THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER

Melanoma HORIZONS

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
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Welcome, Professor Michael Wong, M.D., Ph.D.

Professor **Michael K. Wong, M.D., Ph.D.**, brings extensive clinical expertise, a dynamic entrepreneurial mindset, and startup biotechnology experience to the mix in his new position on the MD Anderson Melanoma Medical Oncology clinical faculty.

Dr. Michael Wong

Dr. Wong's record of leadership spans posts as medical director of clinical drug development at Roswell Park Cancer Institute; professor of medicine, Keck School of Medicine, University of Southern California; Head-Solid Tumors Section, USC Norris Comprehensive Cancer Center; and biopharmaceutical company co-founder.

Asked to elaborate on what he brings to the MD Anderson table, Dr. Wong first pointed out his biotech experience, noting that he started two biotechnology companies, both of which emanated from technology from within his academic institution at the time. In his biotech roles, he has evaluated new technologies; "played matchmaker," bringing the technology to the right people for commercial application; and shepherded applications from the nascent state to a viable biotechnology concern.

"I've been actively involved in acquiring a portfolio of intellectual property," he explained. "I am very interested in novel technology, and that comes directly from my experience as former director of drug development at Roswell Park."

Dr. Wong, who has worked in immunotherapy for nearly two decades, has a special focus on the use of new technologies in conjunction with new therapies. His aim: "to close the gaps in our knowledge of current therapy," he said, citing resistance to checkpoint inhibitors, new combination therapies, and cancer vaccines.

In addition to his focus on cutaneous melanoma, Dr. Wong is interested in other skin malignancies, like squamous cell carcinoma and Merkel cell carcinoma. He has an analytical mind that likes a challenge, given his abiding interest and research experience delving into the mysteries of mucosal melanomas, which arise from pigment-producing cells in the mucosal membranes lining the respiratory, gastrointestinal and urogenital tract.

"Mucosal melanomas are rare, poorly understood neoplasms without a consensus standard of care," Dr. Wong and his USC coauthors observed in their recent Journal of American Academy of Dermatology publication, "Mucosal melanomas in the racially diverse population of California" (Altieri L et al, epub October 2016.) They analyzed nearly 131,000 skin melanomas and 1,919 mucosal melanomas in the population-based California Cancer Registry from 1988 to 2013 to define mucosal melanoma tumor characteristics and the racial/ethnic attributes of patients with mucosal melanomas, noting that population-based data on this type of melanoma in groups other than non-Hispanic whites and blacks are "sparse."

Among their findings: Although only 1% of melanomas occurring in non-Hispanic whites in the California registry were mucosal (similar to the 1.4% found nationally), other racial/ethnic groups had a higher proportion of mucosal melanomas. Specifically, higher incidence was observed in Asian/Pacific Islanders (15%), non-Hispanic blacks (9%), and Hispanics (4%). Further, Asian/Pacific Islanders had the highest rate of metastasis.

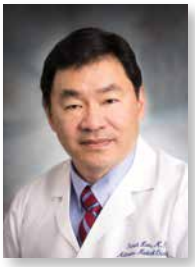
The authors concluded that mucosal melanomas differ by race/ethnicity with regard to anatomic site, stage and depth, and suggested that because early detection offers the best chance of increased survival, "greater awareness will aid clinicians who care for patients at risk for these aggressive tumors." Given the similarities in the demographics of California and Texas, Dr. Wong thinks these findings could well have local application and usefulness.

Dr. Wong has a strong interest in good communications, illustrated by honors including the 2015 USC Faculty of Medicine Teaching Award and the "Dr. Congeniality" trophy he received from the USC oncology fellows in 2014. "I'm not treating cancer; I'm treating people with cancer," Dr. Wong says of his empathetic approach to his patients. "My plan is to cure if possible, but always to look after the person. I want to understand what is important to the patient." As he sees it, his job is "to bring the power of a team to the patient," selecting those needed from the spectrum of subspecialties in MD Anderson's multidisciplinary approach.

"We are not just at the forefront of new treatments," notes Dr. Wong. "Here at MD Anderson, we are part of discovery, bringing the newest thinking and technology to bear on the patient." Besides the savvy the patient expects here, Dr. Wong aims to inspire the patient with the confidence that he can work with and trust his team members – most notably, "someone you can hope with."

MD Anderson melanoma research in the spotlight

MD Anderson melanoma research was prominently represented at major international and national scientific conferences and in the media during the last half of 2016.



Dr. Patrick Hwu

ESMO 2016: An abstract by first author **Patrick Hwu, M.D.**, MD Anderson Cancer Medicine Head and Melanoma Medical Oncology Department Chair, was selected for a poster discussion session at the European Society for Medical Oncology (ESMO) 2016 Congress in Copenhagen, Oct. 7-11, 2016. Entitled "Preliminary safety and clinical activity of atezolizumab combined with cobimetinib and vemurafenib in BRAF V600-mutant metastatic melanoma," the work provided preliminary results of a national clinical trial Dr. Hwu is leading at MD Anderson (No. 2012-0588). This trial is one of the first to evaluate the safety and effectiveness of combining targeted and immune therapies together, building upon research by Dr. Hwu's lab. Dr. Hwu discussed this study in an Oct. 31 OncLive video interview.

An abstract by first author Melanoma Medical Oncology Assistant Professor **Adi Diab, M.D.**, entitled "A first-in-human (FIH) study of PF-04518600 (PF-8600) OX40 agonist in adult patients (pts) with select advanced malignancies," was also selected for poster discussion. Additionally, Melanoma Medical Oncology Deputy Chair and Associate Professor **Michael A. Davies, M.D., Ph.D.,** presented the poster "Pooled analysis of factors to predict durable clinical outcomes with combination dabrafenib and trametinib across registration trials."

Australasian Melanoma Conference 2016: **Jennifer Wargo, M.D.,** Associate Professor of Surgical Oncology and Genomic Medicine, presented "Understanding responses to therapy: the tissue's the issue, but the scoop's in the poop" and "Resection in the age of systemic therapies" at the Australasian Melanoma Conference 2016, hosted by Melanoma Institute Australia and held Oct. 28-29, 2016, in Sydney, Australia.

SMR 2016: MD Anderson melanoma researchers held key posts at the Society for Melanoma Research 2016 Congress, held Nov. 6-9 in Boston. Melanoma Medical Oncology Department Deputy Chair and Associate Professor **Michael Davies, M.D., Ph.D.**, chaired Plenary Session 2, "Oncogenic Signaling Pathways in Immunotherapy Resistance;" Surgical Oncology Associate Professor **Jennifer Wargo, M.D.,** chaired the session "Tumor Heterogeneity in Melanoma Progression and Resistance;" and Melanoma & Skin Center Medical Director and Surgical Oncology Professor **Jeffrey Gershenwald, M.D.**, chaired the session "Melanoma Risk and Prevention/ Epidemiology."

Dr. Jeffrey Gershenwald

Investigators from MD Anderson also were selected for prestigious platform presentations. **Rodabe Amaria, M.D.,** Assistant Professor in Melanoma Medical Oncology, spoke in the session for high impact, late-breaking abstracts, "Treatment with neoadjuvant + adjuvant dabrafenib and trametinib (D+T) is associated with improved relapse-free survival (RFS) versus standard of care (SOC) therapy in patients with high-risk resectable BRAF-mutant melanoma." Dr. Amaria also appeared

Dr. Rodabe Amaria

in a related OncLive video interview published Nov. 10. **Alexandre Reuben, Ph.D.**, Postdoctoral Fellow in Surgical Oncology, presented "Genomic and immune heterogeneity in synchronous melanoma metastases is associated with differential responses to targeted therapy and immune checkpoint blockade." **Chandrani Chattopadhyay, Ph.D.**, Assistant Professor in Melanoma Medical Oncology, presented her research, "Altered mitochondrial activity in uveal melanoma cells with monosomy3." Finally, Dr. Gershenwald gave a presentation, "Melanoma Prevention and Staging: Election Day 2016 Update."

Melanoma Medical Oncology Associate Professor **Hussein Tawbi, M.D., Ph.D.**, presented the poster, "Safety of nivolumab (NIVO) plus ipilimumab (IPI) in patients with advanced melanoma (MEL) metastatic to the brain: Initial results from Phase 2 Checkmate 204," pertaining to promising early findings of a national clinical trial he is leading from MD Anderson (No. 2015-0696). Melanoma Medical Oncology Instructor **Jennifer McQuade, M.D.**, presented the poster, "High body mass index (BMI) is associated with improved clinical outcomes in metastatic melanoma patients treated with anti-PD1: differences by gender." Melanoma Medical Oncology Assistant Professor **Isabella Glitza, M.D., Ph.D.**, presented the poster "Leptomeningeal disease (LMD) from metastatic melanoma: a single institution experience and predictors of survival."

NCRI 2016: At the 2016 National Cancer Research Institute (NCRI) Cancer Conference, Nov. 6-9 in Liverpool, Surgical Oncology Associate Professor **Jennifer Wargo, M.D.**, delivered the plenary session presentation, "Understanding responses to cancer therapy: The tissue is the issue but the scoop is in the poop." The study that Dr. Wargo presented at the conference suggested "it may be possible to boost the effectiveness of immunotherapy by altering the balance of bacteria in the gut," the BBC News wrote in a Nov. 7 story headlined "Gut Bacteria May Help Drugs Fight Cancer." Other media covering the story included Medscape, the ASCO Post, R&D Magazine, and Melanoma News Today.

SITC 2016: At the 31st Annual Meeting of the Society for Immunotherapy of Cancer (SITC), Nov. 9-13, 2016, in National Harbor, MD, Melanoma Medical Oncology Department Chair and Cancer Medicine Division Head **Patrick Hwu, M.D.,** presented "Melanoma: Challenges and Opportunities and the Need for Rational Combinations of Agents." Dr. Hwu also discussed the benefits of music to oncologists as well as patients in an interview with Targeted Oncology stemming from his participation as keyboardist in The CheckPoints band, which performed during the conference. Melanoma Medical Oncology Assistant Professor **Chantale Bernatchez, Ph.D.,** presented a poster based on an abstract on which she was first author, while senior author Melanoma Medical Oncology Assistant Professor **Adi Diab, M.D.,** gave an oral presentation on "A CD122-biased agonist increases CD8+T cells and natural killer cells in the tumor microenvironment: Making cold tumors hot with NKTR-214." In the "New Cancer Immunother-

apy Agents in Development" session, Dr. Diab presented the findings to date from an ongoing clinical trial which he leads at MD Anderson (No. 2015-0573). Dr. Diab was interviewed on the subject by Targeted Oncology.

Melanoma Medical Oncology Instructor **Cara Haymaker, Ph.D.**, was selected for a SITC 2016 Travel Award and oral presentation of her abstract, "Reactivating the anti-tumor immune response by targeting innate and adaptive immunity in a phase I/II study of intratumoral IMO-2125 in combination with systemic ipilimumab in patients with anti-PD-1 refractory metastatic melanoma." The abstract she presented in the "State-of-the-Art Immunotherapies: Challenges and Opportunities" session was based on findings to date from an MD Anderson clinical trial (No. 2015-0530) led by abstract senior author and Melanoma Medical Oncology Assistant Professor **Adi Diab, M.D.**

Cancer Medicine Division Hematology/Oncology fellow **Gustavo Schvartsman, M.D.**, was selected for oral presentation for "Incidence and outcomes of central nervous system metastasis in metastatic melanoma patients treated with anti-PD1 therapy"; Melanoma Medical Oncology Assistant Professor **Isabella Glitza, M.D., Ph.D.,** was senior author. Melanoma Medical Oncology Instructor **Yared Hailemichael, Ph.D.**, presented the poster, "Integrin activator 7HP349 enhances anti-CTLA-4 antibody-based cancer therapy." Melanoma Medical Oncology Assistant Professor **Sapna Patel, M.D.,** presented the poster, "Changes in uveal melanoma immune infiltrate in response to checkpoint blockade." Melanoma Medical Oncology postdoctoral fellow **Faisal Fa'ak, M.D.**, presented a poster based on the abstract on which he was second author, "NKTR-214, an engineered cytokine, synergizes and improves efficacy of anti-cancer vaccination in the treatment of established murine melanoma tumors." Melanoma Medical Oncology postdoctoral fellow **Meenu Sharma, Ph.D.**, was first author, while Melanoma Medical Oncology Professor **Willem Overwijk, Ph.D.,** was senior author.

Melanoma Medical Oncology Deputy Chair and Associate Professor **Michael A. Davies, M.D., Ph.D.,** was the senior author of an article published in December 2016 in the prestigious, high-impact journal Lancet Oncology, entitled "Factors predictive of response, disease progression, and overall survival after dabrafenib and trametinib combination treatment: a pooled analysis of individual patient data from randomised trials."


Dr. Michael A. Davies

In a Dec. 7 story highlighting the article, MD Anderson Cancer Frontline noted: "The largest analysis of metastatic melanoma patients who received a targeted therapy combination shows the treatment provides long-term survival for some and furnishes new, important context for sorting out treatment options."

Providing context, Dr. Davies observed that over the past 5 years, the treatment of advanced melanoma has been revolutionized by both targeted therapies and immune therapies.

"The general thought has been that only immunotherapy can achieve long-term benefit in advanced melanoma," he said. "However, this large study with two years of follow-up shows long-term survival is accomplished in subsets of patients treated with targeted therapy. Ultimately we need to determine what factors accurately predict who will benefit the most from targeted therapy and who will benefit from immunotherapy, so that we can optimize and personalize treatments for each patient."

Oncology Nurse Advisor and Clinical Therapy Advisor covered the retrospective analysis in articles published Nov. 17 and 19, respectively. In addition, Dr. Davies appeared in several OncLive videos published during December, featuring expert panel discussions of "The Current Understanding of Biomarkers in Melanoma" (Dec. 12); "Case I: Newly Diagnosed BRAF Wild Type Advanced Melanoma (Dec. 20); and "Melanoma: Helping Patients Understand Immunotherapy" (Dec. 22.)

Melanoma Moon Shot impact increasing

MD Anderson Melanoma Moon Shot efforts are making increasing strides, as indicated by the widely publicized results of a Texas tanning salon study as well as the expansion of a sun safety program for children.

The MD Anderson study, which was published as a research letter in November 2016 in JAMA Dermatology, found that 81 percent of the facilities contacted in a phone survey complied with the state law banning tanning bed use by individuals under the age of 18.

"This level of compliance with the under-18 ban enacted by the Texas Legislature in 2013 underscores the importance of this approach as a strategy for skin cancer prevention," said **Mary Tripp, Ph.D.**, of Behavioral Science and lead author of the study.

Faculty and governmental relations leaders in the Melanoma Moon Shot and the Cancer Prevention and Control Platform provided information about indoor tanning and cancer risk to Texas legislators and served as the primary clinical and research resources on the Texas ban on indoor tanning for those under 18. Texas was the fourth state to enact a ban, and since it became effective in September 2013, Moon Shot educational efforts have shifted to other states.

Research shows that indoor tanning before the age of 18 increases a person's risk of developing melanoma by 85 percent. In 2013, 1.6 million youths under the age of 18 reported indoor tanning, including 20 percent of female high school students.

Co-authors of the research letter were **Jeffrey Gershenwald, M.D.**, of Surgical Oncology; **Michael Davies, M.D., Ph.D.**, of Melanoma Medical Oncology; **Joxel Garcia, M.D.**, executive director of the Cancer Prevention and Control Platform; **Ernest Hawk, M.D.**, vice president and head of the division of Cancer Prevention and Population Sciences; and **Ellen Gritz, Ph.D.**, and **Susan Peterson, Ph.D.**, of Behavioral Science. Drs. Gershenwald and Davies are co-leaders of the Melanoma Moon Shot.

In other Melanoma Moon Shot developments, the "Ray and the Sunbeatables" program, created by MD Anderson behavioral scientists led by Drs. Tripp, Gritz and Peterson to bring sun protection education to the nation's children, has undergone an expansion. At its launch in early 2015, the sun safety program's curriculum targeted children in preschool classrooms. In August 2016, curriculum targeting kindergarten through first-grade students became available.

Clinical Trials in Melanoma Medical Oncology

For more information on these trials, call the toll-free AskMDAnderson number, 1-877-632-6789. The print version of this list was up to date as of our Jan. 2, 2017 copy deadline. To see all the MD Anderson Melanoma Medical Oncology Department clinical trials that are current at any given time, visit the MD Anderson Melanoma Medical Oncology Department website and click on the Clinical Trials list.

Neoadjuvant

Neoadjuvant and Adjuvant Dabrafenib and Trametinib Compared to Upfront Surgery in Patients with Clinical Stage III or Oligometastatic Stage IV Melanoma (Combi-Neo) (2014-0409) (NCT02231775)

Principal Investigator: Jennifer Wargo, M.D.

Co-Principal Investigator: Rodabe Amaria, M.D.

The goal of this clinical research study is to compare receiving the combination of dabrafenib and trametinib before surgery to having surgery alone in patients with melanoma. The safety of the study drug combination will also be studied.

Neoadjuvant and Adjuvant Checkpoint Blockade in Patients with Clinical Stage III or Oligometastatic Stage IV Melanoma (2015-0041) (NCT02519322)

Principal Investigator: Rodabe Amaria, M.D.

The goal of this clinical research study is to learn if giving nivolumab alone or in combination with ipilimumab before and after surgery can help to control metastatic melanoma. The safety of these drugs will also be studied.

Adjuvant

A Phase III Randomized Trial Comparing High Dose Interferon to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma (S1404) (NCT02506153)

Principal Investigator: Sapna P. Patel, M.D.

This randomized Phase III trial studies how well high-dose recombinant interferon alfa-2B works compared with pembrolizumab in treating patients with stage III-IV melanoma that has been removed by surgery but is likely to come back or spread. High-dose recombinant interferon alfa-2B may help shrink or slow the growth of melanoma. Monoclonal antibodies, such as pembrolizumab, may block tumor growth in different ways by targeting certain cells. It is not yet known whether high-dose recombinant interferon alfa-2B is more effective than pembrolizumab in treating patients with melanoma.

Chemotherapy-Naive Patients (no previous chemotherapy)

Phase II Study of Abraxane Plus Ipilimumab in Patients with Metastatic Melanoma (2011-1157) (NCT01827111)

Principal Investigator: Adi Diab, M.D.

The goal of this clinical research study is to learn if the combination of ipilimumab and ABI-007 (abraxane) can help to control metastatic melanoma. The safety of this drug combination will also be studied. Ipilimumab is designed to increase the immune system's ability to fight cancer. ABI-007 is designed to stop cancer cells from making new DNA (the genetic material of cells.) This may stop the cancer cells from dividing into new cells.

A Phase Ib, Open-label Study of the Safety and Pharmacology of Atezolizumab (Anti-PD-L1 Antibody) Administered in Combination with Vemurafenib or Vemurafenib Plus Cobimetinib in Patients with BRAF (V600) Mutation-Positive Metastatic Melanoma (2012-0588) (NCT01656642)

Principal Investigator: Patrick Hwu, M.D.

The goal of this pre-screening test is to learn if you may be eligible to take part in the main study. The goal of the main clinical research study is to find the highest tolerable dose of MPDL3280A (Atezolizumab) that can be given in combination with vemurafenib (Zelboraf) or vemurafenib plus cobimetinib (GDC-0973) to patients with locally advanced or metastatic BRAF mutant melanoma. The safety of the drug combination will also be studied.

Patients with Previous Chemotherapy

A Multi-Center Phase 2 Open-Label Study to Evaluate Safety and Efficacy in Subjects with Melanoma Metastatic to the Brain Treated with Nivolumab in Combination with Ipilimumab Followed by Nivolumab Monotherapy (2015-0696) (NCT02320058)

Principal Investigator: Hussein Tawbi, M.D., Ph.D.

The goal of this clinical research study is to learn about how treatment with the combination of Opdivo (nivolumab) and Yervoy (ipilimumab) may affect the disease that has spread to the brain. Researchers will also test if the drugs can control the disease outside the brain and the safety of the drugs.

A Phase II Study of the Anti-PD-1 Antibody Nivolumab in Combination with Dabrafenib and/or Trametinib in Patients with BRAF or NRAS-mutated Metastatic Melanoma (2015-0605) (NCT02910700)

Principal Investigator: Hussein Tawbi, M.D., Ph.D.

The goal of this clinical research study is to learn if nivolumab and trametinib (either alone or in combination with dabrafenib) can help to control metastatic melanoma in patients who have a BRAF or NRAS mutation.

A Phase 1/2, Open-Label, Multicenter, Dose Escalation and Dose Expansion Study of NKTR-214 and Anti-PD-L1 (Atezolizumab) or Anti-PD-1 (Nivolumab, Pembrolizumab) in Patients with Select Locally Advanced or Metastatic Solid Tumor Malignancies (2016-0753) (NCT02983045)

Principal Investigator: Adi Diab, M.D.

The goal of this clinical research study is to find the highest tolerable dose of the study drug NKTR-214 that can be given in combination with standard drugs to patients who have melanoma, non-small cell lung cancer (NSCLC), renal cancer, or bladder cancer that is metastatic (has spread) or has returned. Researchers also want to learn more about the safety and effects of the study drug combinations. There are 2 parts to this study: Part 1 (dose escalation) and Part 2 (dose expansion). The standard drugs being used in this study are Tecentriq (atezolizumab), Opdivo (nivolumab), and Keytruda (pembrolizumab).

A Phase I/II Study to Assess the Safety and Efficacy of Intratumoral IMO-2125 in Combination with Ipilimumab in Patients with Metastatic Melanoma (2015-0530) (NCT02644967)

Principal Investigator: Adi Diab, M.D.

The purpose of this clinical research study is to find the highest tolerated dose of the study drug IMO-2125 that can be given in combination with ipilimumab to patients with metastatic melanoma. Researchers also want to learn if the study drug combination can help to control the disease. The safety of the drug combination will also be studied.

A Phase 1/2, Open-Label, Multicenter, Dose Escalation and Dose Expansion Study of NKTR-214 in Subjects with Locally Advanced or Metastatic Solid Tumor Malignancies (2015-0573)

Principal Investigator: Adi Diab, M.D.

The goal of this clinical research study is to find the highest tolerable dose of the study drug NKTR-214 that can be given to patients with advanced or recurrent solid tumors. Researchers also want to learn if NKTR-214 can help to control the disease. This is the first study using NKTR-214 in humans.

Phase I/II Study of Dabrafenib, Trametinib, and Navitoclax in BRAF Mutant Melanoma and Other Solid Tumors (2014-0020) (NCT01989585)

Principal Investigator: Michael A. Davies, M.D., Ph.D.

The purpose of the second part of this study (Phase II) is to compare the good and bad effects of navitoclax in combination with dabrafenib and trametinib to using the usual approach of dabrafenib and trametinib in patients with BRAF-mutant melanoma. This study will allow the researchers to know whether this different approach is better, the same, or worse than the usual approach.

A Phase I, Open-Label, Dose Escalation Study of PF-04518600 in Patients with Locally Advanced or Metastatic Hepatocellular Carcinoma (HCC), Melanoma, Clear Cell Renal Cell Carcinoma (RCC) or Squamous Cell Head and Neck Cancer (SCCHN) (2014-0996) (NCT02315066)

Principal Investigator: Adi Diab, M.D.

The goal of this clinical research study is to find the highest tolerable dose of the study drug PF-04518600 that can be given to patients with advanced cancer. Researchers also want to learn more about the effects of the study drug. The safety of the drug will also be studied.

A Phase II Open-Label, Two-Arm Study of the MEK Inhibitor, Trametinib, to Investigate the Safety and Anti-Cancer Activity in Subjects with Melanoma with BRAF non-V600 Mutations (2014-0766) (NCT02296112)

Principal Investigator: Michael Davies, M.D., Ph.D.

Some types of melanoma have a kind of BRAF mutation called a BRAF V600 mutation. A drug called trametinib is FDA-approved and commercially available to treat these types of melanoma. The goal of this clinical research study is to learn if trametinib can help to control melanoma with a BRAF mutation that is not a BRAF V600 mutation. The safety of this drug will also be studied.

Phase II Study of MK-3475 in Conjunction with Lymphodepletion, TIL, and High or Low Dose IL-2 in Patients with Metastatic Melanoma (2014-0922) (NCT02500576)

Principal Investigator: Rodabe Amaria, M.D.

The goal of this clinical research study is to learn if pembrolizumab, an infusion of T-cells, chemotherapy (cyclophosphamide and fludarabine), and either high- or low-dose interleukin-2 (IL-2) can help to control metastatic melanoma. The safety of this drug combination will also be studied. T-cells are white blood cells in your body that are important to the immune system. The T-cells used in this study will be collected and grown in a separate study (MD Anderson Protocol 2004-0069.)

An Open-Label, Multicenter, Dose-Escalation, Phase 1b/2 Study of the Safety, Efficacy, Pharmacodynamics, and Pharmacokinetics of RTA 408 in Combination with Ipilimumab in the Treatment of Patients with Unresectable or Metastatic Melanoma (2014-0613) (NCT02259231)

Principal Investigator: Sapna Patel, M.D.

The goal of Part 1 of this clinical research study is to find the highest tolerated dose of RTA 408 that can be given with ipilimumab to patients with unresectable or metastatic melanoma. The safety of this drug combination will also be studied. The goal of Part 2 of this study is to learn if giving RTA 408 with ipilimumab can help to control unresectable or metastatic melanoma.

Lymphodepletion Plus Adoptive Cell Transfer with TGF-beta Resistant (DNRII) and NGFR Transduced T-Cells Followed by High-Dose Interleukin-2 in Patients with Metastatic Melanoma (2012-0758) (NCT01955460)

Principal Investigator: Rodabe Amaria, M.D.

The goal of this clinical research study is to find the highest tolerable dose of T-cells injected with the genes TGFb-DNR and NGFR that can be given in combination with chemotherapy (cyclophosphamide and fludarabine) and aldesleukin to patients with metastatic melanoma.This study involves gene therapy. T-cells are types of white blood cells that help your body fight infections. They may recognize and kill melanoma cells. Researchers want to grow your T-cells in a laboratory, inject them with TGFb-DNR and NGFR genes which may help them recognize tumor cells, and then give them back to you by vein. This may help to control melanoma. Cyclophosphamide is designed to block cancer cells from dividing, which may slow or stop their growth and spread throughout the body. This may cause the cancer cells to die. Fludarabine is designed to interfere with the DNA (genetic material) of cancer cells, which may cause the cancer cells to die. Aldesleukin is designed to block the activity of cells that may decrease the immune system's ability to fight cancer.

A Phase I/II Study of Lymphodepletion Plus Adoptive Cell Transfer with T-Cells Transduced with CXCR2 and NGFR Followed by High-Dose Interleukin-2 in Patients with Metastatic Melanoma (2009-0471) (NCT01740557)

Principal Investigator: Rodabe Amaria, M.D.

The goal of this clinical research study is to learn the side effects of T-cells injected with CXCR2 and NGFR when given in combination with chemotherapy (cyclophosphamide and fludarabine) and aldesleukin to patients with metastatic melanoma in an attempt to allow them to better localize the tumor. The safety of this combination will also be studied.

T-Cells +/- Dendritic Cells (2004-0069) Phase II (NCT00338377)

Principal Investigator: Patrick Hwu, M.D.

In this study, T-cells capable of recognizing and killing melanoma will be isolated from tumor biopsies and expanded in the laboratory. The T-cells will then be reinfused into the patients with or without dendritic cells, which are immune cells capable of potently activating T-cells. This study is for patients with a good performance status, with measurable metastatic melanoma, and a site that can easily be biopsied.

Induction of antitumor response in melanoma patients using the antimicrobial peptide LL37 (2013-0422) (NCT02225366)

Principal Investigator: Rodabe Amaria, M.D.

The goal of this clinical research study is to find the appropriate dose of LL37 that can be given to patients with melanoma. Researchers also want to learn if LL37 can stimulate the immune system to help control the disease.

Phase II Study of Cellular Adoptive Immunotherapy Using Autologous CD8+ Antigen-Specific T Cells and Anti-CTLA4 for Patients with Metastatic Melanoma (2012-1055) (NCT02027935)

Principal Investigator: Cassian Yee, M.D.

The goal of this clinical research study is to learn about the safety of giving CD8+ T cells with ipilimumab, cyclophosphamide, and IL-2 (aldesleukin). Researchers also want to learn if this combination can help to control metastatic melanoma.

A Phase 1/2 Dose Escalation and Cohort Expansion Study of the Safety and Tolerability of Urelumab Administered in Combination with Nivolumab in Advanced/Metastatic Solid Tumors and B Cell Non-Hodgkins Lymphoma (2014-0651) (NCT02253992)

Principal Investigator: Vali Papadimitrakopoulou, M.D.

Co-Principal Investigator: Adi Diab, M.D.

The goal of Part 1 of this study is to find the highest tolerable dose of urelumab and nivolumab when given in combination to patients with advanced solid tumors or B-cell NHL. The goal of Part 2 is to learn if the dose found in Part 1 can help to control melanoma, NSCLC, SCCHN, and/or DLBCL. The safety of this drug combination will be studied in both parts of the study. The goal of this part of the study (called "Continuation of Therapy") is to continue to study the effects of the study drug after the disease has appeared to get worse.

Patients with Uveal Melanoma

A Phase 2 Study of CDX-011 (Glembatumumab Vedotin) for Metastatic Uveal Melanoma (NCI9855) (NCT02363283)

Principal Investigator: Sapna P. Patel, M.D.

The primary objective of this study is to characterize the clinical anti-tumor activity of CDX-011 (glembatumumab vedotin) as a single agent in the treatment of patients with metastatic uveal melanoma. Secondary objectives include a description of the clinical safety and benefit of CDX-011 and pharmacodynamics changes in glycoprotein NMB (GPNMB) expression. Exploratory objectives include characterization of the anti-tumor immunophenotype of patients receiving treatment. Post hoc, correlation of rash with clinical benefit, or lack of rash with lack of benefit, will also be explored.

Phase II Study of Nivolumab in Combination with Ipilimumab for Uveal Melanoma (2011-0919) (NCT01585194)

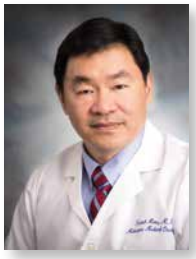
Principal Investigator: Sapna P. Patel, M.D.

The goal of this clinical research study is to learn if ipilimumab and nivolumab can help to control uveal melanoma. Ipilimumab is designed to increase the immune system's ability to fight cancer. Nivolumab is an antibody (a protein that attacks foreign cells) that is designed to allow the body's immune system to work against tumor cells.

Major grants fund MD Anderson melanoma research

MD Anderson melanoma research projects recently received major grant funding from the Cancer Prevention and Research Institute of Texas (CPRIT) and the National Institutes of Health/ National Cancer Institute (NIH/NCI.)

Overall, MD Anderson Cancer Center was awarded $22 million from CPRIT in November 2016, receiving 24 percent of the total $93 million awarded through CPRIT's academic research and product development research programs. Cancer Medicine Division Head and Melanoma Medical Oncology Chair **Patrick Hwu, M.D.**, and Melanoma Medical Oncology Department Assistant Professor **Scott E. Woodman, M.D., Ph.D.**, received two of the grants awarded in the Individual Investigator Research category.



Dr. Patrick Hwu

Dr. Scott Woodman

The first CPRIT grant provides $900,000 for a proposal by Dr. Hwu, principal investigator (PI), and Co-PI **Weiyi Peng, M.D., Ph.D.**, entitled "Targeting the Glycolysis Pathway to Overcome Resistance to Cancer Immunotherapy." While immunotherapies have demonstrated durable cures in many patients with metastatic melanoma, most cancer patients still fail to respond. In order to develop new strategies to evoke better responses, there is a critical need to improve our understanding of the factors that cause resistance.

Previous studies by this team have shown that some tumor cells escape the immune system's attack by increasing glycolysis, which breaks down glucose to generate energy and other building blocks required for cell growth. Building upon those initial findings, the investigators will perform in-depth studies of the role of tumor cell metabolism in immunotherapy resistance. "The potential benefits of these studies include identifying patients who are most likely to benefit from immunotherapies, and the development of personalized combinations that can be tested in future clinical trials."

The second CPRIT grant provided $899,507 for Dr. Woodman's proposal, "Developing Effective Immunotherapeutic Strategies for Advanced Uveal Melanoma." Uveal melanoma is the most common malignant tumor of the eye in adults. Dr. Woodman observed that while genes in cutaneous melanoma are highly mutated, those in uveal melanoma have very few mutations and are more resistant to recognition and elimination by the immune system and immune-boosting therapies.

"We hypothesize that the few hallmark genetic alterations that characterize uveal melanoma play an important role in creating an immunosuppressive environment within the tumor," Dr. Woodman explained. "We will determine the key genetic and molecular mechanisms by which UM cells evade and are resistant to elimination by immune cells. A deeper understanding of these fundamental pathological processes will provide insight into potentially more effective therapeutic strategies for uveal melanoma." Melanoma Medical Oncology Assistant Professor **Sapna Patel, M.D.,** is co-PI on Dr. Woodman's CPRIT grant.

Dr. Sapna Patel

Dr. Patel was also awarded an NIH/NCI R21 grant providing $377,580 for 2 years in support of her project, "Unlocking Tumor Immunophenotype in Responders versus Non-Responders in Metastatic Uveal Melanoma Patients Receiving Immune Checkpoint Blockade."

Dr. Jennifer Wargo

"We will study patients on our clinical trial 2011-0919 as well as those receiving checkpoint blockade outside of the clinical trial, and evaluate their blood and tumor biopsies to determine if there are signatures at the blood/tumor level that predict or correlate with response to treatment," Dr. Patel explained. Surgical Oncology Associate Professor **Jennifer Wargo, M.D.**, is co-PI on Dr. Patel's grant.

MD Anderson Melanoma Medical Oncology Associate Professor **Greg Lizee, Ph.D.**, received subcontract funding on the $900,000 CPRIT grant "Structural Modeling of Peptide-HLA Complexes Presenting a Melanoma-Associated Antigen for Cross-Reactivity Assessment" awarded to Rice University Computer Science and Bioengineering Professor Lydia Kavraki, Ph.D.

Dr. Greg Lizee

T-cell-based immunotherapies have proven to be very effective at eradicating tumor cells in many cancer patients, but its application in a larger scale has been prevented in part by safety concerns, such as incidents of unexpected off-target toxicity of the therapeutic T-cells. The proposal presented a new approach to perform T-cell cross-reactivity assessment in melanoma-associated peptides, employing new computer methods combined with standard assays, to select T-cell lines that are safe for use in clinical trials. These studies are predicted to contribute to the development of other T-cell-based therapies and open new research avenues that will have a positive impact in other human diseases.

Dr. Lizee is also PI on a subaward from an NIH/NCI exploratory/development grant to project leader Dr. Kavraki. The NIH/NCI grant will fund $182,000 for their work on a project entitled "Structure-based selection of tumor antigens for T-cell-based immunotherapy." This research project will focus on providing new computer methods needed to improve the selection of targets in the development of personalized immunotherapies for cancer patients.

Lab coup leads to new hope for immunotherapy-resistant patients

A melanoma research team's breakthrough, which became a top-ranking journal's cover story in early 2016, has led to a promising clinical trial aimed at overcoming immunotherapy resistance in melanoma patients.

Expected to open in early 2017, the trial follows the February 2016 publication of the article, "Loss of PTEN promotes resistance to T cell-mediated immunotherapy" in Cancer Discovery by a team of investigators headed by Melanoma Medical Oncology Assistant Professor **Weiyi Peng, M.D., Ph.D.**

Dr. Weiyi Peng

Checkpoint inhibitors block molecules on the surface of T cells that act as brakes on the immune system. Blocking these inhibitory factors releases the immune cells to attack tumors. Treatment with anti-PD-1 antibodies, such as pembrolizumab and nivolumab, has become well known for its many success stories, including that of former President Jimmy Carter, but it doesn't work for all melanoma patients.

Dr. Hussein Tawbi

In the study led by Dr. Peng, she and her colleagues show that loss of a tumor-suppressor gene called PTEN in melanoma tumor cells promotes resistance to checkpoint inhibitor immunotherapy. Dr. Peng cited two key study observations: "First, PTEN loss in melanoma patients was associated with reduced numbers of T cells – the key immune cells that kill cancer cells - in the tumors. Second, in comparison to melanoma patients with intact PTEN, melanoma patients with loss of PTEN were less likely to respond to anti-PD-1 immunotherapy." Thus, PTEN loss may be an important biomarker to predict resistance to immunotherapy.

Further, they showed that treatment with an experimental PI3K-beta inhibitor, which targets the pathway that is activated in tumor cells with loss of PTEN, improved the efficacy of anti-PD-1 treatment in laboratory models. "These results allowed us to devise a means to combat PTEN loss in melanoma patients," said Dr. Peng.

Based on these results, Associate Professor **Hussein Tawbi, M.D., Ph.D.**, is leading a phase I/II clinical trial that will test the safety and efficacy of combining pembrolizumab, an FDA-approved anti-PD-1 antibody, with GSK2636771, a PI3K-beta inhibitor, in patients with metastatic melanoma who lack the PTEN gene.

"About one-third of melanoma patients respond to pembrolizumab, which means there are two-thirds of patients in whom we need to do better. This trial is a very significant step in that direction," said Dr. Tawbi, explaining the rationale and significance of the trial, for which he obtained funding from two major pharmaceutical companies familiar with his outstanding clinical trial track record.

This effort capitalizes on the skills of targeted therapy experts like Melanoma Medical Oncology Department Deputy Chair **Michael Davies, M.D., Ph.D.**, and immune therapy experts like Dr. Peng and **Patrick Hwu, M.D.**, Melanoma Medical Oncology Department Chair and Cancer Medicine Division head. Dr. Davies and Dr. Hwu were co-senior authors of the article.

"This exciting clinical trial builds upon the collaborative research we have undertaken at MD Anderson to understand the interactions between oncogenic signaling pathways and the anti-tumor immune response, using our combined expertise and resources in these two areas," said Dr. Davies. "In addition to representing an important new clinical trial for patients with advanced melanoma, the results and translational research from this trial may have impact for many other cancer types in which loss of PTEN occurs."

Melanoma Philanthropic Funding

Special appreciation is extended to the following donors, who were reported by MD Anderson's Development Office as among those recently contributing $1,000 or more:

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Gifts fuel MD Anderson melanoma mission: To donate by mail to our melanoma research efforts, please send a check made out to "MD Anderson Cancer Center" specifying "Melanoma Vaccines" in the memo line to **Dr. Patrick Hwu**, Chair, Melanoma Medical Oncology Department, 1515 Holcombe Blvd., unit 430, Houston, TX 77030. Thank you!

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Mulva gift benefits melanoma research

James and Miriam Mulva and the **Mulva Family Foundation** have donated $25 million to support melanoma and prostate cancer research at MD Anderson.

The use of the funds will be overseen by Melanoma Medical Oncology Department Chair **Patrick Hwu, M.D.**, and Genitourinary Medical Oncology Department Chair **Christopher Logothetis, M.D.** Both melanoma and prostate cancer are diseases included in MD Anderson's Moon Shots Program, launched in 2012 to significantly reduce cancer deaths and transform care. The gift, to be divided equally, is designed to accelerate the conquest of these two aggressive cancers and change the standard of care for patients around the world.

"This transformational gift is a reflection of the Mulva family's extraordinary generosity and dedication to advancing the fight to end two of our most menacing foes — melanoma, the deadliest form of skin cancer, and prostate cancer, the second leading cause of cancer deaths in men," said MD Anderson President **Ronald A. DePinho, M.D.** "We are profoundly grateful for the Mulva Family Foundation's remarkable support of MD Anderson's mission."

James and Miriam Mulva and the **Mulva Family Foundation** also donated $50 million to advance neuroscience at The University of Texas at Austin. The donation creates the Mulva Clinic for the Neurosciences, which will be located at the Dell Medical School at UT Austin. The Mulva Clinic will underwrite neuroscience patient care, research and clinical operations, with a special emphasis initially on Alzheimer's disease, Parkinson's disease, stroke and bipolar disorder.

Next Melanoma Walk set for September after 2016 success

MD Anderson Cancer Medicine Division Head and Melanoma Medical Oncology Department Chair **Patrick Hwu, M.D.**, extends his thanks to all the supporters of the successful 9th Annual AIM for the CURE Melanoma Walk & Fun Run on Sept. 17, 2016, at MD Anderson and invites everyone to the next Walk, slated for Sept. 23, 2017.

On Oct. 18, 2016, AIM at Melanoma Foundation representatives presented Dr. Hwu with a check for $96,000 to support MD Anderson melanoma research. The funds will be used to support many new clinical trials for patients with advanced melanoma, providing them with more treatment options. These include new trials in patients with earlier stages of disease, with early results showing unprecedented benefits that have the potential to change the way melanoma will be treated in the future. Funds will also be used to support clinical sample collections, analysis of biospecimens from patients being treated for melanoma, and cutting-edge lab research to identify and overcome the causes of therapeutic resistance.

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