UPMC HILLMAN CANCER CENTER

CANCER INSIGHTS

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UPMC HILLMAN CANCER CENTER

Inside This Edition

Introduction

We are pleased to present you with this issue of *Cancer Insights.*

As one of the largest integrated cancer networks in the United States, UPMC Hillman Cancer Center delivers quality patient care and participates in groundbreaking research. With more than 500 clinical trials and more than 2,000 physicians, researchers, and staff, we are advancing the latest research discoveries, driving clinical innovation, and pioneering new therapies to ensure that patients receive the best care possible.

In this issue of *Cancer Insights,* we highlight four areas in which we are translating innovative bench research into cutting-edge care at the bedside:

- **T-Cell Metabolism and the Tumor Microenvironment: Cracking the Metabolic Pathways to Enhanced Immunotherapy Response** – An overview of the role of T-cell metabolism and exhaustion in the tumor microenvironment.
- **Adoptive Cell Transfer Immunotherapy Trials Show Promising Results for Metastatic Uveal Melanoma** – A look into the research and clinical trials using immunotherapy to treat this exceptionally rare cancer.
- **Atezolizumab and Nab-Paclitaxel as First-Line Treatment for Metastatic Triple-Negative Breast Cancer** – New combination therapy shows promise for advanced disease.
- **Melanoma and Immunotherapy: Therapeutic Firsts and Ongoing Advances at UPMC Hillman Cancer Center**.

We are extremely proud of the research and clinical activities at UPMC Hillman Cancer Center. We also are pleased to announce a major opportunity for growth — the founding of a new immunotherapy center at UPMC Hillman, made possible by a generous $5 million pledge from the Mario Lemieux Foundation. To learn more about the research this gift will make possible, don't miss the next issue of *Cancer Insights.*

For more information about our program, please visit **UPMCPhysicianResources.com/Cancer**.

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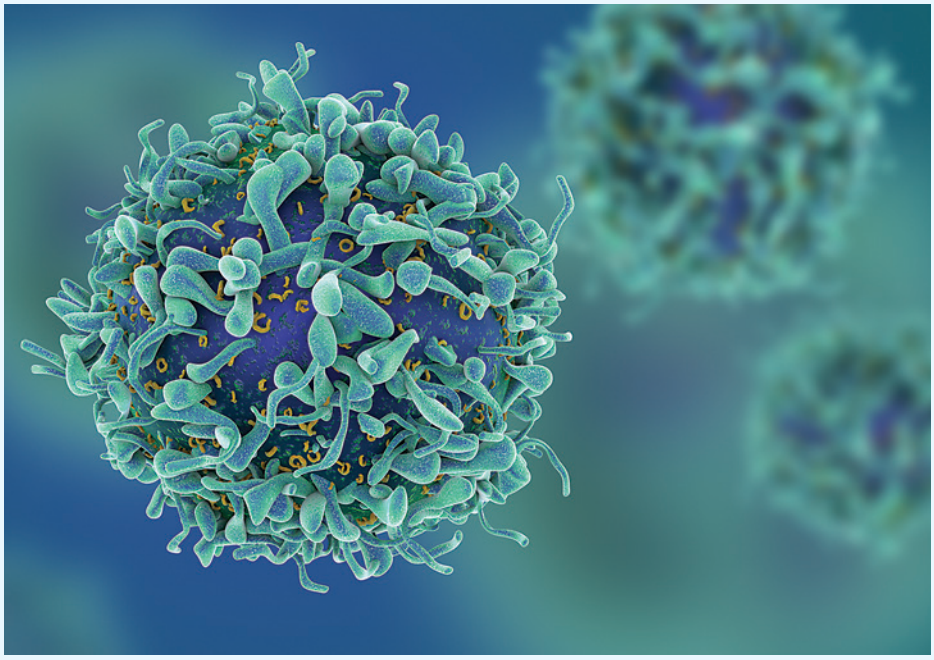
T-Cell Metabolism and the Tumor Microenvironment:

Cracking the Metabolic Pathways to Enhanced Immunotherapy Response

The role of T-cell metabolism and exhaustion in the world of the tumor microenvironment and with respect to increasing the efficacy of immunotherapy agents is the focus of research for **Greg M. Delgoffe, PhD** and his laboratory in the Department of Immunology at the University of Pittsburgh and UPMC Hillman Cancer Center.

Dr. Delgoffe joined the University of Pittsburgh in 2014 after completing his PhD at Johns Hopkins, followed by postdoctoral work at St. Jude Children's Research Hospital. Much of the work at the Delgoffe laboratory is devoted to understanding aspects of T-cell metabolism, how T cells respond to or are inhibited by tumor cells and the tumor microenvironment (TME), and how we may be able to enhance or reprogram their ability to withstand and operate within the inhospitable, immunosuppressive world of the tumor. This work, of course, is related to understanding how immunotherapies such as PD-1 or PD-L1 checkpoint inhibitors can be improved to benefit more individuals and how to enhance the response factor in those that do see benefits from these therapies. The lab currently has investigations into aspects of T cell metabolic exhaustion and metabolic reprogramming, how to remodel or reshape the TME to provide a more hospitable environment for immunotherapy agents and native T-cell function, and aspects of T-cell signaling.

More recent work in Dr. Delgoffe's lab has uncovered how the scarcity of nutrients within the tumor microenvironment affects T-cell function and survivability. "The tumor microenvironment is poorly perfused, relatively speaking, and this is part of what makes it a not very ideal working environment for cytotoxic T cells to do their job. Cellular nutrients, which T cells need to thrive and work efficiently, are in low supply, and they have to compete for these resources with the very tumor cells they are trying to eliminate. It makes for difficult work," says Dr. Delgoffe. Improving this working environment is one of the ways in which it might be possible to elicit better responses from existing immunotherapy agents.



Another important finding from the lab in recent years has uncovered the fact that the mitochondria inside the T cells actually degrade, or shrink, in the face of the TME, which causes them to essentially starve, thereby losing the capacity to carry out their proper functions.

Tumor Microenvironment Immunosuppressive Characteristics

What makes the tumor microenvironment generally immunosuppressive in nature and hostile to T cells? It lacks glucose to support cellular energy needs. The environment tends to be acidic in nature from the accumulation of metabolic byproducts of tumor cell respiration, and tumor cells actively work to suppress the immune function of cytotoxic T cells by upregulating regulatory T cells.

The tumor microenvironment also is hypoxic, and this aspect of the TME is becoming more of a focus of study for Dr. Delgoffe and his laboratory — the role of oxygenation, or lack thereof, of the tumor and the consequences of this with respect to immunotherapy response.

Feed a Regulatory T Cell, Starve a Cytotoxic One — Or Maybe Asphyxiate It

Dr. Delgoffe published work in 2016 showing that tumors are actively feeding regulatory T cells to help them evade detection by cytotoxic T cells. In essence, by providing

needed nutrients to regulatory T cells, the tumors help them to proliferate and create an overly suppressive environment, which works to shut down or inhibit the cytotoxic response that would otherwise occur.

"We have found that regulatory T cells are very happy in the tumor microenvironment. They seem to thrive in this kind of environment and are in fact among the most proliferative cells that we can find in the TME. The reason that we found for this is they are able to live off tumor-rich nutrient sources, one of which is lactic acid, a byproduct of the tumor fermenting glucose. Regulatory T cells, we have learned, are very adept at utilizing this fuel source. A lot of cells can use lactic acid for energy production, but regulatory cells have adopted this alternative metabolic pathway. If we deprive regulatory T cells of the ability to take up lactic acid, they cease to function properly. They no longer are able to engender an immunosuppressive effect in that tumor, resulting in a heightened response to immunotherapies."

Predicting the Response to Therapy

One of the biggest challenges and goals with any kind of therapy — for any disease — is knowing in advance who is most likely to benefit from a specific therapy and for whom the therapy will essentially be a waste of time. It's already well established that immunotherapy regimens work for only small fractions or subsets of cancer patients — at least at present. The ability to identify the likely responders prior to treatment has numerous benefits, but we still have virtually no reliable information to inform these decisions, and we have few verified biomarkers that can be sought in an individual with respect to the prognostication of efficacious treatment.

"Predicting who the responders to treatment will be is hugely important across the entire field of cancer immunotherapy. One of the things that we are exploring in the lab is to see if we can detect the imprint of tumor cell metabolism in patients. We've developed a platform that can measure the kind of fuel [e.g., glucose or oxygen] an individual patient's tumor cells prefer to use, and how much fuel they are using. This is important for several reasons. First, if we know a particular tumor is consuming lots of oxygen, this might lead us to understand that it will be less likely to respond to immunotherapy. At the same time, it tells us that in order to be effective with an immunotherapy such as a PD-1 inhibitor, we must inhibit the oxidative metabolism of the tumor in some way to give the immune system a better chance at fighting it," says Dr. Delgoffe.

References and Further Reading

Scharping NE, Menk AV, Moreci RS, Whetstone RD, Dadey RE, Watkins SC, Ferris RL, Delgoffe GM. The Tumor Microenvironment Represses T Cell Mitochondrial Biogenesis to Drive Intratumoral T Cell Metabolic Insufficiency and Dysfunction. *Immunity.* 2016; 45: 375-388.

Menk AV, Scharping NE, Rivadeneira DB, Calderon MJ, Watson MJ, Dunstane D, Watkins SC, Delgoffe GM. 4-1BB Costimulation Induces T Cell Mitochondrial Function and Biogenesis Enabling Cancer Immunotherapeutic Responses. *J Exp Med.* 2018. 215(4): 1091-1100.

Rivadeneira DB, Delgoffe GM. Antitumor T-cell Reconditioning: Improving Metabolic Fitness for Optimal Cancer Immunotherapy. *Clin Cancer Res.* 2018; 24(11): 2473-2481.

Scharping NE, Delgoffe GM. Tumor Microenvironment Metabolism: A New Checkpoint for Anti-Tumor Immunity. *Vaccines (Basel).* 2016; 4(4): Review.

Scharping NE, Menk AV, Whetsone RD, Zeng X, Delgoffe GM. Efficacy of PD-1 Blockade Is Potentiated by Metformin-Induced Reduction of Tumor Hypoxia. *Cancer Immunol Res.* 2016; 5(1): 9-16.

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Adoptive Cell Transfer Immunotherapy Trials Show Promising Results for Metastatic Uveal Melanoma

With an annual incidence of approximately five cases per million, uveal melanoma is a very rare condition. For metastatic disease, there have been no effective treatments. Uveal melanoma is essentially an orphan disease that has not attracted much attention in the way of clinical trials in the past.

Udai Kammula, MD, FACS, associate professor and director of the Solid Tumor Cell Therapy Program at UPMC Hillman Cancer Center, is a surgical oncologist and immunotherapy specialist with a focus on adoptive T-cell transfer, tumor-infiltrating lymphocytes (TILs), and gene therapy. Dr. Kammula explains that the dearth of treatments and research for the condition has been driven mainly by its exceptionally rare incidence, and the fact that the few trials that have been conducted have not borne results. So why choose to study it further?

"It has been thought that uveal melanoma was simply not amenable or responsive to immunotherapies based on the work that has been done in the past and its lack of response to treatments. I think most researchers have stayed away from this cancer because it is so challenging. But that's exactly the reason why we picked it, because we thought if we could develop a treatment that could benefit these patients, it would become a blueprint for many other challenging cancers like pancreatic cancer and metastatic breast cancer. In many ways, we are using this orphan cancer not just to help these patients but to potentially help a lot of other patients who have not benefitted from current, mainstream immunotherapies," says Dr. Kammula.

In 2016, Dr. Kammula and colleagues at the NIH published a paper in the journal *Clinical Cancer Research* titled "Identification of Immunogenic Subset of Metastatic Uveal Melanoma" that demonstrated for the first time a subset of uveal melanoma tumors that looked as though they may be amenable to immunotherapy treatment.

"This was a pivotal trial. We were able to isolate and replicate the TILs from uveal melanoma metastasis in exactly the same way it has been done for nearly 20 years in skin melanoma."

Dr. Kammula's study then interrogated the function of these isolated TILs through functional assays.

"What we ended up finding was that the T cells that were inhabiting these tumors actually had very potent activity — in a type of cancer that everyone had really written off as being poorly immunogenic. But we were left with a conundrum: the T cells are there and potent, but they can't be activated by conventional immunotherapies."

Dr. Kammula's team then decided that using adoptive cell transfer might be applicable in trying to treat metastatic uveal melanoma.

"Adoptive cell transfer is, in a manner of speaking, a brute force approach that takes the TILs from the harvested tumors, grows and expands them outside of the body to circumvent the constraints of the body itself and the negative or immunosuppressive effects of the tumor, and then delivers them back to the patient with an accompanying lymphodepleting preparative regimen."

Initial Clinical Trial Results: Surprising and Encouraging

In an initial single center, two-stage, phase 2 study, the results of which were published in *Lancet Oncology* in 2017, Dr. Kammula and his study companions treated their first cohorts of metastatic uveal melanoma patients with adoptive cell transfer of TILs.

The trial, for the first time, showed subsets of patients who were deemed to be partial responders to the therapy regimen, while one patient was deemed to be a full and durable responder at two years post-treatment at the time the study was published.

"Now we have to understand why there is this subset of patients showing response, and how we can generate a more effective immune response in as many patients as possible. When you compare the responders versus non-responders (seven versus 15, respectively), the striking difference between the two groups is that the responding patients have very potent TILs with respect to tumor reactivity. We think that this is partly the explanation for the response seen. The converse, unfortunately, in those patients who did not respond was that they all showed little TIL reactivity," says Dr. Kammula.

All of this work has led to new studies and new lines of investigation since Dr. Kammula arrived at UPMC Hillman Cancer Center in 2017.

Confirmatory Trials — Uveal Melanoma and Adoptive Cell Transfer

At Hillman, Dr. Kammula has set up his laboratory's manufacturing capabilities to create the TIL infusions, and he has opened a new clinical trial to confirm the results of the first study and expand upon its findings with new questions.

"Our new trial, which officially opened in April 2018 and is being run jointly out of UPMC Hillman Cancer Center and UPMC Shadyside, with funding coming from the new UPMC Immune Transplant and Therapy Center, has already enrolled several patients. The new trial really is designed to try to replicate our initial results to provide a level of confirmation that we need with respect to repeatability, but we are set to go beyond that with other investigations into the mechanisms and genetic factors leading to treatment response."

New Trials: Details

There are a number of differences between the two trials, however, and they are important to note. First, this treatment for uveal melanoma is quite complex. It's custom-made, and there is much that goes into picking the TIL, growing the TIL, and administering the treatment.

"We wanted to start with a treatment that in many ways was modeled on, and shared a lot of the features of, the initial NIH trial that we conducted. However, I didn't want to just replicate the entire trial. The rationale for this approach is that I wanted to show we could reproduce the results at a new institution. If we had simply revamped and tweaked everything, we would never know whether the results were altered because of some variable that was not accounted for. We very much wanted to recapitulate what we did at the NIH, but where we did make improvements was in the manufacturing process of the TILs. We switched the bioreactors in which we grow the cells to a closed system that we thought would enable a larger number of cells to grow, while at the same time keeping within the FDAs manufacturing requirements."

Also, the current trial is attempting to select patients who are more likely to respond to treatment — in a manner looking at response mechanisms from the first trial as a biomarker to potentially spare patients an unnecessary treatment to which they likely will not respond.

"We are going one step further, though, with our research in an attempt to isolate the genes that are responsible for the TIL recognition response. These genes encode for the T-cell receptors. All T cells see the world through two genes — T-cell receptor alpha chain and beta chain — and these chains combine to form a functional receptor. As we learn more about these unique responding patients, we hope to be able to generate a future treatment for those lacking the potent TILs. In essence, give them what nature didn't through a process called TCR gene therapy. This will be accomplished in an offshoot program that we are building at UPMC Hillman Cancer Center. We will be able to utilize all of the samples from our initial TIL trials to mine them for these T-cell receptors. This will be a very important part of our ongoing research," says Dr. Kammula.

A Pragmatic Approach

Dr. Kammula and his collaborators have made some surprising findings and have seen much success in their research with metastatic uveal melanoma and adoptive transfer therapy with TILs. But he is also cautious in his approach and takes a pragmatic outlook on where the research is headed and to what degree it will succeed.

"I'm a pragmatist about the ability of TIL. At its heart, the great advantage of TILs is that they are the ultimate, personalized immunotherapy. The downside of TIL is that they are living, breathing cells that can become exhausted or may not survive the transfer. One of the things that we are trying to do is reprogram the metabolic fitness of these TILs, and we have ongoing research on this topic. But, again, we are pragmatists about the future of TIL. We have to explore and create its next evolutionary step. We think that TIL is a platform we can use to build creative, and hopefully effective, cancer treatments."

References and Further Reading

Chandran SS, Somerville RPT, Yang JC, et al. Treatment of Metastatic Uveal Melanoma With Adoptive Transfer of Tumour-infiltrating Lymphocytes: A Single-Centre, Two-stage, Single-arm, Phase 2 Study. *Lancet Oncol.* 2017.

Adoptive Transfer of Tumor Infiltrating Lymphocytes for Metastatic Uveal Melanoma. ClinicalTrials.gov identifier: NCT03467516. Primary investigator: Udai Kammula. Sponsor: UPMC Hillman Cancer Center.

Crompton JG, Klemen N, Kammula US. Metastasectomy for Tumor-Infiltrating Lymphocytes: An Emerging Operative Indication in Surgical Oncology. *Ann Surg Oncol.* 2018; 25(2): 565-572.

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Atezolizumab and Nab-Paclitaxel as First-Line Treatment for Metastatic Triple-Negative Breast Cancer

Patients with triple-negative breast cancer have few treatment options and experience poor clinical outcomes. New research and clinical trials show that a paired use of atezolizumab and nab-paclitaxel, administered as a first-line treatment option, improves both progression-free survival and overall survival rates in some patients with triple-negative breast cancer.

Healthy breast cells may contain receptors for the hormones estrogen and progesterone and another receptor for human epidermal growth factor (HER2) that stimulates normal cell growth. Current targeted therapies leverage these receptors to reduce the chances of breast cancer recurrence and to manage cancer during early stages. But these precision therapies prove ineffective for the 10 to 20 percent of breast cancer cases that test negative for all three receptors, leaving this group of patients with a paucity of treatment options.

This particularly aggressive and invasive form of cancer, called triple-negative breast cancer (TNBC), develops in breast ducts and spreads beyond the breast more frequently than other breast cancers. It also recurs at higher rates because of the lack of targeted therapies, speaking to the need for a treatment option that will create a more durable response. For these patients, whose primary systemic treatment is chemotherapy, overall survival rate estimates continue to vary but consistently fall under 18 months.

"Patients with metastatic or unresectable locally advanced triple-negative breast cancer have an unmet need for targeted therapies that can provide better outcomes," says **Leisha Emens, MD, PhD**, co-leader of the UPMC Hillman Cancer Center Immunology and Immunotherapy Program, and director of translational immunotherapy for the Women's Cancer Research Center. This unmet need led to a series of clinical trials focusing on the effects of a promising new pairing of treatment agents: atezolizumab and nab-paclitaxel.

Atezolizumab and Nab-Paclitaxel: Current Uses and Past Trials

In patients with TNBC, expression of programmed death ligand 1 (PD-L1) occurs not on tumor cells but mainly on tumor-infiltrating immune cells, and this tendency impedes anticancer immune responses. A clear opportunity to improve clinical outcomes is to inhibit the ability of PD-L1 to interact with its receptors (PD-1 and B7-1). Designed to prevent this interaction by selectively targeting PD-L1, atezolizumab is an engineered, monoclonal antibody approved to treat other solid tumors, such as metastatic urothelial carcinoma and non-small-cell lung cancer (NSCLC). Early clinical studies have shown it to have a good safety profile and to offer significant clinical benefit in patients with other solid tumors, including TNBC.[1]

Paired with nab-paclitaxel, a common agent used to treat breast cancer, atezolizumab continued to show a good safety profile and clinical activity in patients with TNBC. A phase 1b study showed that concurrent administration of these two agents did not counteract the immunodynamic effects of nab-paclitaxel.

IMpassion130: Details, Results, and Outcomes

IMpassion130 is an international, randomized, double-blind, placebo-controlled trial that tests the effectiveness of first-line atezolizumab plus nab-paclitaxel compared with placebo plus nab-paclitaxel in 902 patients with TNBC. Participants were required to be 18 years of age or older with a histologically documented, representative triple-negative breast cancer specimen that could be evaluated for PD-L1 expression. They also were eligible to receive taxane monotherapy and had received no previous chemotherapy or targeted therapy for metastatic TNBC, among other health-related requirements.

After qualification, participants were randomly assigned to either the experimental or placebo group and received a dose of nab-paclitaxel three times, and a dose of atezolizumab of 840mg or placebo two times in every 28-day cycle with tumor imaging occurring every eight weeks for 12 months. This imaging allowed researchers to assess two main evaluation criteria: progression-free survival and overall survival.

Initial results, published in the *New England Journal of Medicine*,[2] show significant benefits for TNBC patients in the subgroup that tested positive for PD-L1 immune cell expression. This subgroup experienced a median progression-free survival that was 2.5 months longer than the placebo group. The greatest clinical benefit comes from the effect of the treatment on median overall survival, which was only 15.5 months in the placebo plus nab-paclitaxel group but increased to 25 months for PD-L1-positive patients in the atezolizumab plus nab-paclitaxel subgroup.

Of these results, Dr. Emens says, "This is the first phase 3 trial to study a targeted therapy that improves the overall survival rate of triple-negative breast cancer patients. Immunotherapy treatments like atezolizumab are known for their durability of response, so the most exciting thing about this treatment is that responses will last longer than standard chemotherapy."

In this trial, atezolizumab continued to show a good safety profile when paired with nab-paclitaxel, with only 23 percent of patients showing serious adverse side effects as compared to 18 percent in the placebo group, with no new adverse side effects revealed by this research.

For patients with a PD-L1-positive TNBC diagnosis, the results of the IMpassion130 trial represent a significant improvement in their treatment, which will reduce recurrence and slow the progression of this aggressive form of cancer.

Regulatory Approval and Further Research

As the research team continues to monitor the results of the IMpassion130 trial, they have submitted this promising initial set of results to the FDA, hoping to achieve regulatory approval for commercial application of the atezolizumab plus nab-paclitaxel treatment.

The FDA granted priority review status to this treatment and is expected to decide as early as March 2019.[3] Until such approval can be obtained, trial data at least justify routine testing of PD-L1 immune cell status to determine which patients might benefit from a treatment pairing these two agents.

For TNBC patients who will not benefit from this new treatment, namely PD-L1-negative patients, Dr. Emens says that further research must be done to meet this population's unmet need for a targeted therapy. But for PD-L1-positive patients, the combination of atezolizumab plus nab-paclitaxel offers an effective first-line targeted therapy that can markedly improve clinical outcomes.

References and Further Reading

1 Emens L, Cruz C, Eder J, et al. Long-term Clinical Outcomes and Biomarker Analyses of Atezolizumab Therapy for Patients With Metastatic Triple-Negative Breast Cancer: A Phase 1 Study. *JAMA Oncol.* 2018. Identifier: NCT01375842. https://jamanetwork.com/journals/jamaoncology/fullarticle/2701722

2 Emens L, Schmid P, Adams S, Rugo HS, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. *N Engl J Med.* 2018; 379 (22): 2108-2121. https://www.nejm.org/doi/pdf/10.1056/NEJMoa1809615

3 Basel. FDA Grants Priority Review to Roche's Tecentriq in Combination With Abraxane for the Initial Treatment of People With PD-L1-positive, Metastatic Triple-negative Breast Cancer. *Roche.* https://www.roche.com/media/releases/med-cor-2018-11-13.htm

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Melanoma and Immunotherapy: Therapeutic Firsts and Ongoing Advances at UPMC Hillman Cancer Center

John M. Kirkwood, MD, is the Usher Professor of Medicine in dermatology and translational science at the University of Pittsburgh School of Medicine. Dr. Kirkwood was recruited to UPMC Hillman Cancer Center in 1986 and has since led the UPMC Hillman Melanoma Program, with Hassane M. Zarour, MD, joining as co-leader in 2014.

Dr. Kirkwood is principal investigator of the UPMC Hillman Cancer Center Specialized Program of Research Excellence (SPORE) in Melanoma and Skin Cancer. Dr. Kirkwood has chaired the Melanoma Committee of the National Clinical Trials Network ECOG-ACRIN since 1989 and formed the International Melanoma Working Group with the Aim at Melanoma advocacy group, bringing together leading translational researchers from the melanoma centers of 14 countries semi-annually since its inception in 2005.

Dr. Kirkwood and UPMC Hillman have pioneered the development of biological therapies to treat melanoma, beginning with vaccines, cytokines, and interferons, and now spanning checkpoint blockade inhibitors and targeted therapies. Dr. Kirkwood has authored or co-authored more than 300 peer-reviewed papers and been responsible for numerous breakthroughs in cancer therapeutics with new agents and novel combinations.

His early work at UPMC led to the first FDA approval of an adjuvant therapy for melanoma — interferon alfa 2b (IFN-2b) — in 1995.[1] More recently, after nearly a dozen new trials of vaccines and combinations, Dr. Kirkwood's work led to the approval of the first oral combination of targeted therapies for adjuvant therapy of melanoma — the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib.

Dr. Kirkwood's research focuses upon melanoma immunobiology, therapy, and prevention. His translational laboratory studies have shown the immunological basis of IFN adjuvant benefits and are now probing the role of molecularly targeted agents (BRAF, MEK) and novel combinations that may improve upon the efficacy of anti-PD1 immunotherapy, both for treatment of advanced melanoma and for the adjuvant therapy of operable high-risk melanoma. His work with monoclonal antibodies to melanoma and peptide differentiation antigens as vaccines, as well as combinations of these immunomodulators, antedated the recent surge of immunotherapies to treat cancer. This work now is oriented to accelerate the pace of progress using novel trial designs including treatment before surgery for operable disease (neoadjuvant treatment) and adaptive trials that will yield results sooner in smaller numbers of patients.

Dr. Kirkwood also has advanced the multimodal therapy of melanoma with surgery, stereotactic radiotherapy, and molecular antitumor agents that have displaced chemotherapy in the management of melanoma. He is now pioneering novel clinical trials to assess the myriad potential combinations of recently approved molecular and immunological therapies anticipated to be the focus of the next decade of translational clinical research trials in melanoma.

Metastatic Inoperable Melanoma: Immunotherapy Advances and New Trials

Before 2011, there had been no new treatments tested that significantly altered survival in metastatic melanoma. Since 2011, there has been an absolute revolution in treatment efficacy for advanced disease with numerous antibody agents.

"The importance of these advances cannot be understated. Metastatic melanoma was bleak; nothing worked. Contrast that with what has occurred since 2011; we now have a minimum of 13 FDA-approved effective drugs in our arsenal and more in the pipeline. Half of these agents are the BRAF/MEK inhibitors, and the others are the first- and second-generation checkpoint blockade agents — CLTA-4, PD-1, and others," says Dr. Kirkwood.

BRAF/MEK inhibitors, of which there are three current pairs, each with varying degrees of toxicity and therapeutic benefit, are effective in more than half of patients and can show dramatic regression of disease. The PD-1 inhibitors nivolumab and pembrolizumab that arose in 2013 show efficacy in 40 percent of patients upfront and 30 percent as a second-line therapy. They are highly active despite BRAF mutations, with most responses being durable for years.

"These advances and their benefits, of course, are spectacular for metastatic disease. So what is the challenge now? It is overcoming PD-1 resistance, and what to do with the patient who fails PD-1 checkpoint blockade therapy," says Dr. Kirkwood.

Checkpoint blockade therapy is evolving as the discovery and testing of the third-generation agents targeted at the disinhibitory receptors TIM3, TIGIT, and LAG-3 progresses. These third-generation agents are the focus of past and recent studies by researchers in the Melanoma Program at UPMC Hillman.

"Hassane Zarour, MD, is working with TIGIT inhibitors in combination with PD-1 to try to overcome resistance, and he has published several papers to date. Dario Vignali, PhD, professor and vice chair, and leader of cancer immunology in the Department of Immunology is focused on LAG-3 and PD-1 combinations as a front-line therapy. He will have a new trial open soon evaluating several combinations that we believe will have categorically better results," says Dr. Kirkwood.

Other research into treatments for metastatic disease with third-generation checkpoint inhibitors includes the work of Greg Delgoffe, PhD, who is interested in metabolic checkpoints in T cells, specifically

mitochondrial deficiencies in the cells proving to be responsible for some aspects of T-cell suppression in the tumor microenvironment (see article about Dr. Delgoffe's research in this issue of *Cancer Insights)*.

Also of note are the novel trials in progress led by Dr. Zarour and Diwakar Davar, MD, who are studying the role of the gut microbiome and its implication in disease state modulation and enhanced immunotherapy responses in metastatic melanoma.

"This is fascinating and potentially revolutionary research that Drs. Zarour and Davar are conducting with fecal microbiome transplants (FMT) from individuals who have responded successfully to immunotherapy into those individuals who have failed checkpoint blockade therapy in an attempt to reverse PD-1 resistance or otherwise help improve treatment efficacy. Their published work on the role of the microbiome two years ago in *Science Translational Medicine* was quite elegant and forms the basis of their continuing studies. Their current clinical trial is recruiting patients and has generated much excitement in the field. Only a handful of places in the world are experimenting with this approach, which speaks volumes about the nature of our collective research programs at UPMC Hillman," says Dr. Kirkwood.

Melanoma and Adjuvant Therapy: The Treatment Arsenal Expands

Pittsburgh was the place where the first adjuvant treatment for melanoma was shown to be of benefit in patients with either deep primary disease or lymph node involvement who had prior surgery but were likely to relapse without some additional treatment. Dr. Kirkwood led these trials at what was then called the University of Pittsburgh Cancer Institute, now UPMC Hillman Cancer Center.

"We were the first to test interferon alpha 2b and show that it reduced relapse by 40 percent and mortality by 28 percent with a one-year treatment. The FDA approved IFN-2b in July 1995, and from then until 2015, it was the only adjuvant treatment worldwide for melanoma. Without a doubt, thousands of patients have benefitted from the therapy and have not relapsed, and that started here in Pittsburgh," says Dr. Kirkwood.

Since those early days, there has been much progress with adjuvant therapies, and new trials are continuing to open at UPMC Hillman and elsewhere that are evaluating therapies in the adjuvant setting. CTLA-4 blockade therapy arrived in 2015 and was easier to administer than IFN, but it can have significant toxicity.

In September 2017, the COMBI-AD[2] trial that Dr. Kirkwood designed showed, along with a trial conducted by Bristol-Myers Squibb (BMS) called Checkmate 238, significant reductions in relapses with nivolumab with much less toxicity and better tolerability as seen with IFN-2b.

Now, Dr. Kirkwood is designing a trial that would combine PD-1 inhibitors with BRAF and MEK agents in a triple therapy trial in the adjuvant setting.

"We are figuring out which agent we will pursue. Adjuvant treatments of earlier stage disease have not been done yet, but it may be the future. With PD-1, despite BRAF mutation, and maybe even with BRAF/MEK inhibitors for individuals who have BRAF-V600E or K mutations, we may be able to treat patients who have no lymph node involvement but can still have the relapse risk reduced," says Dr. Kirkwood.

Early Detection and Prevention: Novel Methods and New Targets

Dr. Kirkwood and collaborators at UPMC Hillman also are leading efforts to improve early detection and prevention of melanoma using novel techniques and experimenting with potential new therapeutic agents.

A novel primary care provider (PCP) training program was rolled out at UPMC in 2014 and was designed to increase the frequency and rates of skin cancer screening and detection of melanomas in patients 35 years and older. The initiative entailed a voluntary training program

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for UPMC PCPs delivered through an internet-based e-learning platform called the INternet curriculum FOR Melanoma Early Detection (INFORMED).[3]

"This Internet-based training system trial, the results of which were published by Laura Ferris, MD, PhD, showed that disease could be detected earlier by providing the necessary training to PCPs and reinforcing the necessity for screening via the electronic medical record. The study showed that trained PCPs were able to detect cases of melanoma in situ many times more frequently than those who had not received the training. Teaching PCPs how to better detect possible cases of melanoma at an early stage is a logical extension of our prevention methods, and I expect this kind of innovative work to continue across our system in the years to come," says Dr. Kirkwood.

Another clinical trial that recently completed patient recruitment, and for which Dr. Kirkwood has published results,[4] was a novel investigation evaluating the nutritional agent sulforaphane and its ability to alter tumor progression from atypical/dysplastic nevus precursors with minimal toxicity.

"The non-obligate risk marker and potential precursor of melanoma is known as the atypical or dysplastic nevus. We wanted to conduct a trial on agents that could influence or mitigate the development of melanoma. One of these potential agents is a cruciferous vegetable product known as sulforaphane that has shown some impressive activity against melanoma in mouse model research conducted by a colleague at the National Cancer Institute, Shivendra Singh, who is now at UPMC Hillman Cancer Center" says Dr. Kirkwood.

For this pilot trial, Dr. Kirkwood's study obtained brussel sprout extract containing the isothiocyanate compound sulforaphane and tested its safety and tolerability in a small cohort. Seventeen patients were given sulforaphane orally for 28 days. Doses of 50, 100, and 200 micromoles per day were well tolerated, and there were effects of the sulforaphane that were dose-dependent. Since sulforaphane modulates several pathways important for melanoma development, Dr. Kirkwood is hoping to expand this work into a large, phase II study in the near future.

References

1 Kirkwood JM, Stawderman MH, Ernstoff MS, Smith TJ, Borden EC, Blum RH. Interferon Alpha-2b Adjuvant Therapy of High-Risk Resected Cutaneous Melanoma: The Eastern Cooperative Oncology Group Trial EST 1684. *J Clin Oncol.* 1996; 14(1): 7-17.

2 Long GV, Hauschild A, Santinami M, et al. Adjuvant Dabrafenib Plus Trametinib in Stage III BRAF-Mutated Melanoma. *N Engl J Med.* 2017; 377(9): 1813-1823.

3 Ferris LK, Saul MI, Lin Y, Din F, Weinstock MA, Geller AC, Yuan JM, Neuren E, Maddukuri S, Solano FX, Kirkwood JM. A Large Skin Cancer Screening Quality Initiative: Description and First-Year Outcomes. *JAMA Oncol.* 2017; 3(8): 1112-1115.

4 Tahata S, Singh SV, Lin Y, et al. Evaluation of Biodistribution of Sulforaphane After Administration of Oral Broccoli Sprout Extract in Melanoma Patients With Multiple Atypical Nevi. *Cancer Prev Res (Phila).* 2018; 11(7): 429-438.

Further Reading

Davar D, Wang H, Chauvin JM, Pagliano O, Fourcade JJ, Ka M, Menna C, Rose A, Sander C, Borhani AA, Karunamurthy A, Tarhini AA, Tawbi HA, Zhao Q, Moreno BH, Ebbinghaus S, Ibrahim N, Kirkwood JM, Zarour HM. Phase Ib/II Study of Pembrolizumab and Pegylated-Interferon Alfa-2b in Advanced Melanoma. *J Clin Oncol.* 2018 Oct 25: JCO1800632. Epub ahead of print.

Suciu S, Eggermont AMM, Kirkwood JM, Markovic SN, Garbe C, Cameron D, Kotapati S, Chen TT, Wheatley K, Ives N, de Schaetzen G, Efendi A, Buyse M. Relapse-Free Survival as a Surrogate for Overall Survival in the Evaluation of Stage II-III Melanoma Adjuvant Therapy. *J Nat Cancer Ins.* 2018; 110(1): 87-96.

Callahan MK, Kluger H, Postow MA, Segal NH, Losokhin A, Atkins MB, Kirkwood JM, Krishnan S, Bhore R, Horak C, Wolchok JD, Sznol M. Nivolumab Plus Ipilimumab in Patients With Advanced Melanoma: Updated Survival, Response, and Safety Data in a Phase I Dose-Escalation Study. *J Clin Oncol.* 2018; 36(4): 391-398.

Kashani-Sabet M, Nosrati M, Miller JR 3rd, Sagebiel RW, Leong SPL, Lesniak A, Tong S, Lee SJ, Kirkwood JM. Prospective Validation of Molecular Prognostic Markers in Cutaneous Melanoma: A Correlative Analysis of E1690. *Clin Cancer Res.* 2017; 23(22: 6888-6892.

Kalinsky K, Lee S, Rubin KM, Lawrence DP, Iafrarte AJ, Borger Dr, Margolin KA, Leitao MM Jr, Tarhini AA, Koon HB, Pecora AI, Jaslowski AJ, Cohen GI, Kuzel TM, Lao CD, Kirkwood JM. A Phase 2 Trial of Dasatinib in Patients With Locally Advanced or Stage IV Mucosal, Acral, or Vulvovaginal Melanoma: A Trial of the ECOG-ACRIN Cancer Research Group (E2607). *Cancer.* 2017; 123(14): 2688-2697.

Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, Lazar AJ, Faries MB, Kirkwood JM, McArthur GA, Haydu LE, Eggermont AMM, Flaherty KT, Balch CM, Thompson JF, for members of the American Joint Committee on Cancer Melanoma Expert Panel, International Melanoma Database and Discovery Platform. Melanoma Staging: Evidence-based Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual. CA: A Cancer Journal for Clinicians. 2017; 67(6): 472-492.

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UPMC Hillman Cancer Center News and Highlights

Research Award

Adrian V. Lee, PhD, and **Steffi Oesterreich, PhD**, both of the Women's Cancer Research Center, a collaborative effort between Magee-Womens Research Institute (MWRI) and UPMC Hillman Cancer Center, recently received the Susan G. Komen Greater Pennsylvania Terri L. Chapman Award. The award was established in 2010 to recognize individuals who demonstrate leadership qualities, impact and influence decision makers, and who support Susan G. Komen Greater Pennsylvania.

Faculty News

Chad A. Ellis, PhD, joined UPMC Hillman Cancer Center as our new deputy director for research administration in April. In this role, he will work in collaboration with our associate director of clinical investigation and oversee our Clinical Research Office to support an effective and productive clinical research infrastructure. Dr. Ellis holds a doctorate in pharmacology from the University of Illinois School of Medicine and completed postdoctoral training at the National Cancer Institute. He also has experience in collaborating with the private sector, having helped launch two biotechnology companies.

Leisha Emens, MD, PhD, joined UPMC Hillman Cancer Center in September. Dr. Emens is a medical oncologist and immunologist specializing in breast cancer. She received her medical degree at Baylor University and completed her residency at the University of Texas, followed by fellowships at the National Cancer Institute and Johns Hopkins University School of Medicine.

Shou-Jiang Gao, PhD, joined UPMC Hillman Cancer Center this spring and leads our cancer virology program. He is an internationally recognized expert on how the Kaposi's sarcoma-associated herpesvirus (KSHV) causes cancer and has five RO1 grants funded by the National Cancer Institute. Dr. Gao holds a doctorate from the University of Bordeaux in France and received postdoctoral training at the University of Massachusetts at Amherst and Columbia University in New York.

Bhanu Pappu, PhD, MHA, joined UPMC Hillman Cancer Center in April as vice president of clinical research operations and strategy. In this role, he works closely with physician leadership on strategic initiatives to improve clinical trial enrollment and community network integration. Dr. Pappu holds a doctorate in tumor immunology from the State University of New York at Buffalo and a master's degree in health care administration from the University of Houston Clear Lake.

Amer H. Zureikat, MD, FACS, was appointed chief of the Division of Surgical Oncology in April. Dr. Zureikat is an associate professor of surgery at the University of Pittsburgh School of Medicine and has served as co-director of the UPMC Pancreatic Cancer Program since 2012. He is board-certified in general surgery and received his medical degree from the Royal College of Surgeons in Ireland (RCSI) in Dublin. Dr. Zureikat completed his residency in general surgery at the University of Chicago Medical Center, followed by a fellowship in surgical oncology at UPMC.

Mohammed Saiful Huq, PhD, was elected to the presidency of the American Association of Physicists in Medicine (AAPM), a scientific and professional organization of more than 8,000 scientists dedicated to the accuracy and safety of imaging and radiation therapy. Dr. Huq is the director of medical physics at the Department of Radiation Oncology at UPMC Hillman Cancer Center.

Center Highlights

Survivorship After Cancer of the Head and Neck: A Multidisciplinary Symposium

A multidisciplinary team of specialists, including **Jonas Johnson, MD**, and **Marci Nilsen, PhD, RN**, at UPMC hosted the region's first survivorship symposium for patients with head and neck cancer to improve care for this often-debilitating disease. Head and neck cancer is often aggressive, and the treatments can result in disfigurement and lifelong side effects that require multiple physician interventions. Survivorship care focuses on a patient's individual physical, psychosocial, and economic issues that can arise after treatment has ended.

UPMC to Advise Cancer Treatment Center in Beijing

Tahoe Hospital Management Co. Ltd. has reached a five-year agreement with UPMC to assist in the planning and operation of an expanded cancer center within an existing private hospital in Beijing.

From facility planning to clinical protocols, UPMC will advise Tahoe on all aspects of operating an advanced cancer treatment center, which will include medical and surgical oncology, cancer rehabilitation, and an oncology clinical research program.

"This collaboration with UPMC is just the start of what we hope will be a long and fruitful partnership to expand world-class medical care for our patients," said Chairman Qisen Huang of Tahoe. "Together, UPMC and Tahoe share the same vision of developing a comprehensive cancer network that encompasses all facets of care, including treatment, rehabilitation, survivorship and research, with an international standard of practice."

The expanded center is intended to be the "hub" facility of Tahoe's future oncology network in Beijing and the surrounding region.

"UPMC is uniquely prepared to partner with Tahoe because of our internationally renowned clinical expertise, teaching capability, research experience, oncology-focused organizational practices, and long history of operating advanced cancer care services throughout the world," noted Chuck Bogosta, president of UPMC International and UPMC Hillman Cancer Center.

Cancer is the leading cause of death in China, with an estimated 4.3 million new cancer cases and more than 2.8 million cancer deaths in the country in 2015. An aging population and lifestyle factors like smoking are major factors in the nation's rising cancer rates.

The first phase of the Tahoe project will involve onsite assessment and recommendations by a multidisciplinary team of UPMC experts, who will advise on facility design and equipment selection, information technology, infrastructure, and a staffing plan for oncology services, among other activities. Key Tahoe clinical staff will receive training in Pittsburgh as the cancer center aims to meet the highest international standards.

After the initial study, UPMC will provide ongoing guidance regarding Tahoe's clinical and quality assurance practices. In the years to come, UPMC expects to help the cancer center with the process of achieving Joint Commission International accreditation.

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UPMC HILLMAN CANCER CENTER

UPMC Hillman Cancer Center gives patients access to comprehensive care through an entire network of medical, radiation, and surgical oncologists, evidence-based treatment options, and the latest advances in cancer clinical care. We are proud to be one of the nation's top centers for cancer care and research, where our nationally and internationally recognized specialists are changing the landscape of oncology.

A Network of Physicians and Locations

UPMC Hillman Cancer Center offers convenient access to cancer care and innovative treatments close to home for cancer patients throughout western Pennsylvania and beyond. This model of patient care provides easy access to care for an aging western Pennsylvania population and accommodates referrals between specialists in Pittsburgh and our more than 60 locations.

With more than 180 affiliated oncologists, this network represents a collection of some of the nation's most highly qualified and respected physicians and researchers in cancer medicine.

A Resource for You: UPMC Physician Resources brings world-class physicians and free educational opportunities to your computer. Learn new information while watching CME-accredited videos in the convenience of your home or office. Find out more at UPMCPhysicianResources.com/Cancer.

To learn more about UPMC Hillman Cancer Center, please visit **UPMCPhysicianResources.com/Cancer.**

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For more information about UPMC Hillman Cancer Center clinical services, call **412-647-2811** or visit **UPMCHillman.com**.

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