preventing the Precursor

Lynch syndrome is the most common hereditary cause of colorectal cancer, seen mostly in people younger than 50. We seek to prevent the development of colorectal cancer in these patients. In early studies, our preclinical examination of genetically engineered Lynch syndrome mice and organoids derived from Lynch syndrome patients showed efficient prevention of colorectal cancer with naproxen.

We are completing preclinical studies in support of a Phase I clinical trial testing a prophylactic common neo-antigen vaccine (with and without naproxen) for colorectal cancer prevention in people with Lynch syndrome.

Leveraging Immunotherapy

While anti-PD-1/PD-L1 checkpoint blockade immunotherapy has been highly successful in many patients, approximately half of the colorectal cancer patients eligible for these immunotherapies do not respond.
We are using cutting-edge strategies discovered right here at MD Anderson to change this paradigm. We performed fecal microbiome transplants from PD-1-responsive and non-responsive cancer patients into laboratory mice and showed correlations between the microbiome and the way patients responded to immunotherapy. We now are investigating differences in microbiome compositions between colorectal cancer patients who did and did not respond. We are opening a Phase II single-arm, open-label study to evaluate treatment combining immune checkpoint inhibitors with fecal microbiome transplants in patients who do not respond to initial immunotherapy.

> We helped to define the colorectal cancer consensus molecular subtypes (CMS); the four primary disease subtypes now commonly recognized by the medical community.

The success of our program is made possible by generous philanthropic funding. Your support of our Moon Shot enables this leading-edge work that is not commonly funded through outside governmental sources. We are exceedingly grateful for your continued support and extend to you our utmost appreciation for helping us find cures for the many forms of colorectal cancer.

GLIOBLASTOMA

Program Leaders: Candelaria Gomez-Manzano, M.D., Frederick Lang, Jr., M.D., Vinay Puduvalli, M.D.

Even today's most advanced standards of cancer care — aggressive surgery, radiation and chemotherapy — have done little to improve survival for patients with glioblastoma (GBM), the most common malignant primary brain tumor in adults and the most frequently occurring solid tumor in children. We must better address the multiple abnormalities that drive deadly GBM tumors — no two are alike — and their ability to change and resist current treatments.

The Glioblastoma Moon Shot® leverages a robust track record, including establishing the current adult standard of care for GBM, the oral chemotherapy drug temozolomide, which was first tested at MD Anderson.

Biological Therapies

New approaches for treating GBM and other gliomas (cancers arising in the brain's neuron-protecting glial cells) include biological therapies — viruses, stem cells, proteins and other naturally occurring agents. These "living" therapies offer potential solutions to the many problems of treating cancer, such as precisely targeting tumor cells, halting cell growth, overcoming resistance to therapy and activating anti-tumor responses by the immune system. One prominent example is the viral agent Delta-24-RGD, a genetically engineered variation of the common cold virus, invented by MD Anderson experts Juan Fueyo-Margareto, M.D., and Candelaria Gomez-Manzano, M.D., in collaboration with David Curiel, M.D., at the University of Alabama at Birmingham.

A Phase I trial of this virus-turned-tumor-killer showed dramatic results, a 15% complete and durable response in patients with recurrent GBM. These encouraging results have led to a deeper exploration of this novel and highly potent agent. We are conducting a Phase I trial assessing a new way to transport Delta-24-RGD directly to tumors. This delivery method, which uses mesenchymal stem cells as carriers, shows promise in crossing a major therapy stumbling block: the blood-brain barrier, which protects the brain from foreign agents (including cancer therapies). This human trial is the first to assess delivering stem cells — loaded with an oncolytic virus — to a tumor through a patient's arteries. A successful outcome could pave the way for a new field of neuro-oncology: endovascular neurosurgical oncology.

Immunotherapies

Our MD Anderson team was the first to use precision immunotherapy in patients with GBM, and we continue to investigate the most effective use of this approach in fighting the disease. Natural killer (NK) cells — a type

of immune cell — attack tumor cells even in the absence of identifying antigens (or proteins) on the surface. But GBM tumors are resilient and build a defense against attacking NK cells at the molecular level.

Thus, we are engineering NK cells in the laboratory that will halt tumor molecular defenses and then infusing these cells into the patient. This strategy will be assessed in an upcoming Phase I/II clinical trial. We also are creating "armored" NK cells that express proteins that enable anti-GBM activity. The efficacy of this approach will be evaluated in mouse models.

The Glioblastoma Moon Shot leverages a robust track record, including establishing the current adult standard of care for GBM, the oral chemotherapy drug temozolomide, which was first tested at MD Anderson.

Learning from our Patients

Another initiative of our GBM scientists, CNS Tumor AnaLYsis STream (CATALYST), exemplifies the team science approach of the Moon Shots Program®. Comprising efforts across several departments and Moon Shot platforms, CATALYST aims to create comprehensive profiles of patients by profiling every available biospecimen: tumor tissue with matching cerebrospinal fluid (CSF), blood and stool. Access to patients' biospecimens will be provided to multiple principal investigators, allowing them to perform cross-functional analyses — sequencing samples, building mouse models and creating tumor-infiltrating lymphocytes.

The intricately coordinated effort for biospecimen analyses will uncover correlations between tumor tissue and the markers in a patient's blood, CSF and gut microbiome. CATALYST will be the most comprehensive analysis of GBM biology ever completed, enabling us to better understand central and peripheral nervous system tumors and design novel therapies to treat them.

To accelerate the development of new therapies, we recently created and implemented an effort called Analysis of Central Nervous System Cancer response to ExperimentaL agEnts and ResistAnce to ThErapy (ACCELERATE). This initiative is a large-scale pipeline intended to vigorously vet promising agents targeting novel mutations identified within CATALYST. ACCELERATE will leverage existing platforms at MD Anderson and push through candidate agents rapidly to complete IND-enabling studies leading to clinical trials.

We are sincerely grateful for philanthropic funding, which makes so much of what we can do for our patients possible.

HIGH-RISK MULTIPLE MYELOMA

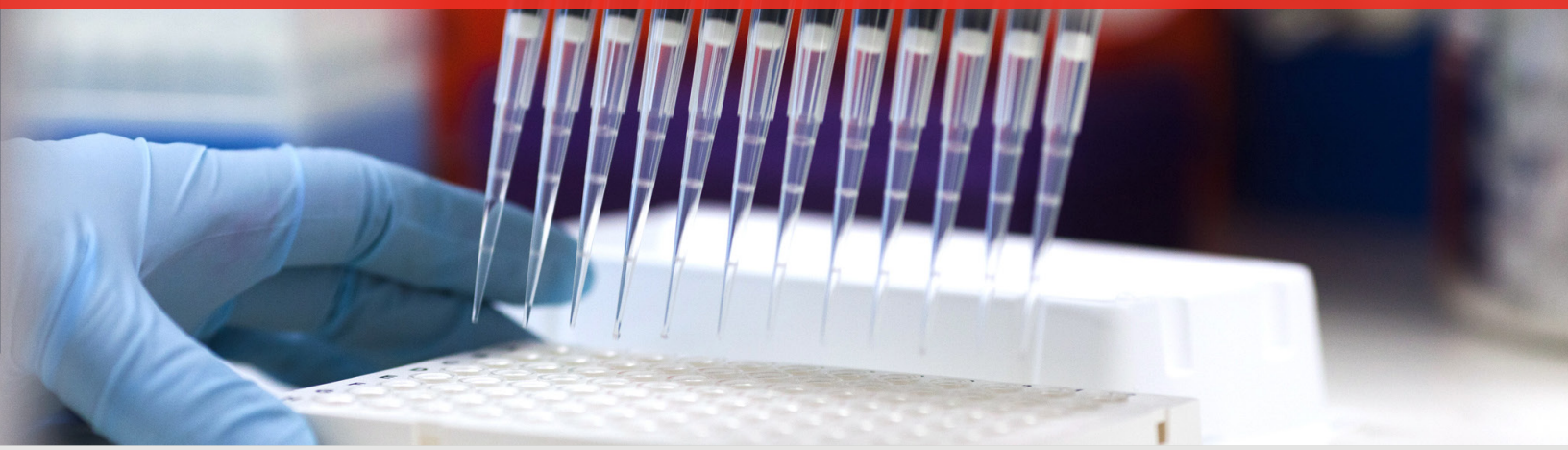
The High-Risk Multiple Myeloma Moon Shot® is focusing on the mechanisms underlying advancement from precursor states to active multiple myeloma to develop a reliable model that can predict disease progression. This will help clinicians better triage patients and aid in the implementation of novel therapeutic strategies.

Multiple myeloma is the second most diagnosed hematologic malignancy. Estimates indicated that it was diagnosed in more than 32,000 new patients in the U.S. in 2020. Novel drugs have more than doubled the median overall survival in this disease, but until 2012, most of this improvement was seen in patients with standard risk disease, defined by clinical and molecular criteria. Unfortunately, without a curative therapy, virtually all patients will develop and succumb to relapsed/refractory multiple myeloma. Our research aims to advance new and effective treatment options for our patients to combat the disease's high rates of morbidity and mortality.

Understanding Disease Progression

We are developing new, effective therapies by focusing on the progression of multiple myeloma; understanding how the disease advances allows us to exploit its vulnerabilities. The disease is distinctive for having well-defined precursor states, including monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM. While we have defined factors predicting the likelihood of progression to symptomatic disease, even high-risk patients in precursor states are not routinely treated. This indicates that high-risk MGUS, as well as smoldering and symptomatic multiple myeloma, represent important and urgent areas of unmet medical need for the development of novel, more effective therapies. To this end, the following are the goals of the High-Risk Multiple Myeloma Moon Shot:

> We are achieving our goals by applying novel immunotherapeutic approaches to prevent disease progression and to deepen minimal residual disease (MRD), an important predictor of progression-free survival in multiple myeloma.



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

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

Leveraging Immuotherapies

We are achieving our goals by applying novel immunotherapeutic approaches to prevent disease progression and to deepen minimal residual disease (MRD), an important predictor of progression-free survival in multiple myeloma.

We are evaluating the efficacy of available immunotherapies, such as monoclonal antibodies and personalized vaccines, in high-risk smoldering multiple myeloma to prevent disease progression.

For patients with symptomatic multiple myeloma, we use adoptive cord blood-derived natural killer (CB-NK) cell therapy approaches to eradicate multiple myeloma cells, and ultimately, neoplastic stem cells. We have validated the use of CB-NK cells with anti-multiple myeloma activity (pioneered at MD Anderson) in high-risk patients undergoing autologous (from the patient) stem cell transplantation and are now developing approaches to target immune cells to specific antigens to enhance their anti-myeloma activity.

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

Our program benefits from the generosity of donors. We are grateful for the trust you have placed in us and will continue to work hard, every day, to improve the lives of our patients.

HPV-RELATED CANCERS

MOON SHOT

In 2012, 4.5% of all cancers diagnosed worldwide were caused by human papillomavirus (HPV) infections. This includes 640,000 cases of cervical, vaginal, vulvar, anal, penile, and head and neck cancers. Although HPV vaccines and cervical cancer screening programs could prevent most of these cancers, access is still limited for the world's most vulnerable populations. The burden of HPV-caused cancers continues to rise: 770,000 cases of cervical cancer alone are anticipated in 2030. In the same year, 30,000 new cases of HPV-positive head and neck cancer are anticipated in the U.S.

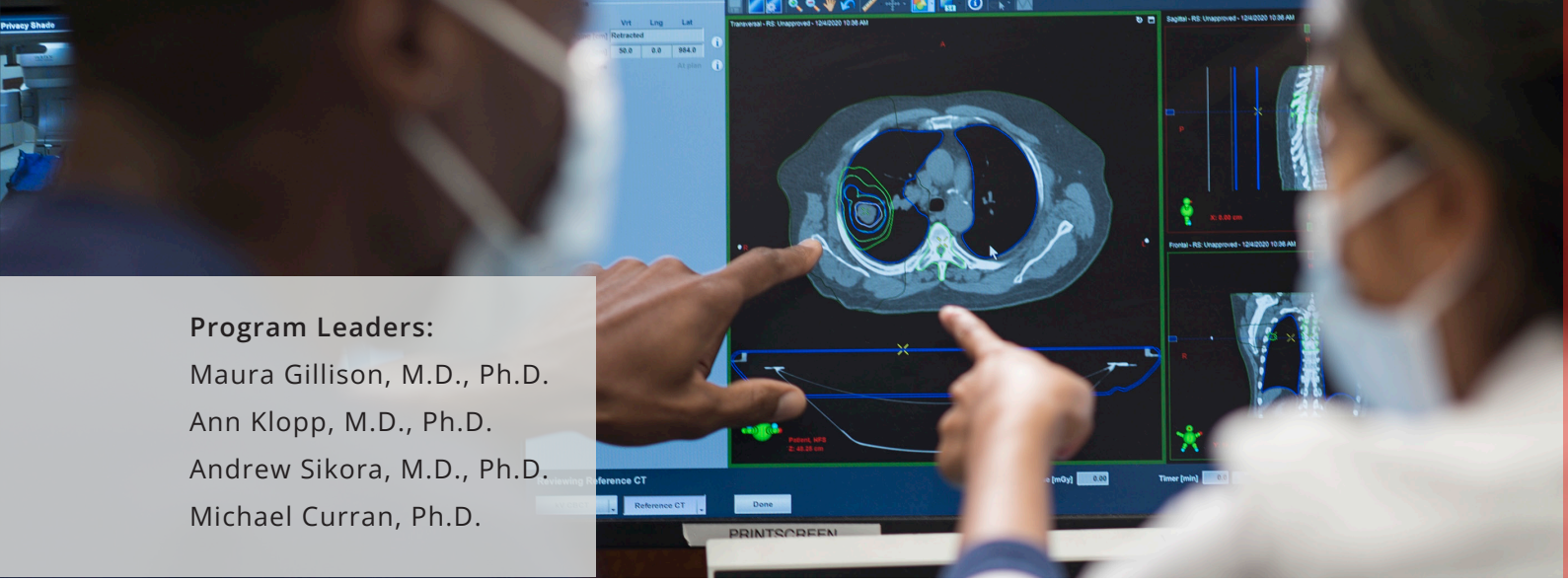
Public health programs at MD Anderson strive to increase access to HPV vaccination to reduce the number of young men and women at risk of HPV-caused cancers.

The HPV-Related Cancers Moon Shot® is a comprehensive program designed to address several unmet clinical needs for patients with cancers caused by HPV. The program integrates clinicians and scientists across MD Anderson who are dedicated to research and treatment of HPV-related cancers. We are improving our understanding of outcomes for HPV-related cancers through the following approaches:

- Identifying factors that suppress the body's immune response to the virus.
- Developing new immunotherapies for HPV-caused cancers.
- Optimizing new prognostic biomarkers and translating them to clinical practice.
- Studying and manipulating the body's microbiome to improve response to treatment.
- Identifying and targeting genetic alterations common across all HPV-caused cancers.

Looking Beyond the Tumor

Research suggests that the the tumor microenvironment — the ecosystem that surrounds a tumor inside the body — plays a key role in cancer development. We are using the latest single-cell sequencing technologies to identify factors enriched within HPV-positive cancers that suppress the body's immune responses. We identified several such factors within the last year, and



Program Leaders:
Maura Gillison, M.D., Ph.D.
Ann Klopp, M.D., Ph.D.
Andrew Sikora, M.D., Ph.D.
Michael Curran, Ph.D.

we are actively accruing patients to clinical trials with drugs that target these factors.

We are also detecting and characterizing T cells in patients that can kill HPV-infected tumor cells. In the last year, we began studies to identify these T cells.

The HPV-Related Cancers Moon Shot is a comprehensive program designed to address several unmet clinical needs for patients with cancers caused by HPV.

Liquid Biopsies

Once identified, we aim to develop new T cell therapies and improve anti-cancer vaccines.

Our investigators are also developing a new blood test that measures tumor cell death in response to treatment.
We are now translating this blood test to the clinic for use in research protocols and plan to make the test available for routine clinical practice in the next year.

Additionally, we are identifying relationships between the microbiome and responses to standard-of-care therapies. We have identified bacterial species associated with reduced response of cervical cancer to radiation therapy. We are now investigating ways to study and manipulate these bacteria to improve outcomes.

Finally, recent studies have suggested that some cancer cells can be reprogrammed to behave like normal cells. We are using CRISPR genome editing to study a gene mutation common across HPV-caused cancers. Researchers are analyzing the effects of these mutations on cell programming to better understand why some anti-cancer drugs are less effective than others.

We are thankful for donors to our program and sincerely appreciate every dollar provided by generous supporters for the benefit of our patients.

LUNG CANCER
MOON SHOT

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

Not just one disease, lung cancer comprises multiple subtypes defined at the molecular level by genomic alterations. The Lung Cancer Moon Shot® continues to perform deep molecular profiling on all MD Anderson patients with lung cancer at every disease stage — not just those on clinical trials. This has helped our scientists reveal new targetable mutations and identify subgroups of patients likely to benefit from new therapies, including combination treatments that employ immunotherapies and other novel approaches. The goal is to ensure more effective therapies for all patients with lung cancer, including those with rare and treatment-resistant disease.

The Moon Shot® also aims to identify molecular and imaging markers of benefit for novel immunotherapeutic approaches for lung cancer patients. We are identifying personalized, biomarker-driven strategies to help individuals quit smoking, the leading and most preventable cause of lung cancer, and reduce their likelihood of developing the disease.

Lung Cancer Therapeutics

The Lung Cancer Moon Shot seeks to identify, develop and test new targets and therapies for more effective lung cancer treatments. The emphasis is on drug-resistant disease in both non-small cell lung cancer (NSCLC), the most common type of lung malignancy, and small cell lung cancer (SCLC), which comprises about 15% of lung cancer cases. Infrastructure created within the Moon Shot is uniquely positioned to support these efforts, which include identifying cell surface targets of molecularly defined subsets of SCLC — first defined by MD Anderson — and developing novel antibody-based therapies that are effective against those targets.

Other approaches in the pipeline aim to help patients with NSCLC subtypes that do not respond to immune checkpoint blockade therapies that unleash the body's own immune system to combat cancer. To tackle this, the team is focused on developing novel adoptive T cell therapies. This approach entails surgically removing a tumor, isolating

the tumor-infiltrating lymphocytes within it, analyzing and selecting those most actively fighting against the cancer, expanding and then reinfusing large numbers of these disease-fighters into patients to eliminate residual tumor cells and prevent recurrence.

Additionally, pipeline researchers are leading efforts to find new therapeutic approaches for lung cancer patients bearing genetic alterations in the epidermal growth factor receptor (EGFR). These alterations occur in approximately 15% of patients with lung cancer in Western countries (40-60% in East Asia). For these patients, EGFR tyrosine kinase inhibitors, drugs that target the EGFR protein, are highly effective therapies. Unfortunately, resistance to these drugs emerges in most cases. To address this challenge, the team is developing novel drugs for new targets that have been identified by the Lung Cancer Moon Shot in collaboration with MD Anderson drug development platforms. The therapeutic pipeline also aims to discover and test new therapeutics for patients bearing atypical EGFR mutations.

Markers for Immunotherapy

This element of the Moon Shot focuses on predicting response and resistance to immunotherapies. These therapies have shown profound results in the management of metastatic NSCLC — but only for some subsets of patients. To answer critical questions about how and why patients

respond differently to treatment, this initiative seeks to define the mechanisms that drive response or resistance to immunotherapy combinations across early- to late-stage NSCLC to benefit more patients. The effort has three goals:

- Identify biomarkers (molecules in blood, other bodily fluids and tissues) that can signal response or resistance to specific treatments.
- Develop imaging-based (radiomic/radiogenomic) models that can predict response to neoadjuvant treatment (including chemotherapy and/or immune checkpoint blockade therapies to shrink the tumor prior to surgery or another main treatment).
- Investigate the mechanisms of response and resistance to immunotherapy strategies and novel combinations to improve immune-based treatment regimens.

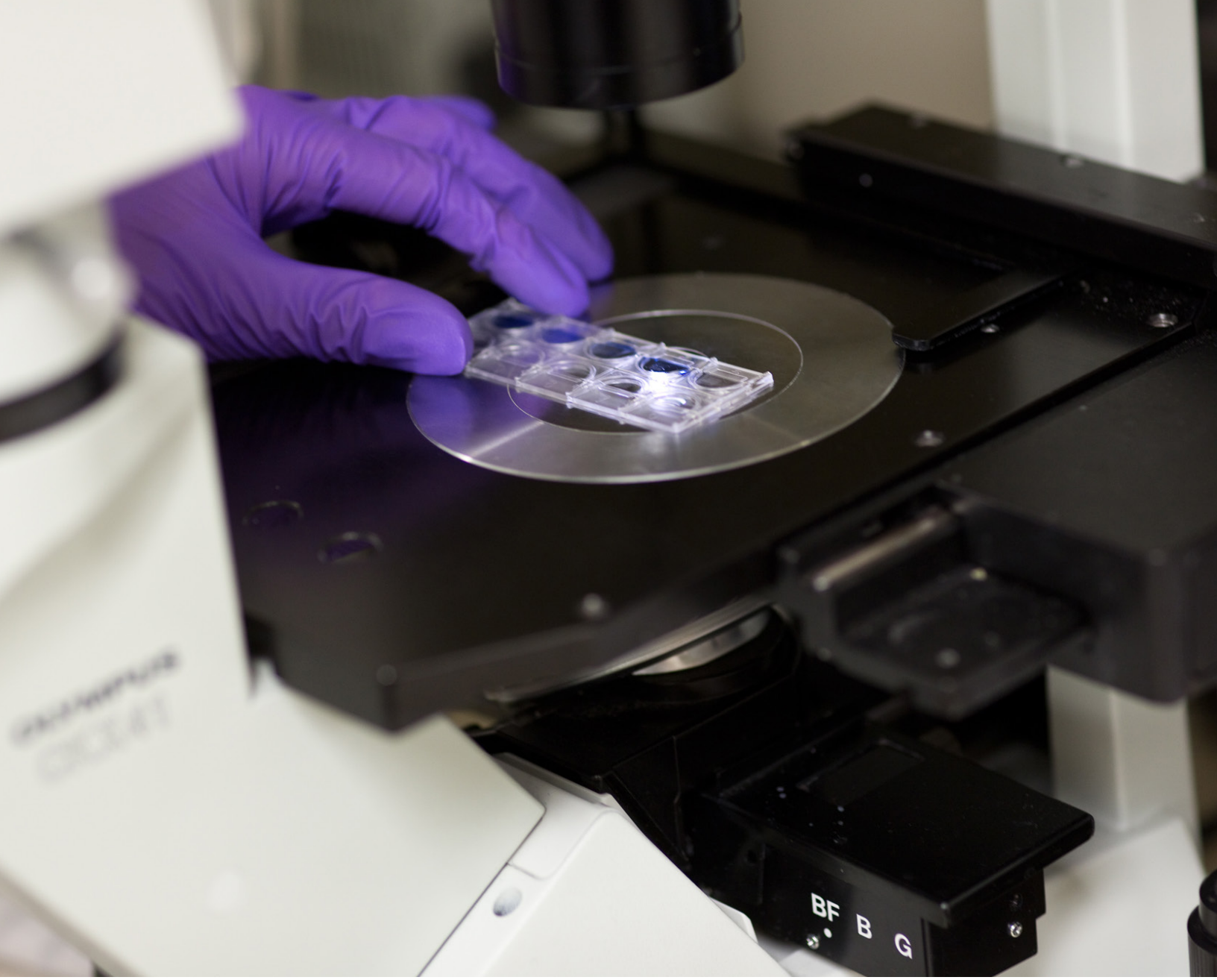
Genomic Marker-Guided Therapy Initiative (GEMINI)

Initially created and tested to guide lung cancer treatment decisions, the Genomic Marker-Guided Therapy Initiative (GEMINI) GEMINI database combines molecular data with robust clinical information from thousands of patients. The result allows correlation of treatment responses with genetic mutations. Infrastructure forged for GEMINI now can be accessed for any lung tumor type by clinicians and researchers across MD Anderson and beyond. In collaboration with MD Anderson's data science experts, efforts are underway to use the GEMINI database as a "gold standard" and integrate many of its capabilities with the electronic medical record. The goal is to collaborate across the institution to create a comprehensive, user-friendly data hub that makes molecular biomarker data available to all MD Anderson physicians in real-time. This will make treatment decisions and clinical trial matching for each individual patient as efficient as possible and improve the quality of patient care overall. For this coming year, GEMINI will serve as an important platform to expand our reach into novel areas of patient care. It will allow us to identify patients who may benefit from lung cancer screening to identify early-stage cancers or precancers that can be cured. And it will let us identify patients with metastatic lung cancers who can benefit, even be cured by an aggressive therapeutic approach incorporating systemic therapy (chemotherapy, immunotherapy, targeted therapy, etc.) and proactive local therapy (radiation and surgery).

> The Lung Cancer Moon Shot continues to perform deep molecular profiling on all MD Anderson patients with lung cancer at every disease stage — not just those on clinical trials.

Precision Implemented Smoking Cessation Evaluation Study (PISCES)

Just as MD Anderson led early efforts to personalize lung cancer therapies, patient by



patient, the same emphasis on customization is now being applied to tobacco cessation strategies. Data from three Moon Shot clinical trials yielded a promising algorithm, which integrates molecular, behavioral and neurophysiological markers to guide selection of the most effective quit strategy for each individual. This led to the pioneering cancer prevention trial, Precision Implemented Smoking Cessation Evaluation Study (PISCES), which aims to change clinical practice and show how a single health care institution can optimize treatment delivery for a large population. In a collaborative effort with MD Anderson's marketing team, PISCES is reaching smokers in underserved, high-prevalence regions across the state of Texas in this novel, virtually delivered treatment study.

Philanthropic support drives our advances to help more patients. We thank those who so generously help fund our research.

MDS *and* AML

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

The Moon Shot® is creating novel methodologies and technologies that improve patient outcomes.

Different Populations, Different Strategies

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

Innovative Cellular Therapies

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

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

glucocorticosteroids, drugs commonly used to reduce inflammation; therefore, the CAR NK cells will be engineered to be resistant to glucocorticosteroids and improve treatment efficacy. This approach will increase accessibility to stem cell transplantation, reduce the time between diagnosis and treatment, and lower the cost of cellular therapies.

Targeting Minimal Residual Disease

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

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

> The MDS and AML Moon Shot is creating novel methodologies and technologies that improve patient outcomes.

We are incredibly appreciative of every gift to the Moon Shot as the funding climate is very competitive. Philanthropic gifts help us bridge funding gaps and take on projects we may otherwise be incapable of exploring. Thank you for your support.

MELANOMA

Melanoma, the deadliest form of skin cancer, is an aggressive yet often preventable disease. It is largely caused by exposure to ultraviolet radiation, the sun and indoor tanning devices.

Prevention and Detection

Our team recognized the clear opportunities to reduce the impact and burden of melanoma through improved primary and secondary prevention initiatives. In 2013, Texas became the fourth state to prohibit indoor tanning for youth under the age of 18. Since then, 21 states and the District of Columbia now have such legislation — many as a direct result of our leadership and partnership with the Cancer Prevention and Control platform and the American Cancer Society - Cancer Action Network. When diagnosed early, melanoma is highly treatable. However, despite evidence that early-stage melanoma diagnosis is associated with favorable outcomes, there are no universally available, effective screening strategies for this disease. Our team has developed a dermoscopy curriculum to educate primary care and dermatology residents on its use for early diagnosis and detection of cutaneous melanoma.

The management and outcomes for patients with stage IV metastatic melanoma have been revolutionized with the approval of 11 targeted therapy and immune checkpoint blockade (ICB) immunotherapy regimens for melanoma since 2011. Single agent anti-PD-1 ICB achieves responses in about 40% of stage IV patients, but most of them still fail to respond, while others progress after initial response. Combined treatment with anti-PD-1 and anti-CTLA4 therapies achieves higher response rates (about 55%), particularly in patients with brain metastases, but frequently incurs high-grade toxicities with only modestly improved overall survival compared to anti-PD-1 alone.

Leveraging the Microbiome

Our program recognizes the need to identify novel strategies for patients who have failed frontline treatments. Our Moon Shot is dedicated to understanding predictors of response to standard therapies. Building upon our insights gained in identifying a microbiome signature to predict response to ICB, our team has launched a clinical trial evaluating the ability of a controlled diet modification to augment the microbiome. In this study, and in collaboration with the immunotherapy platform, we will gain insights into the diet's impact on the immune system of melanoma patients being treated with immunotherapy. In tandem with ongoing sample collection efforts, this study

Program Leaders:
Jeffrey Gershenwald, M.D., Michael Davies, M.D., Ph.D., Jennifer Wargo, M.D., Hussein Tawbi, M.D., Ph.D.

will provide invaluable insights into host factors associated with response to standard treatments.

Our team recognized the clear opportunities to reduce the impact and burden of melanoma through improved primary and secondary prevention initiatives.

Novel Treatment Strategies

Melanoma spreading to the central nervous system remains a prevalent problem in stage IV patients and is frequently the initial — and sometimes only — site of systemic treatment failure. While both ICB and targeted treatments have improved outcomes, we need more effective strategies to overcome central nervous system metastases once patients have failed approved therapies. Our team is currently focusing on predicting and treating central nervous system metastases to further reduce deaths from melanoma. In particular, leptomeningeal disease — when melanoma cells invade the cerebrospinal fluid — is a major challenge as it portends a survival of less than eight weeks on average and has very few treatment options or laboratory models amenable to preclinical research. We have led the development of intrathecal immunotherapy — injection into cerebrospinal fluid — as a novel strategy for these patients, with proof-of-principle long-term survival in subsets of patients to build upon.

We are applying treatments approved for stage IV disease in earlier settings, with ICB and targeted therapies now FDA approved as adjuvant therapy for stage III disease. However, there are no approved systemic therapies, beyond high-dose Interferon-α2b, for patients with stage II disease. Patients with resected high-risk primary cutaneous (stage II) and stage III melanoma vastly outnumber (almost by three times) patients with stage IV metastatic melanoma. We must identify risk-informed strategies for adjuvant treatment in clinically localized and particularly “high-risk” patients with stage II and III disease to better individualize prognosis and disease management.

We wish to extend our gratitude to the generous donors that keep our program on the forefront of science. On behalf of our patients, thank you.

OVARIAN CANCER MOON SHOT

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

High-grade serous ovarian cancer (HGSOC), the most common type of ovarian cancer, remains the deadliest gynecologic cancer, with a five-year survival rate of approximately 45%. The Ovarian Cancer Moon Shot® is focused on improving outcomes for patients with HGSOC, as well as those with the less common low-grade serous ovarian cancer (LGSOC) and clear cell carcinoma histological subtypes.

> We envision a "chemotherapy-free" future for patients with advanced or recurrent LGSOCs.

Our engagement of Moon Shot® platforms has allowed for deep interrogation of each sample from our therapeutic trials, with an emphasis on longitudinal changes and integration of DNA, RNA and proteomic data. These studies have provided insights into how adaptive and other resistance mechanisms limit therapy efficacy and provide rationale for development of new combination treatments to overcome resistance to therapy. Our current research projects focus on areas of significant potential clinical impact.

Focusing on Resistance

Most women with ovarian cancer will receive anti-VEGF therapies. Although many have benefitted from improved outcomes, many tumors do not respond or develop adaptive resistance following temporary response. Moreover, there is a rapidly expanding pool of patients who have received bevacizumab but need new therapeutic options due to disease progression. In this project, we are looking closely at the mechanisms by which therapy resistance develops so that we can develop rational treatment combinations to overcome resistance to therapy. We are leveraging MD Anderson's innovative clinical trials infrastructure to enable these studies and evaluate novel therapeutics aimed at new targets in the tumor blood vessels or in tumor metabolism that may benefit our patients.

PARP inhibitors have moved into the frontline in HGSOC, with more than 50% of patients expected to receive a PARP inhibitor at

some point in their care. There is a rapidly expanding group of patients who have experienced disease progression on PARP inhibitor treatment due to innate or adaptive resistance. Importantly, our therapeutic trials include pre- and on-treatment biopsies to identify new agents and rational combination strategies.

Predicting Immunotherapy Efficacy

Immunotherapy has had modest success in ovarian cancer, unlike some types of cancer, and represents an unmet need. Our Moon Shot team has made major discoveries related to efficacy of immune therapy in ovarian clear cell carcinoma. The team is focused on identifying biomarkers for predicting exceptional survival following immune therapy and developing translational strategies aimed at expanding the potential benefits of immunotherapy to patients.

We see the largest number of patients with LGSOC in the country, positioning us to leverage the unique molecular landscape of these tumors to develop novel therapies. LGSOC is a subtype that accounts for roughly 10% of all ovarian cancers, and it is more likely to be resistant to available chemotherapies. Fortunately, there are frequent genetic mutations that may be effectively targeted with novel treatments. Researchers have led the development of MEK inhibitors for treatment of patients with LGSOC. This project is focused on identifying the markers of response and resistance to MEK inhibitors with a view toward identifying the next generation of rational combination studies.

Innovative Combination Treatments

We led the clinical development of endocrine therapy (e.g., aromatase inhibitors) for patients with LGSOC. We have generated unprecedented preliminary clinical response data using a combination of endocrine therapy and cell cycle inhibition, and the team is well positioned to identify biomarkers for response and resistance aimed at developing even more effective targeted therapies for this rare gynecologic cancer. We envision a “chemotherapy-free” future for patients with advanced or recurrent LGSOCs.

The Ovarian Cancer Moon Shot relies on philanthropic funding to bring effective therapeutic strategies to our patients. We are so thankful for your consistent, generous support.


VERSITY OF TEXAS
Anderson
Center
Michael Green, Ph.D.
Andrew Sabin Family Fellow

MOON SHOT

PANCREATIC CANCER

Program Leaders: Anirban Maitra, M.B.B.S., Robert Wolff, M.D., Florencia McAllister, M.D.

Pancreatic cancer is a challenging disease. Five years after diagnosis, only 10% of patients are still alive. The Pancreatic Cancer Moon Shot® team is focused on pancreatic ductal adenocarcinoma (PDAC), which is aggressive and difficult to treat. It is the most common type of pancreatic cancer.

Translating Research into Trials

One major effort is the design of therapies that target the KRAS protein, which is abnormal in 95% of PDAC tumors. We have been exploring the direct genetic inhibition of KRAS using a novel delivery system called iExosomes. Four years of Moon Shot®-funded work has resulted in the design of a first-in-human Phase I trial that is enrolling patients now. In addition, we have begun the first PDAC-centric clinical trial focused on a drug that specifically targets abnormal KRAS protein. This trial is paired with an extensive Moon-Shot-funded scientific initiative that will enable us to learn from every patient and develop even more powerful combination therapies. We also are aggressively pursuing the promise of immunotherapy as seen through one of our industry partnerships.

Four years of Moon Shot–funded work has resulted in the design of a first-in-human Phase I trial that is enrolling patients now.

Leveraging Immunotherapies

In our collaborative Phase I trial, patients receive an infusion of immune cells called tumor-infiltrating lymphocytes (TILs), along with a high dose of Interleukin-2, a protein that stimulates white blood cells. We now are engineering next-generation TILs with the capacity to circumvent the body's attempt at immune suppression, allowing the TILs to infiltrate the tumor in hopes of boosting efficacy.

In another cutting-edge approach, our Pancreatic Cancer Moon Shot team is investigating the use of natural killer (NK) cells, which are another type of immune cells, as therapeutic agents against PDAC. Our team has developed a novel strategy to genetically modify cord-blood-derived NK cells to target proteins expressed on tumor cells. In addition, we have implemented a state-of-the-science gene editing technique to silence receptors on the surface of NK cells that attempt to inhibit the cells' immune activity. The team currently is conducting pilot preclinical studies. In the future, we plan to evaluate the potential of this promising approach in a Phase I/II clinical trial.

Improving Liquid Biopsies

It also is crucial to find this disease at its earliest stage. A low-cost blood test for the early detection of pancreatic cancer will have a truly transformational impact on survival rates for patients. To be accurate and reliable, a blood test will need to be based on not one, but several biomarkers in the blood. Thus far, we've built a three-protein anchor panel and are validating more markers to improve accuracy.

The pioneering Pancreatic Cancer High-Risk Clinic — which has both clinical and research arms — has screened and advised more than 200 patients at increased risk for pancreatic cancer.

We have conducted promising research, such as studying the rates of genetic mutations in patients with young-onset pancreatic cancer, as well as the associations between long-term survivors and tumor micro-organisms. The latter work has led to an exciting discovery.

The Moon Shot established that long-term survivors of pancreatic cancer have different bacterial signatures on their tumors than those who succumb quickly to the disease — and that this difference results in a more vigilant immune system. This important finding could lead to a game-changing treatment that will help patients fighting pancreatic cancer.

We are proud of the advancements this innovative program is making. We rely on donor support to continue improving care for patients with pancreatic cancer. Thank you for your generosity.

PROSTATE CANCER

M O O N S H O T

Program Leaders:
Ana Aparicio, M.D., Christopher Logothetis, M.D., Nicholas Navin, Ph.D.

The goal of the Prostate Cancer Moon Shot® is to develop novel effective therapies based on an understanding of all the components of the tumor. We also consider the important biological differences that underlie the clinically evident heterogeneity in therapy response and progression towards lethality. By identifying clinically meaningful, biologically defined subsets and understanding how they evolve under the pressures of existing therapies, we are developing novel effective treatments specific to each subset in anticipation of the expected path of progression. Moreover, early recognition of the lethal subsets of the disease will spare those with non-lethal prostate cancers the toxicities of unnecessary treatments.

Informing through Biomarkers

It is becoming increasingly clear that, in addition to the cancerous epithelial cells, the immune and non-immune components of the tumor microenvironment play critical roles in shaping the progression and response to therapies of solid tumors. Moreover, while genetic markers have proven valuable in identifying specific drug vulnerabilities in a subset of prostate cancers, it also is becoming evident that regulatory mechanisms (epigenetic and others) are key determinants of tumor behavior. The integration of biomarkers that reflect the various cellular and tumor component interactions will refine the therapeutically relevant molecular classification of prostate cancer needed to arrive at therapies with curative intent.

By identifying clinically meaningful, biologically defined subsets and understanding how they evolve under the pressures of existing therapies, we are developing novel effective treatments specific to each subset in anticipation of the expected path of progression.

The bone-centric nature of advanced prostate cancer makes the study of the interactions between the tumor microenvironment components and their evolution uniquely challenging. We previously developed and applied new technologies to study the evolution of circulating biomarkers (e.g., plasma-free DNA and circulating tumor cells) to anticipate and monitor the progression of metastatic prostate cancer under the influence of therapy. We have further developed single-cell DNA sequencing technologies and deployed them to study patient samples — to identify genetic

determinants of response to androgen signaling inhibition and of genetic events that underlie metastasis of the disease. Additionally, we developed methods to perform single-cell RNA sequencing in patient samples to elucidate the interactions among cancerous epithelial cells and immune and non-immune tumor cells. The application of these technologies to serially

collected prostate tumor biopsies donated by prospective clinical trial participants will inform the development of novel therapies and biomarkers that can prompt their early administration, in anticipation of the disease's emerging treatment resistance.

We defined aggressive variant prostate cancers (AVPC) to provide a framework for the study of the most virulent of the lethal prostate cancers, those that exhibit indifference to androgen signaling inhibitors and for which effective therapies are urgently needed.

Refining a Patient Subset

We were the first to describe the AVPC molecular profile that characterizes this androgen-indifferent subset, which has since been shown to be prognostic in multiple data sets. We showed that the addition of carboplatin to cabazitaxel benefitted patients with AVPC, but not those without AVPC, and today platinum-based chemotherapy is the standard therapy for androgen-indifferent prostate cancers. Moreover, the AVPC molecular profile is being used by external investigators in multi-institutional clinical trials designed specifically for this rapidly lethal, androgen-indifferent subset. Using immunohistochemistry, we have continued to refine the AVPC molecular profile by shedding light on the association between the specific genomic alterations in Tp53, RB1 and PTEN, their transcriptional output and their expression at the protein level. Based on the observation that the AVPC molecular profile is linked to lineage plasticity mediated by epigenetic changes — and that the androgen-indifferent tumors are particularly resistant to current immunotherapies — our ongoing work is defining the epigenetic and immune profiles of AVPC and their modulation with novel drug combinations.

Combination Immunotherapies

Although we have observed profound and durable responses to immune checkpoint inhibitors in some patients with advanced prostate cancer, efforts to incorporate these agents into our treatment options have been hampered by their previous evaluation in unselected patient

populations and the predilection of the disease for the immunosuppressive bone microenvironment. Our in-depth evaluations of patient samples and reverse translation studies have identified mechanisms of response and resistance to these agents in patients with prostate cancer, which prompted the evaluation of combined immune checkpoint therapies to overcome the resistance to monotherapy. The promising initial results led to the design of a large multi-institutional trial that has completed accrual and allowed us to identify additional biomarkers of response to the agents. More recently, the evaluation of prostate cancer bone metastases led to the identification of the TGF-beta pathway as a driver of resistance to anti-CTLA-4 checkpoint inhibition in the bone microenvironment. This new knowledge informed the design of a clinical trial with the novel combination in patients with castration-resistant prostate cancer metastatic to the bone.

Generous support from our donors each year allows and accelerates our progress toward the goal of increasingly effective therapies specific to each of the prostate cancer subsets. We deeply value this generosity and are indebted to the philanthropic individuals and organizations that partner with us to make these advances possible.

For more updates, visit:

MDAnderson.org/CancerMoonShots

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