Moffitt's Program In Malignant Hematology:
A decade of discovery: from cytotoxic treatments to targeted therapies

Moffitt Cancer Center’s program in Malignant Hematology was established almost two decades ago. The past 20 years have seen a period of rapid growth for the Program, according to Moffitt’s Eduardo Sotomayor, MD, Susan and John Sykes Endowed Chair in Hematologic Malignancies. And, thanks to evolving new classes of drugs, he also has seen a revolution in how blood cancers are approached clinically.

“Over the past 20 years, we have advanced from offering only chemotherapy to treat hematologic malignancies to today, when we can use DNA sequencing to uncover the genetic makeup of a patient's tumor and then use specifically selected targeted therapies,” says Dr. Sotomayor.

In addition to evaluating and treating patients with hematologic malignancies such as leukemia, myelodysplastic syndromes, lymphoma and myeloma, Moffitt offers the opportunity to biobank samples of a patient’s tumor through the Total Cancer Care™ approach to personalized medicine and provide state-of-the-art clinical trials for patients with blood cancers. Moffitt’s clinical trials offer the potential for better outcomes for patients with hematologic malignancies as well as the opportunity to advance research and improve the quality of life and longevity of future patients. Indeed, Moffitt is among the nation’s top institutions for accrual to clinical trials that focus on leukemia, myelodysplastic diseases (MDS), multiple myeloma (MM) and lymphoma.

Malignant hematology encompasses disorders of the bone marrow, blood and/or lymph nodes and includes a wide spectrum of diseases, including acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), Hodgkin disease (Hodgkin lymphoma), non-Hodgkin lymphoma, multiple myeloma and other plasma cell disorders and myelodysplastic and myeloproliferative diseases.

The pathologist’s crucial role

Combined expertise in pathology, molecular biology and immunology is critical in establishing the correct diagnosis for patients with hematologic malignancies and a crucial starting point. Establishing an accurate diagnosis requires specialized expertise, the kind offered by Moffitt’s Jianguo Tao, MD, PhD, hematopathologist and director of Moffitt’s Susan and John Sykes Lymphoma Research Laboratories.

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“Teamwork is essential, and teamwork is the beauty of Moffitt,” says Dr. Tao. “We constantly meet with the clinical research team as well as with hematologist/oncologists, the bone marrow transplantation team and physicians with specialized expertise such as radiation and surgical oncology to discuss each patient’s case.”

When he came to Moffitt 11 years ago, Dr. Tao was one of two pathologists. He is now among a staff of 10 pathologists, all of whom assist in the conduct of clinical trials. Also a researcher, he seeks to obtain a better understanding of molecular signaling pathways with a special focus on the tumor microenvironment, disease progression and drug resistance.

“We work very closely with Dr. Tao,” says Bijal Shah, MD, who is conducting a number of clinical trials, including one for patients with previously untreated mantle cell lymphoma. “He has unique expertise in the evaluation of mantle cell lymphoma: a rare but often aggressive type of B-cell non-Hodgkin lymphoma. His insights, both clinically and as a translational investigator, have helped us to better risk stratify patients with this lymphoma, as well as better predict the efficacy of novel targeted therapies.”

Kendra Sweet, MD, who specializes in the treatment of AML and CML, also cites the importance of the pathologist’s specialization in ensuring that the diagnosis is accurate. “Unlike a general pathologist who may spend time looking at a great variety of cells and tissues, from breast to colon cancers, Dr. Tao and his team spend all of their time looking at bone marrow, blood and lymph nodes.”

The clinical trials

Rachid Baz, MD, director of clinical research for the Department of Malignant Hematology, is conducting a phase I clinical trial (MCC#17088) for patients with advanced hematologic malignancies. The trial of KPT-330 is aimed at blocking the transport of proteins from the cell nucleus to the cytoplasm and thereby trapping proteins that suppress the growth of cancer in the nucleus where they are active.

Another phase I clinical trial (MCC#16659) investigates the mechanism to disrupt the propensity for myeloma cells to become resistant to chemotherapy when they attach to the bone marrow microenvironment. “If we can disrupt this attachment, we could potentially detach the cancer cells and render them more susceptible to chemotherapy,” says Dr. Baz, adding that there is a need to develop more drugs that are capable of overcoming resistance of cancer cells to standard chemotherapy because ultimately all patients with myeloma will become refractory to conventional treatment.

Dr. Baz emphasizes the importance of basic and translational scientists who would define new targets as well as inhibitors of these targets. “We are moving steadily toward more rational drug design,” he explains. “Instead of empirically testing drugs in the clinic across different diseases, finding specific ‘targets’ for each disease for therapy is today’s goal.”

Dr. Shah agrees. “We are no longer talking wildly about the possibility of targeted treatments,” he says. “We are in that era now, and it’s a good era to be in because with rationally designed, targeted therapies, we have a real opportunity to improve both the quality and longevity of peoples’ lives.”
Dr. Shah is conducting three clinical trials, and all are based on specific targets. One trial (MCC#16775) is a combination drug study (lenalidomide and rituximab) for patients with previously untreated mantle cell lymphoma. This combination builds on the concept of lenalidomide-induced immune activation to facilitate improved response to the antibody rituximab, and has already demonstrated early and exciting clinical responses. His two other studies are designed around the idea of using antibodies as a carrier to more selectively deliver potent chemotherapy to cancer cells. These include MCC#17208, a study of SGN-CD19A for patients with B-lineage ALL, and a companion study (MCC#17303) using SGN-CD19A in patients with relapsed/refractory aggressive B-lineage non-Hodgkin lymphomas.

“All of these studies use next-generation, targeted non-chemotherapy drugs and highlight our ability to successfully treat those who previously had limited options – and doing so with far less toxicity,” he says.

**Chemotherapy-free trials**

For medical oncologist and hematologist Javier Pinilla-Ibarz, MD, PhD, the most important aspect of clinical trials for patients with chronic lymphocytic leukemia (an incurable condition in older patients) is for them to be conventional chemotherapy-free.

“Increasingly, patients want chemotherapy-free treatments,” he says. “We want to offer more chemotherapy-free trials and also offer trials with new drug combinations that will help patients get off treatments altogether.”

Moffitt medical oncologist and hematologist Celeste Bello, MD, is working as principal investigator with Dr. Pinilla-Ibarz on two similar studies that use the same combination of drugs (ofatumumab in combination with high-dose methylprednisolone followed by ofatumumab and lenalidomide consolidative therapy. One trial (MCC#16622) is designed for patients with untreated CLL or small lymphocytic leukemia (SLL); the other trial (MCC#16631) treats patients who are relapsed or refractory to CLL/SLL treatments.

Dr. Sweet, whose research and clinical interests include combination therapy for treatment of CML, is working with Dr. Pinilla-Ibarz on several trials, including a phase I/II study of ruxolitinib in combination with nilotinib (MCC#17114) for patients with CML. She describes nilotinib as a “second generation of Gleevec.”

“Since it became available more than a decade ago, Gleevec (imatinib), the first tyrosine kinase inhibitor, or TKI, has done a good job of controlling CML, which is the prototype of all hematologic malignancies,” Dr. Sweet notes. “But it does not get to the leukemia stem cells in the bone marrow. Without killing the stem cells, patients frequently relapse if treatment is discontinued. We believe the combination of drugs we are using will sensitize the stem cells to the apoptotic effects of our currently used treatments, with the hope of someday getting the patient off treatment altogether.”

Dr. Pinilla-Ibarz calls efforts to get CML patients completely off treatment “great news” for patients and for the health economy.

Drs. Sweet and Pinilla-Ibarz are also working on a trial using oral ponatinib as second-line therapy – described as a third-generation TKI - for patients with CML or patients with Philadelphia chromosome-positive ALL with resistance or intolerance to other TKIs. Prior to the development of TKIs, most patients with CML were referred to bone marrow transplants because that was the only way to possibly cure their leukemia. Since the development of TKIs, it is rare to send a patient with CML for a bone marrow transplant. Patients with AML, however, still routinely receive bone marrow transplants. “AML and CML are two very different diseases,” notes Dr. Sweet.

**Looking to the pathways and signaling**

Another “very different disease” is chronic myelomonocytic leukemia, or CMML, an aggressive, poorly understood and rare disease, with low survival rates and no known disease-modifying therapy, possibly until now. CMML, affecting only 4 people in 1,000,000, is a singular focus for Eric Padron, MD, section head, Genomics and Personalized Medicine, in the Department of Malignant Hematology. He is conducting a CMML clinical trial using ruxolitinib, an inhibitor of JAK2, a protein necessary for granulocyte-macrophage colony-stimulating factor (GM-CSF), to which CMML is hypersensitive.

The approach comes with the awareness that CMML demonstrates similar vulnerabilities of another disease - juvenile myelomonocytic leukemia (JMML). The vulnerabilities of JMML to GM-CSF, says Dr. Padron, have been known for decades.
“Because of the similarities between JMML and CMML, including the sensitivity and response to GM-CSF, we investigated the signaling cascade in CMML in the laboratory to see if the response to CMML to GM-CSF was similar to, or greater than, the response from JMML,” Dr. Padron explains. “Investigations of mutation profiles in patients with CMML correlated to those with JMML. The signaling pathways of the two diseases converged into a relatively similar clinical phenotype.”

The multicenter CMML trial with ruxolitinib is a two-stage dose-escalation study to determine dose safety and efficacy.

Making the disease “as chronic as possible”

A more common malignancy, and the focus of several clinical trials at Moffitt, is multiple myeloma, or MM.

“We are trying to make multiple myeloma as chronic as possible,” says Kenneth Shain, MD, PhD, who is conducting two MM clinical trials in which patients receive medication orally rather than intravenously. “Patients with multiple myeloma should be referred to a comprehensive cancer center like Moffitt because not only will they be evaluated and followed by an MM expert, but also they will have access to and be able to participate in clinical trials. Clinical trials provide patients with an opportunity to receive treatments they could not otherwise have access to in the community setting. Critically, their participation also will help to define the next generation of therapies for patients who come after them.”

Dr. Shain’s trials for MM include investigating the efficacy of TH-302 (MCC#17223), a hypoxia-activated prodrug for patients who are refractory or relapsed from other treatments and a phase I/II combination drug trial (MCC#17155) of plerixafor (AMD3100), bortezomib and dexamethasone, also for refractory/relapsed MM patients.

“The unique presence of hypoxia in the diseased bone marrow presents a new mechanism to specifically target multiple myeloma because TH-302 is activated by hypoxia,” says Dr. Shain.

According to Dr. Sotomayor, targeted therapies that are available in Moffitt’s clinical trials program in hematologic malignancies have great benefit for patients.

“Our clinical trials are based on confirmation of diagnosis, state-of-the-art genetic analysis, patient tumor biobanking and multidisciplinary teamwork to conduct clinical trials,” he concludes.

From chemotherapy, to Gleevec, and beyond

“In the past, all patients with hematologic malignancies would get the same treatment – chemotherapy,” recalls Eduardo Sotomayor, MD, who has been at Moffitt for 15 years. “The first big step away from this was in the mid-1990s, when a monoclonal antibody that targets CD20 entered the picture and was found to be effective for treating patients with B-cell lymphomas. Eventually more monoclonal antibodies were developed, and combinations of monoclonal antibodies and chemotherapy have cured some patients and improved outcomes for others. In the late 1990s, Gleevec, the first tyrosine kinase inhibitor, or TKI, changed everything in the field of cancer.”

The TKIs are targeted to specific cancer abnormalities and cause fewer and more manageable adverse side effects. For Dr. Sotomayor, the second-, third- and fourth-generation oral TKIs for chronic leukemias and the first generation of TKIs for B-cell malignancies are making such a difference that he can joke with patients about “taking two pills and call me in the morning.”

“These advancements are based on new knowledge about the pathways, tumor microenvironment and targets by which the TKIs can impede the malignant cell’s survival or change the tumor microenvironment to be less amenable to tumor growth,” explains Dr. Sotomayor. He adds that in the past, patients with CML needed bone marrow transplants. The TKIs have been so effective in treating CML that transplants are generally no longer needed for this type of blood cancer.

Although the newest treatments are effective, he stresses the continued need for accurate diagnosis, especially since lymphoma includes about 60 subtypes of lymphoma. While patients can be treated in the community clinical setting, he emphasizes the value of Moffitt’s pathologists in arriving at the correct diagnosis. Dr. Sotomayor also notes the value of Moffitt’s Total Cancer Care® program, in which a patient’s tumor tissue is banked and matched to future treatments as they become available.

“Personalizing medicine is our goal and we are here to serve our community colleagues,” says Dr. Sotomayor, who in addition to serving as chair of the Malignant Hematology Department, is the scientific director of the DeBartolo Family Personalized Medicine Institute. “We want to tailor treatments to the patient’s genetic makeup. This approach saves time and money and ensures that the right patient gets the right treatment at the right time.”
Select Malignant Hematology Clinical Trials at Moffitt Cancer Center

**MCC#16775**: Phase II study of lenalidomide plus rituximab in patients with previously untreated MCL.
**Contact**: Elyce Turba, 813-745-1706.

**MCC#17208**: Phase I, open-label, dose-escalation study of SGN-CD19A in patients with B-lineage ALL and highly aggressive lymphomas.
**Contact**: Deb Mimo, 813-745-7362.

**MCC#17114**: Phase I/II study of ruxolitinib in combination with nilotinib in CML patients with evidence of molecular disease.
**Contact**: Yuriama Rodriguez, 813-745-5758.

**MCC#17419**: Phase Ib/II multicenter, open-label study of oprozomib and dexamethasone in patients with relapsed or refractory multiple myeloma.
**Contact**: Liza Abramson, 813-745-7362.

**MCC#17155**: Phase I/II trial of combination plerixafor (AMD3100), bortezomib and dexamethasone in relapsed/refractory patients with multiple myeloma.
**Contact**: Yuriama Rodriguez, 813-745-5758.

**MCC#17223**: Phase I/II open-label study to assess the safety, tolerability and preliminary efficacy of TH-302 (a hypoxia-activated prodrug) and dexamethasone with or without bortezomib in subjects with relapsed/refractory multiple myeloma.
**Contact**: Liza Abramson, 813-745-7362.

**MCC#17259**: A sequential, two-stage dose-escalation study to evaluate the safety and efficacy of ruxolitinib for treating CMML.
**Contact**: Nancy Hillgruber, 813-745-2071.

**MCC#17577**: Phase II randomized, multicenter study of treatment-free remission in chronic myeloid leukemia in chronic-phase (CML-CP) patients who achieve and sustain MR4.5 after switching to nilotinib.
**Contact**: Yuriama Rodriguez, 813-745-5758.

**MCC#16631**: Phase II study of ofatumumab in combination with high-dose methylprednisolone followed by ofatumumab and lenalidomide consolidative therapy for the treatment of relapsed/refractory CLL/SLL, The HiLOG Trial.
**Contact**: Megan Borase, 813-745-2591.

**MCC#16622**: Phase II study of ofatumumab in combination with high-dose methylprednisolone followed by ofatumumab and lenalidomide consolidative therapy for the treatment of untreated CLL/SLL, The HiLOG Trial.
**Contact**: Megan Borase, 813-745-2591.

### Moffitt Instrumental In FDA Approval Of New Two-Drug Combination Therapy For Advanced Melanoma

Moffitt researchers have laid the groundwork for a revolutionary new combination therapy for the treatment of advanced melanoma - melanoma that cannot be removed surgically or has spread to other areas of the body. The newly FDA-approved therapy, Mekinist (trametinib) in combination with Tafinlar (dabrafenib), is one of the biggest advancements in melanoma treatment in the last three decades.

“Melanoma is the most aggressive type of skin cancer and the leading cause of death from skin disease,” said Jeffrey S. Weber, MD, PhD, director of Moffitt’s Melanoma Research Center of Excellence. “This new combination therapy is a huge step in the right direction for the treatment of melanoma, and our researchers played a large role in bringing this treatment option to patients.”

Mekinist and Tafinlar are used to block signaling in different sites of the same molecular pathway - the MAP kinase pathway. Keiran S. Smalley, PhD, scientific director of the Melanoma Research Center of Excellence, and his team began investigating this pathway in 2010 and discovered the best way to block its ability to promote cancer cell growth was with combined inhibitor therapy.

The new combination therapy is indicated for melanoma patients whose tumors express gene mutations called BRAF V600E and V600K. Approximately half of all metastatic melanoma patients’ tumors have a BRAF mutation, an abnormal change that can enable melanoma tumor cells to grow and spread.

BRAF-inhibitor resistance has long been a problem in the melanoma field, but Moffitt researchers found that using two inhibitors to block different growth pathways during treatment prevented resistance in patients with this mutation. “A clinical trial in which Moffitt was the major contributor showed a 76 percent success rate for patients treated with the Mekinist and Tafinlar combination. We also found this therapy reduced the incidence and severity of some of the toxic effects patients experienced when the drugs were used alone,” said Dr. Weber.

The FDA approved the combination of Mekinist and Tafinlar through its accelerated approval program, which allows the agency to approve drugs to treat a serious disease based on clinical data showing that the therapy has a proven effect and clinical benefit for patients.
Moffitt Medical Group considers it a great privilege to participate in the care of your patients and to complement the services you provide in the community. Therefore, we have developed a new site to assist you and your staff in accessing Moffitt’s resources and services. Now you can follow patient progress and stay informed from anywhere.

To schedule an appointment, call 1-888-MOFFITT or visit REFER2MOFFITT.COM

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