Melanoma Research and Treatment

Melanoma kills an estimated 10,130 people in the U.S. annually. Without early detection, the cancer can advance to other parts of the body, where it becomes harder to treat. But thanks to an array of treatment options, patients with metastatic melanoma can extend their lives by months or years. A rising number of patients go into long-term remission.

*Melanoma Research and Treatment* is a recently published series of articles that brings you the stories behind the research and celebrates the researchers and organizations committed to improving health care. Please accept this complimentary copy as our way of thanking you for your commitment to advancing medicine and improving patients’ lives.

A Series by [REALWORLDHEALTHCARE.org](http://REALWORLDHEALTHCARE.org)

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The Mechanics of Melanoma

By Emily Burke, PhD, Director of Curriculum Development, BiotechPrimer.com

May is Melanoma Awareness Month. This article originally appeared in the Biotech Primer WEEKLY. For more on the science behind the headlines, subscribe.

Melanoma 101

Melanoma accounts for less than one percent of skin cancer cases, yet accounts for the vast majority of skin cancer deaths (skincancer.org). If detected early enough, melanoma is almost always curable. If it is not detected early, it is likely to spread to other parts of the body, where it is more difficult to treat. It's estimated that in 2017, there will be 87,110 new cases of melanoma in the U.S., and 9,730 melanoma-related deaths (Aim at Melanoma Foundation). Melanoma is one of the types of cancers most common in young adults, with 25 percent of new cases occurring in people under age 45. Its prevalence is growing – the number of new cases/year relative to the total population has doubled since 1973.

In this column, we’ll review the basics of melanoma, and discuss the latest new therapies recently approved and in development.

Melanoma’s Method

Melanoma is the uncontrolled growth of the pigment-producing cells known as melanocytes, which are located in the bottom layer of the skin’s top layer (the epidermis). Like other types of cancers, melanoma arises from gene mutations in these cells that impact cell growth and division. In the case of melanoma and other skin cancers, the DNA damage is usually caused by ultraviolet (UV) radiation, resulting in a tumor that initially grows in the skin, spreading along the epidermis. If the melanoma is detected at this stage, it can often be surgically removed. If the out of control cell growth is not caught in these early stages, it penetrates deeper layers of the skin, eventually coming into contact with lymph and blood vessels which enable it to spread to other parts of the body. When the melanoma reaches this stage, it is called metastatic melanoma.

Although anyone can get melanoma, fair-skinned people are at higher risk for all types of skin cancer, since increased skin pigmentation helps to block the damaging UV rays from penetrating and damaging skin cell DNA. However, darker-skinned people can and do get skin cancer, and thus should also be vigilant about sun protection.
Atypical moles have also been linked to an increased risk of melanoma. Moles are clusters of melanocytes, and there is a slightly increased risk of melanoma arising within these clusters. Of course, most moles are harmless and do not lead to melanoma. However, any sudden changes in the color, shape, or size of a mole should be evaluated by a doctor.

**Genetic Factors: p53 & BRAF**

Although most cases of all types of skin cancer are traceable to excessive sun exposure, about 10% are likely due to genetic factors. The gene most commonly mutated in familial melanoma is p53. p53 is a “tumor suppressor,” which means that it detects DNA damage in cells, and triggers either DNA repair pathways or activates cell death if the DNA damage cannot be repaired. Another gene, known as the BRAF gene, regulates cell growth and is mutated in inherited forms of melanoma. About half of all genetically-based melanomas have the BRAF mutation.

Let’s take a closer look at BRAF. BRAF codes for a protein required for the transmission of a growth signal from a cell surface receptor to the cell nucleus (growth signal transduction). Growth signaling is initiated by a growth factor binding to its receptor. This binding transmits a signal through the membrane, causing the internal portion of the receptor to interact with and activate a protein inside of the cell. This activation is then transferred to the next protein in the pathway, and so on until the signal reaches the last protein in the pathway. When this protein is activated, it enters the nucleus, where it turns on specific genes that make proteins which initiate cell division. BRAF is one of the proteins in this pathway. In BRAF-associated melanoma, the mutated BRAF is always turned on even when no growth factor is present.

Small molecule drugs that inhibit overactive BRAF have been developed and approved for the treatment of late-stage melanoma.

**Immunotherapies in the Fight**

A few different checkpoint inhibitor therapies have been approved to treat metastatic melanoma. These are drugs that enable killer T-cells – immune system cells that recognize and kill threats such as cancer cells – to become fully active against a tumor cell target. These drugs target inhibitory proteins on the surface of T-cells such as CTLA-4 and PD-1. These proteins act as “off switches” for killer T-cells. By inhibiting these off switches, the killer T-cells become fully activated, and able to target and kill melanoma cells.

A second type of immunotherapy that has been approved for melanoma is an oncolytic virus therapy. An oncolytic virus is a virus that infects and kills cancer cells. The cancer cells are killed through cell lysis – as the virus multiplies inside of the cells, it causes them to burst open. This in turn releases new infectious particles that can target remaining tumor cells. In addition to direct killing of cancer cells via lysis, the presence of an actively replicating virus helps to activate the patient’s immune response to target the area.
In the Pipeline

A new type of immunotherapy drug is in Phase 3 clinical development. The drug is a small molecule inhibitor of the enzyme IDO1. IDO1 helps regulatory T-cells to develop and become activated. Regulatory T-cells suppress the immune response, and therefore help cancer cells to escape immune surveillance. Inhibiting IDO1 should suppress the development of regulatory T-cells, bolstering the immune response against melanoma.

Implications of microRNA

Last year, researchers at Tel Aviv University published a report describing how melanoma metastasizes. Their work suggests that melanoma cells release tiny vesicles that contain microRNA, a type of regulatory RNA produced by all cells. These micro-RNA filled vesicles induce changes in the dermis – the layer of skin just below the epidermis where the melanoma begins. The dermis contains blood vessels, and thus a pathway for metastasis. The changes in the dermis induced by the small vesicles released from the melanoma cells makes the cancer cells able to access those blood vessels. The Tel Aviv team is identifying drug candidates that may interfere with this process, preventing the metastasis that makes melanoma so deadly.

The best strategy for melanoma remains prevention and proactive monitoring – limiting sun exposure and monitoring the skin for any unusual growths or changes in moles. Increased understanding of the molecular pathways that contribute to melanoma’s development and spread will provide physicians with additional tools to fight those cases of metastatic melanoma that inevitably will continue to arise.

Read this article at Real World Health Care.
Skin Cancer Awareness and Prevention Efforts in Focus at American Academy of Dermatology

This week, Real World Health Care continues our recognition of May’s Melanoma and Skin Cancer Awareness Month by highlighting the work of the American Academy of Dermatology. We spoke with the AAD’s new President, Henry W. Lim, MD, about the organization’s mission and some of the challenges and opportunities associated with preventing and treating melanoma and other skin diseases.

Real World Health Care: Please tell our readers about the overall mission of the American Academy of Dermatology.

Henry Lim: The American Academy of Dermatology promotes leadership in dermatology and excellence in patient care through education, research and advocacy.

As the largest, most influential and representative dermatology group in the United States, and the largest such organization in the world, the AAD works to make sure its values reflect this mission. The AAD’s values include putting patients first, encouraging its members to adhere to an uncompromising code of clinical and ethical standards, fostering an interest in our members to pursue lifelong learning, encouraging collaboration and working within our communities and embracing diversity.

Public Education: Sun Safety

RWHC: How does the AAD’s mission address melanoma?

HL: It is estimated that 161,790 new cases of melanoma will be diagnosed in the U.S. in 2017. That is a staggering number that could be reduced if people incorporated skin cancer detection and prevention behaviors into their lives.

The AAD works to increase public awareness of skin cancer and its risks through its SPOT Skin Cancer™ campaign, which is designed to create a world without skin cancer through public awareness, community outreach programs and services, and advocacy that promote the prevention, detection and care of skin cancer.

The first step toward a world without skin cancer is educating the public about prevention. The Academy has long communicated sun-safety messages to the public about the importance of skin cancer prevention and detection.
In addition, dermatologists have led the medical community in finding and treating skin cancer. For more than 30 years, dermatologists across the country have hosted 2.5 million free SPOTme® skin cancer screenings that have detected 28,822 suspected melanomas and 256,329 suspected skin cancer lesions.

To assist the public with learning more about skin cancer prevention and detection, the AAD offers a variety of free, online videos, downloadable handouts and skin self-exam resources, including a body mole map, as well directories to find a dermatologist and skin cancer screenings.

**Melanoma & Skin Cancer Awareness**

**RWHC:** What is the AAD doing in 2017 to recognize Skin Cancer Awareness Month?

**HL:** The AAD’s 2017 SPOT Skin Cancer campaign, *Check Your Partner. Check Yourself*, encourages the public to be aware of changes on their skin that could be signs of skin cancer. Research has shown that women are more likely to detect suspicious spots on others. Men over the age of 50 have a higher risk of developing melanoma, than the general population, so the campaign encourages women – often the health care decision makers of a household – to check their partner’s skin regularly, check their own skin, and to visit the AAD’s SpotSkinCancer website to find a free SPOTme® screening in their area.

**RWHC:** Do you have additional initiatives you’d like to highlight?

**HL:** In addition to the activities for Skin Cancer Awareness Month in May and the SpotSkinCancer™ website, the AAD works with state dermatology societies and state legislatures to introduce and support laws and regulations that protect consumers and promote awareness about skin cancer prevention and the dangers of indoor tanning. As a result, 42 states have enacted tanning bed restrictions to potentially reduce the risk of melanoma and other forms of skin cancer.

The AAD’s Shade Structure Program awards shade structure grants to schools and non-profit organizations across the country in order to protect children and adolescents from the sun’s harmful rays. Since its launch in 2000, the AAD’s Shade Structure Program has awarded 350 shade structure grants, which provide shade for more than 600,000 individuals each day.

The AAD also has a strategic social media presence on Facebook, Twitter, YouTube and Pinterest, designed to raise awareness about skin cancer detection and prevention. Social media, including paid, promoted posts, reach our targeted audiences – the public, our members and the media – with links to AAD resources. We encourage our followers to like, share and re-tweet our skin cancer awareness videos and tips.
Melanoma Research

**RWHC:** Does the AAD underwrite or otherwise support research into melanoma detection and/or treatment?

**HL:** While AAD is not a research funding organization, the AAD does provide annual awards for [Young Investigators in Dermatology](#). These awards recognize outstanding basic and clinical/translational research by young dermatology investigators and some of the projects are related to melanoma.

The purpose of the award is to acknowledge research contributions by individuals at the start of promising research careers that further the improvement of diagnosis and therapeutics in the practice and science of dermatology.

**RWHC:** What do you see as the biggest challenges facing researchers studying melanoma treatments and clinicians treating melanoma?

**HL:** The rapidly changing health care environment presents major challenges to researchers and clinicians in all aspects of dermatologic care, not just those studying and treating melanoma.

A significant challenge is the inadequate funding for research, together with the pressure to increase clinical revenue generated by clinician researchers. For many years, the American Academy of Dermatology Association (AADA) has been active in advocating increased research funding by NIH to dermatology research, including through our support of the 21st Century Cures Act.

The current health care system also presents barriers that impede patient access to the best possible care from a qualified physician. To combat this, the AADA is working with all dermatology care providers and other physicians to confront these challenges.

In particular, the AAD recently launched a new specialty positioning campaign, [SkinSerious](#), to raise awareness of the serious impact of skin disease. Our goal is also to improve access to dermatologists' expertise and increase collaboration with our physician peers to ensure high-quality patient care. We know that when dermatologists work with other physicians as part of the health care team, everyone can benefit from improved patient outcomes and lowered health care costs.

Other concerns within the health care environment that the AADA is closely monitoring include the rise of big data and the growth of teledermatology. We closely follow developments at the federal and state levels and, when appropriate, the AADA will take action on issues that can be influenced positively for dermatology and pursue opportunities to impact health care policy.
Promising Melanoma Treatments

**RWHC:** What do you see as the most promising or breakthrough melanoma treatments on the horizon?

**HL:** This is an exciting era in melanoma research. In-depth understanding of the molecular pathways of melanoma development has led to the availability of immune checkpoint inhibitors; combinations of these medications are being looked at in clinical trials. Metabolic manipulation of the peri-tumoral environment to inhibit the growth of melanoma is being actively investigated. Understanding of the genes responsible for melanoma resulted in the availability of gene expression profile (GEP) test that can be used to determine biologic behavior of melanoma.

Melanoma Prevention

**RWHC:** What are the biggest challenges facing the medical community in terms of increasing awareness of and adherence to melanoma prevention efforts among the general public?

**HL:** The challenges facing the medical community around melanoma prevention are two-fold.

One is the misconception that a tan is a sign of health. Tanning is a protective physiologic response of our skin to damage caused by ultraviolet radiation. There is no such thing as a healthy tan, yet people continue to seek the sun or use indoor tanning, thereby increasing their risk of skin cancer. This is a particularly challenging message to get across to young women and men, who feel peer and societal pressure to be tan.

The AADA was instrumental, along with several other organizations, in having the FDA re-classify tanning lamps from the Class I to Class II medical device category, which requires more supervision and restriction in their purchase and use. For the past several years, the AAD has released a new public service advertisement that focuses on the dangers of tanning, particularly targeting young women. We know that melanoma is the second most common cancer in young women, and this may be due in part to their tanning habits.

The 2016/2017 public service advertisement is called “Arms,” and features two young women comparing their tans at various stages in their lives. The emotional ad concludes with the two friends clasping hands in the hospital as one of them reveals she has advanced stage melanoma. This PSA, and our previous ones, have resonated strongly with young women, especially on social media, where they have liked and shared the video with their friends.

The second challenging misconception is that many people believe that sun exposure is the best source of vitamin D.
While our bodies need vitamin D to build and maintain strong, healthy bodies, the AAD does not recommend getting vitamin D from sun exposure or indoor tanning because of the increased risk of skin cancer. In fact, it has been demonstrated that sun exposure that results in increased vitamin D levels is directly correlated with DNA damage.

Vitamin D from food and dietary supplements offers the same benefits — without the danger of skin cancer — as vitamin D obtained from UV light. Vitamin D cannot be used by the body until it is processed by the liver and the kidneys. The usable form of vitamin D created by this process is the same, regardless of how it enters the body.

The AAD recommends dietary sources (foods naturally rich in vitamin D, fortified foods and beverages) and vitamin supplements as sources of vitamin D that are available year-round and can easily be incorporated into a healthy lifestyle. Good sources include fortified milk, cheeses and yogurt, fortified cereal, and oily fish like salmon and tuna. Research shows that vitamin D supplements are well tolerated, safe, and effective when taken as directed by a physician.

The fact is these myths are harmful because the consequences of this misinformation could be potentially fatal.

**RWHC:** What personally inspires you to build awareness of the importance of preventing melanoma?

**HL:** Having been in dermatology practice for 40 years, I see on a regular basis the devastating effects that melanoma has on patients and their family. The risk of developing melanoma can be significantly decreased by sensible photoprotection, and avoidance of tanning beds. The exciting new developments in the treatment and genetic profiling of melanoma reflect the value of investment in scientists and research projects, and I look forward to additional treatments in the future that will benefit patients.

**A MESSAGE FROM OUR SPONSOR:**

The HealthWell Foundation, sponsor of Real World Health Care, is proud to have supported the melanoma patient community in recent years with copayment and premium assistance. We have helped more than 2,230 melanoma patients afford their treatments since approving our first Melanoma grant in 2011 — thanks to the generous support of our corporate partners. Due to high patient volume, our melanoma fund is temporarily closed until we receive additional funding. We invite corporations and individuals to help us meet this demand by contributing to our Melanoma-Medicare Access Fund, so nobody goes without essential medications because they cannot afford them.

[Read this article](#) at Real World Health Care.
Accelerating Melanoma Research

It’s Melanoma Awareness Month and this week, Real World Health Care is pleased to shine a light on The Society for Melanoma Research. We spoke with the Society’s President, Keith Flaherty, MD. In addition to his role with SMR, Dr. Flaherty serves as director of the Henri & Belinda Termeer Center for Targeted Therapy and the Richard Saltonstall Chair in Oncology at the Massachusetts General Hospital Cancer Center.

Supporting a Diverse Melanoma Research Community

Real World Health Care: Please describe the mission of the Society for Melanoma Research.

Keith Flaherty: The Society for Melanoma Research was intended to be a scientific home for the melanoma research community. When it was created in 2003, there was no organization run by and for melanoma scientists that convened regular scientific meetings to provide a venue for publication of melanoma research. Our research community is quite diverse, spanning many medical specialties and numerous scientific disciplines. Simply bridging the divide between the clinical research community and laboratory-based investigators was central to the SMR mission.

RWHC: What type of research programs do you support and how do you support them?

KF: Our primary supporting role is served by organizing and hosting an annual, international, scientific conference focused on melanoma research. We support travel to the meeting for trainees and young scientists. Plus, we maintain a web-based presence and newsletter to update our members on emerging discoveries. Additionally, we partnered with the International Federation of Pigment Cell Societies to transform a pre-existing Journal (Pigment Cell Research) into Pigment Cell and Melanoma Research in order to have a peer-reviewed journal supported by SMR with scientific leadership by melanoma researchers.

Combination Therapy Research

RWHC: Are there any studies your members are involved in that are particularly promising at this moment?

KF: As ours is the only international scientific society focused on melanoma research, our membership includes all of the clinical investigators from the major academic centers who have been conducting groundbreaking clinical trials in melanoma over the past eight years. Outcomes for patients with metastatic melanoma have been transformed by the development of molecularly targeted and immunotherapies. The most promising current trials have been investigating combinations of these...
two approaches at the same time. Preliminary results presented at the 2016 SMR Congress suggest that these combination approaches may further improve outcome significantly.

**Multidisciplinary Collaboration**

**RWHC:** Why are multidisciplinary collaborations so important in developing new therapies for melanoma? How is the SMR working to encourage or create such collaborations?

**KF:** Multidisciplinary collaborations can be defined by teams of clinical investigators, such as medical oncologists, surgical oncologists, pathologist, and radiologists. Or, they can encompass clinical and laboratory-based investigators partnering together. We have numerous examples of each kind within and across the major academic medical centers with a focus on melanoma research.

For years, the melanoma research community was characterized by empiric clinical trials in which therapies that had been successful in other cancer types were tried in melanoma, but with little scientific basis and focus on understanding whether those therapies were doing their molecular “job” or not. Since the late 2000s, the emergence of BRAF, MEK, CTLA-4 and PD-1 inhibitors has provided not only substantial benefit to patients, but it has transformed the research approach by bringing clinical and laboratory-based scientists together. Even for these FDA approved therapies, there remain questions regarding mechanisms of action and resistance which are critical to informing rational combination therapies that will be the focus of the next generation of clinical trials. This approach literally taught us how to define the limits of these partially effective therapies and will hopefully accelerate our pace of progress.

**More Funding, More Time**

**RWHC:** What are the biggest challenges melanoma researchers face today and how can they be overcome?

**KF:** Funding and time. For a decade, we have seen a decline in publicly funded research. The U.S. has always been the largest investor in biomedical research, and pairing that down has had global impact. New discoveries are made through publicly funded research before private sector research comes in to take those discoveries and reduce them to practice. This has made the melanoma research field increasingly dependent on philanthropic foundations and individuals.

Additionally, clinical researchers are constantly pulled between clinical duties and research activities. Many medical centers cannot afford to have their clinicians spending time on research. Therefore, research funding is needed to cover the portion of their time that is away from direct patient care. With the accelerated pace of technology development relevant to biomedical research and the inroads that we have made in the past eight years with regard to therapeutic approaches, there is more opportunity now than ever to accelerate the application of science to medicine for melanoma patients. But, these rate limiting factors are unquestionably slowing us down.
**Industry’s Role**

**RWHC:** What role do you think the biopharmaceutical industry should play in furthering research into new melanoma therapies?

**KF:** As always, advancing diagnostic and therapeutic approaches to widespread use requires risk-taking and investment by the biopharmaceutical industry.

In the cancer field overall and melanoma specifically, we have seen tighter integration between the public and private sectors that has come as a consequence of the initial successes with the now FDA-approved drugs. This has drawn in more interest from companies developing novel diagnostic technology that may allow us not only to find localized, advanced melanoma at an earlier point, but also allow us to deploy the optimal therapy for each patient in a personalized way. And, of course, the very costly process of drug development requires involvement of the biopharmaceutical industry from beginning to end.

Through close collaboration with the academic scientific community, we are able to discern very early in development whether a new therapy is accomplishing its biological task before investing massive additional resources in large-scale clinical trials to prove whether or not it has a clinical impact.

**Dramatic Unmet Need**

**RWHC:** What initially attracted you to the field of melanoma research?

**KF:** I was attracted to the melanoma field first and foremost by the dramatic unmet need. It is a cancer that has an awe-inspiring ability to metastasize from tiny primary tumors, making the challenge of early detection a key hurdle. And, when melanoma metastasizes, it is one of the most aggressive cancer types. Melanoma affects a far greater proportion of young adults than other more common cancers, making it one of the leading cancers with regard to aggregate years of life lost. At the time that I was entering the field, it seemed that the pace with which biologic insights into melanoma were being made was increasing. And, right at the end of my training, BRAF mutations were discovered and that drew my focus for all of the years since.

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Read this article at Real World Health Care.
Profiling Melanoma to Predict Immune Therapy Success

May is Melanoma awareness month, and our series on melanoma continues with a discussion with Dr. Douglas B. Johnson of the Vanderbilt-Ingram Cancer Center. Dr. Johnson leads Vanderbilt’s melanoma clinical and research program, overseeing clinical trials, patient care and translational research. His research interests focus on developing new immune and targeted therapies for melanoma, and in using existing treatments in the most effective ways. Specifically, he is exploring ways to profile cancers to predict which patients will benefit from immune therapies.

Combination and Targeted Therapies Allow Long-Term Survival

Real World Health Care: You published a review of therapeutic advances and treatment options in metastatic melanoma. Can you summarize the review and discuss its implications for patients with the disease?

Douglas Johnson: Treatment options for advanced melanoma have been rapidly advancing. We now have multiple options for patients with this disease, when even 5-10 years ago very few existed. Immune therapies, which unleash the immune system against the cancer, result in long-lasting responses in a large fraction of patients. The number of patients who benefit from treatment increases when two immune therapy treatments are combined, although at the cost of increased side effects. Targeted therapies, which block the effects of particular genetic mutations, have also made a big difference, particularly for patients who have mutations in the gene BRAF, which represents about half of melanoma patients. These treatments have transformed a disease which was essentially uniformly fatal to one that is often associated with long-term survival.

RWHC: Are you currently working on any new studies or trials relating to melanoma?

DJ: We have a number of combination immunotherapy trials. These types of trials are attempting to use strategies that extend the benefits of immune therapy to more patients. We are also working on developing biomarkers for immune therapy responses. In particular, we are evaluating whether the number and types of mutations in melanoma, as well as the expression of particular immune proteins, can predict which patients will respond to immune therapy. We also are studying the side effects and toxicities of immune therapy, to understand why they occur, who is affected, and develop effective prevention and treatment strategies.
Melanoma Research and Treatment

RWHC: What do you see as the most promising treatments on the horizon for melanoma?

DJ: A number of promising immune therapy combinations are being developed. It is very difficult to say which is the most promising, but likely some combination of anti-PD-1 therapy with other immune or targeted therapy agents.

RWHC: What are the biggest challenges facing melanoma researchers?

DJ: One of the biggest challenges is predicting who will respond to current immune and/or targeted therapies so we can assign the right treatment to the right patient. Researchers also are challenged to develop the most effective combination therapies and to prevent and manage toxicities. In some ways, the development of effective therapies has made it more difficult to enroll patients in clinical trials. This is a good problem to have, but it limits the speed of developing new effective therapies.

RWHC: What are the biggest challenges facing clinicians treating patients with melanoma?

DJ: From a clinical standpoint, the challenges are similar. Despite the current advances, there is still a large subset of patients who do not respond well to treatments. We need to understand who those patients are upfront, and develop more effective treatment strategies for them.

Toxicities are also a major consideration, particularly for patients with other medical problems or who have limited functional status. It is always a difficult balancing act deciding between single agent and combination immune therapy. On one side is the potential for a somewhat higher response rate, on the other side is the significant increase in side effects (which are typically manageable). Every clinician and patient has a different threshold regarding when to offer these therapies.

Improving the Lives of Melanoma Patients

RWHC: What initially interested you in studying and treating melanoma? What continues to inspire you?

DJ: I had a friend during my medical training who developed stage III melanoma and I was struck by the lack of treatment options at the time. When I joined Vanderbilt, my mentor Dr. Jeff Sosman was doing amazing research, and I become very excited about the prospect of doing groundbreaking research that would affect patient lives. That approach continues to drive and inspire me.

Read this article at Real World Health Care.
Harnessing the Immune System to Treat Melanoma

Real World Health Care continues our series on melanoma with a discussion with Howard Kaufman, MD, FACS, surgical oncologist at Rutgers Cancer Institute of New Jersey. Dr. Kaufman’s clinical and research work focuses on using the immune system to fight cancer. He also runs a scientific laboratory focusing on oncolytic viruses and had his first agent approved in 2015. He authored The Melanoma Book as a resource for patients and family members dealing with the diagnosis of melanoma and currently serves as editor-in-chief for the Journal of Immunotherapy Applications.

Directions in Research & Treatment

Real World Health Care: How can the immune system be used to treat melanoma?

Howard Kaufman: We’ve known for many years that the immune system can recognize some cancer cells, and when this happens the immune system can eradicate the cancer cell. We’ve seen this most prominently in melanoma, where a small percentage of patients with advanced melanoma don’t even know they have the disease because their immune system eradicates it without treatment.

About two decades ago, interleukin-2 (IL-2) was approved to treat melanoma. IL-2 is a natural part of the immune system. It’s a messenger protein called a cytokine, which activates part of the immune system. IL-2 doesn’t kill tumor cells directly like chemotherapy. Instead, it activates and stimulates the growth of immune cells: T-cells and Natural Killer Cells, both of which are capable of destroying cancer cells directly.

I trained under IL-2’s developer, Dr. Steven Rosenberg, at the National Cancer Institute, and was one of the first oncologists in the country to start treating patients with the therapy. It worked well, and it even cured some patients. But only about 15-20 percent of patients responded, and the research community began to ask why more patients didn’t respond.

We subsequently found that melanoma cells express a protein, called PDL-1, that shuts off the T-cells in the immune system (by binding to PD-1, which is expressed by the T-cells) so the cancer can grow. Over the last five years or so, antibodies have been developed to block PDL-1 immune inhibitory receptors. We started to see dramatic results in patients, similar to that of IL-2. Even though large numbers of patients are not responding, when responses do occur, they are sometimes complete and often long-term.
Now, other researchers and I are starting to use oncolytic viruses, which are injected directly into tumor cells. The viruses replicate in cancer cells, but not in normal cells. This replication generates an immune response in the cancer cells and overcomes the immune inhibitory receptors. We've seen benefit of this therapy in clinical trials for about 25 percent of patients. Even for patients with metastatic melanoma, if the virus is injected in a melanoma cell in the arm or the leg, it will eradicate melanoma in the lung as well.

Our next step in terms of research is to look at putting immunotherapy together with oncolytic virus therapy to see if we can increase response rates among more patients.

**Immunotherapy Challenges**

**RWHC:** What are some of the biggest challenges in using immunotherapy to treat melanoma patients?

**HK:** Like every drug, there are side effects, but not the type of side effects typically associated with chemotherapy or radiation therapy. These side effects relate to over-active immune response. Typical side effects include inflammation of the colon, liver or even lungs. These side effects are manageable, if treated quickly with corticosteroids. Unfortunately, if they’re not treated quickly, immunotherapy needs to be stopped. I’m a member of the Society for Immunotherapy of Cancer (SITC), which is working with the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) to develop guidelines to teach the clinical community how to best recognize and treat side effects due to immunotherapy drugs.

Another challenge facing the clinical community is how long to treat patients with these newer drugs. There’s not a lot of consensus on whether treatments should last one year, or two years, or if therapies should be stopped as soon as the patient responds to avoid the risk of side effects. It’s possible that some patients are being over-treated. Ideally, we will be able to find biomarkers that indicate whether a patient will be cured or will need more treatment.

Melanoma is an interesting field. Ten years ago there were very few treatment options, and today we have many. We’re just beginning to understand how to sequence therapies so patients get the right treatment at the right time. We also need better therapies for patients with mucosal melanoma and ocular melanoma, because they don’t respond as well to immunotherapy.

**Promise of Combination Therapies**

**RWHC:** What are some of the most promising combination therapies on the horizon to treat melanoma patients?

**HK:** Right now, I’m excited about combining oncolytic viruses with anti-PD-1 and anti-PDL-1 agents.
We’re seeing high response rates in clinical studies, without the increase in side effects common with other combinations. Other than a mild fever, chills and injection site reactions, the viruses have been very safe. This could be a powerful way to increase the number of patients who respond and cut down on side effects.

**RWHC:** How did you get interested in melanoma?

**HK:** I did a fellowship at the National Cancer Institute and became interested in how patients’ immune systems responded to IL-2. Melanoma seemed to be the most sensitive to immune system manipulation, and I’ve been honored to help develop what is today considered the paradigm in cancer care. During my fellowship, I became comfortable working with melanoma patients and was fortunate to build my practice quickly.

Melanoma knows no boundaries. It can affect people of all ages; I have personally treated patients as young as 5 years of age and up to 98 years of age. It’s such an evil type of cancer and it can spread anywhere. Offering hope to patients has been very rewarding, and I’ve enjoyed the opportunity to get students and residents interested in treating the disease and studying immunotherapies.

[Read this article](https://www.realworldhealthcare.com/) at Real World Health Care.
Fighting Melanoma with Immunotherapy

For this week’s post in our series on melanoma melanoma, Real World Health Care interviewed Kelly M. McMasters, MD, PhD. Dr. McMasters serves as the director of the Multidisciplinary Melanoma Clinic at the University of Louisville’s James Graham Brown Cancer Center. Here, he works with colleagues to identify the most effective combination of therapeutic modalities including surgery, immunotherapies, and targeted therapies for stage I-IV melanoma patients.

Dr. McMasters also directs a basic and translational science laboratory studying adenovirus-mediated cancer gene therapy and melanoma biomarkers, which has been funded by the National Institutes of Health, the American Cancer Society, the Melanoma Research Foundation and other agencies.

Sunbelt Melanoma Trial

Real World Health Care: You are the author and principal investigator of the Sunbelt Melanoma Trial. Can you briefly summarize the focus of this trial and its results?

Kelly McMasters: This was a multi-institutional study involving 3,500 patients from 79 institutions across North America. We studied whether interferon should be used for patients with minimal spread of melanoma to their lymph nodes. We found that this toxic, expensive treatment — which is like having the flu, but worse, for a whole year — was not necessary and did not result in survival benefits. This is important because many patients have been spared unnecessary treatment.

While interferon is still approved for adjuvant therapy for high-risk melanoma, other options now in the pipeline, and further research into the molecular basis of melanoma metastasis and immune system evasion will result in improvements in adjuvant therapy for patients at high risk of recurrence.

We also evaluated molecular tests to find patients at high risk of recurrence, but these tests turned out to not be clinically useful.

Immunotherapy Studies

RWHC: Are you currently working on any new studies or trials relating to melanoma?

KM: We currently are conducting and participating in several studies of immunotherapy for
Immunotherapy has revolutionized the treatment of melanoma in the past few years. Five years ago, there were essentially no treatments that were effective for patients with advanced melanoma. Now, we frequently can use immunotherapy that results in durable, complete remissions and even cure in such patients.

Former President Jimmy Carter is an example. He had metastatic melanoma in his brain and elsewhere, with a life expectancy of a few months. He got an immune checkpoint inhibitor and his cancer went away.

Immunotherapy Combinations and Resistance

**RWHC**: What are some of the biggest challenges facing researchers studying melanoma?

**KM**: Right now, the challenge is to figure out the best combination of immune therapies to get the greatest benefit for patients with the least side effects. We need to better understand the immune system and how it fights cancer.

Newer studies of melanoma adjuvant therapy using immune checkpoint agents, such as PD-1 inhibitors, show much promise. More work needs to be performed to understand the significance of molecular detection of melanoma cells in the lymph nodes and in the circulating bloodstream. We now suspect that melanoma, like other cancers, routinely sheds cancer cells into the lymphatic system and bloodstream. A small minority of these cells that have the ability to evade the immune system, attach, invade, develop their own blood supply and grow, becoming metastatic tumors.

**RWHC**: What are some of the biggest challenges facing clinicians studying melanoma?

**KM**: We need to find out why some patients have miraculous responses to immunotherapy and why some are resistant. Finding out how these mechanisms of resistance work will help us design treatments that are more effective for most people.

Clinicians also need to pay attention to side effects, which are variable, from very mild or virtually none, to potentially life-threatening. Early recognition and treatment — often immediately with corticosteroids — can be lifesaving, especially for autoimmune colitis, which can lead to bowel perforation and serious infection.

Beyond Surgery

**RWHC**: What interests you in studying melanoma, and treating patients with the disease?

**KM**: After so many years in which surgery was about the only truly effective treatment for melanoma, it is encouraging to see the development of other effective therapies. I find it gratifying when I now refer patients with advanced melanoma to my medical oncology colleagues for immunotherapy with
realistic hope of remission or even cure, rather than engage in desperate attempts to surgically resect all of the cancer. Surgery still has a very important role, but we now have a lot of other possibilities.

Read this article on Real World Health Care.
Cutting-Edge Melanoma Treatment at Rutgers Cancer Institute of New Jersey

This week, Real World Health Care continues our series on melanoma by interviewing two colleagues from the Rutgers Cancer Institute of New Jersey, a National Cancer Institute-designated Comprehensive Cancer Center.

Sharad Goyal, MD, is Associate Professor and Director of Clinical and Translational Research in the department of Radiation Oncology. He treats patients with brain tumors, melanoma and skin cancers, providing comprehensive cancer evaluation and the latest treatment planning technology to “map” tumors. He designs radiation treatments with pinpoint accuracy, ensuring that tumors get the most effective dose while healthy tissues and organs are spared.

Ann W. Silk, MD, is a medical oncologist who cares for patients with melanoma, and other skin cancers. She also leads clinical trials focused on combination treatment with immunotherapy and viral therapy for melanoma and other cancers.

Drs. Goyal and Silk discuss their work as part of a multidisciplinary team that translates research of investigational treatments and directly applies them to patient therapies.

Managing Multiple Melanoma Brain Metastases

Real World Health Care: How is treatment advancing for patients with multiple brain metastases (MBM) from melanoma?

Sharad Goyal: The treatment of brain metastases from melanoma is controversial and includes surgical resection, stereotactic radiosurgery (SRS) and whole brain radiation (WBRT). Several new classes of agents have revolutionized the treatment of metastatic melanoma, allowing for subsets of patients to have long-term survival. Given this, management of MBM from melanoma is continually evolving.

As patients are living longer due to more effective systemic therapy, surveillance and management of intracranial disease is increasingly important. At this time, the standard of management for patients with MBM from melanoma includes SRS, WBRT, or a combination of both.
In addition, emerging data supports the notion that SRS, in combination with targeted therapies or immune therapy, may reduce the need for whole brain radiation. Prospective studies are required to fully evaluate the efficacy of these novel regimens in combination with radiation therapy. Given the advances in systemic therapy of melanoma, it is critical that oncologists treating these patients be aware of new treatment paradigms to optimize the outcomes for all patients with metastatic melanoma.

**RWHC:** Are there ways to treat melanoma in order to avoid or lessen the chances of brain metastases? Does early initial detection of melanoma help?

**SG:** Early detection of melanoma will always help reduce the chance a patient develops brain metastases. There is usually a fairly lengthy period when the tumor expands beneath the top layer of skin but doesn’t go any deeper. This allows time for screening, early detection, treatment, and a full recovery if the tumor is discovered before it spreads.

After a patient is diagnosed with melanoma, the use of certain anticancer treatments that are given after a cancer is surgically removed, such as interferon alfa and ipilimumab, will allow for an improvement in overall survival in patients with stage III or IV melanoma. In addition, the use of anti-PD-1 checkpoint inhibitors prolongs overall survival in patients with stage IV melanoma. Currently, many studies are underway investigating the optimal anticancer treatment in patients with Stage III melanoma.

**Promising Therapies**

**RWHC:** What are the most promising therapies on the horizon for metastatic melanoma?

**Ann Silk:** Melanoma is the “posterchild” for breakthrough immunotherapies. At Rutgers CINJ, we are testing novel combinations of new agents coupled with immunotherapies. Those novel agents help to “prime” tumors so immunotherapies work better. One example of this is combining an immune checkpoint inhibitor pembrolizumab with intra-tumoral injections of talimogene laherperepvec, which is a live herpesvirus that infects cancer cells, replicates within them, and lyases the cancer cell, thus killing the cell. We’re also seeing promising early results in trials that combine intra-tumoral injections of coxsackievirus with injections of pembrolizumab, with response rate of 60%, which we reported at this year’s American Association of Cancer Research Annual Meeting. We have just recently opened a study in which we will combine IL-2 cytokine therapy with pembrolizumab, a combination of two drugs that have already demonstrated good activity in metastatic melanoma. They are each FDA-approved as single-agents, but we are studying them as a combination therapy. The goal of these studies is to build on the success of immunotherapies to increase response rates, particularly complete response rates.
Access to Clinical Trials

RWHC: What are some of the biggest challenges facing researchers studying metastatic melanoma?

AS: Access to clinical trials is a challenge, from a patient or participant status. Running clinical trials requires vast resources and numerous support personnel, so they tend to be concentrated at large medical centers. As a result, only about five percent of the patient population has access to these trials. I think that number should be closer to 80 percent. Trials aren’t only important for the patients receiving the treatment; the knowledge we gain also helps future patients.

Treating Melanoma

RWHC: What are the biggest challenges facing clinicians treating patients with metastatic melanoma?

SG: One of the most challenging types of cancer to treat is melanoma and the most challenging area it can spread to is the brain. With the advancements being made in cancer treatment, the odds of survival for many of these patients are changing dramatically.

In recent years, our understanding of cancer biology has progressed substantially and this has led to the development of targeted therapies and immunotherapies. These novel therapies have prolonged survival in a disease which previously had a dismal outcome. As patients are living longer due to more effective systemic therapy, surveillance and management of intracranial disease is of increasing importance.

AS: There are many standard therapies approved to treat melanoma, and as indicated earlier, there’s lots of research activity in this area as well. Patients benefit from the wealth of approved therapies on the market. But while about 30–40 percent of patients will respond very well to these therapies, the majority still struggle and succumb to their disease. Patients who don’t respond to the first line of treatment must move on to a second line of treatment. Once those treatment options are exhausted, the only course of action is to try and get the patient enrolled in an investigational therapy trial. In many cases, the patient would benefit from earlier involvement in clinical trials.

Early and Current Inspirations

RWHC: What initially interested you in researching melanoma and treating people with the disease? What continues to inspire you?

AS: I became interested in the interplay between cancer and the immune system in my first job as a data manager at the Dana-Farber Cancer Institute, where I managed one of the first clinical trials of ipilimumab, which was later FDA approved with the distinction of being the first drug that prolonged survival in melanoma. I was inspired by researchers who were on the forefront of personalizing medicine by using the immune system to attack cancer cells. Ever since then, in both my research and
clinical practice, I haven’t found any better ally in the fight against cancer than retraining the immune system to attack cancer cells.

SG: Throughout my career, I have been inspired by the cancer patients I treat. The relationships that I have developed with patients and their families are unlike those in almost any other medical specialty. Once a patient has a diagnosis of cancer, I am able to see the patient and his or her family members on a regular basis and develop a long-lasting relationship with them.

Read this article on Real World Health Care.
Advancing Melanoma Research & Supporting Patients

Our series on melanoma concludes as we shine the spotlight on the Melanoma Research Foundation (MRF). We spoke with the MRF’s Director of Education, Shelby Moneer, MS, CHES and MRF’s Scientific Advisory Committee Co-Chair, Michael B. Atkins, MD, PhD, Deputy Director of the Georgetown-Lombardi Comprehensive Cancer Center, Georgetown University.

The MRF is the largest independent organization devoted to melanoma. Its mission is threefold. It supports medical research that leads to more effective treatments and eventually a cure for melanoma. It educates patients, physicians and the public about the prevention, diagnosis and treatment of melanoma. And it serves as an advocate for the melanoma community to raise awareness of melanoma and the need for a cure.

Research & Patient Support Priorities

Real World Health Care: What type of research programs does the MRF support?

Shelby Moneer: The Melanoma Research Foundation is committed to advancing a broad scientific agenda across the disciplines of prevention, diagnosis and treatment. As part of the MRF’s mission to support medical research to find effective treatments and a cure for melanoma, we are proud to collaborate with internationally recognized research institutions, investigators, government entities and leading melanoma organizations. The MRF currently offers research awards for medical students, junior investigators and senior investigators in both clinical and translational science. We fund research related to cutaneous, mucosal and ocular melanoma.

RWHC: How does the MRF support the patient community?

SM: The MRF provides a broad range of patient support programs offering access to peer-to-peer educational information, as well as professionally moderated support networks, financial and treatment assistance and more. These are continually updated and expanded as new resources become available because we believe that educated and informed patients with a strong support network live longer, better lives.

The MRF advocates for the melanoma community on the local, state and federal level on issues that promote melanoma awareness, prevention and treatment. Current priorities include increased federal
funding for melanoma research, restrictions on the use of indoor tanning devices and expanded access to sunscreen in schools. The MRF trains and supports a nationwide network of dedicated volunteers who serve as advocates everywhere from their local communities to the halls of Congress.

**RWHC:** What are some of the biggest challenges facing researchers studying melanoma?

**Michael Atkins:** The MRF feels that the biggest challenge is helping to launch the careers of young investigators who are interested in doing research into the biology and treatment of patients with melanoma. The MRF is addressing this challenge by offering an expanded number of Career Development grants in the coming year targeted toward young investigators.

**Treating Melanoma Patients**

**RWHC:** How are clinicians addressing the challenges of treating patients with melanoma?

**MA:** For clinicians, the big challenges are learning how to optimally use new treatment options for patients with melanoma. For example, identifying how to integrate targeted therapy with immune therapy, when to stop immune therapy, how to treat patients with variant melanoma presentations (acral, mucosal, uveal) and patients with CNS metastases, how to treat patients with resistance to immunotherapy, determining the best adjuvant therapy for patients with resected high and intermediate risk melanoma, identifying predictive biomarkers for particular treatment approaches, identifying safe and effective combination regimens, and learning how to manage the novel toxicities of immunotherapies.

These questions can only be answered through continued clinical research. The MRF is addressing these challenges through the Melanoma Research Foundation Breakthrough Consortium (MRFBC), which brings together clinical investigators from 20 leading academic melanoma centers to design and conduct clinical trials addressing these types of questions.

**RWHC:** How can patients work with clinicians to optimize their treatment?

**MA:** Melanoma patients face the challenge of getting the best treatments for their disease in a setting that is convenient for them and will get them back to their normal lives as quickly and as functionally intact as possible. Patients can work with clinicians by participating in clinical trials aimed at both providing tomorrow’s treatments today and addressing the important unanswered questions facing researchers. Patients can also go to organizations like the MRF to gather information about optimal management of their disease, unanswered questions and available clinical trials. Their support community can work with and contribute to MRF to foster the clinical and basic research that will lead to even further advances in the treatment of patients with melanoma.
**RWHC:** What does the MRF see as the most promising treatments on the horizon for melanoma?

**MA:** The MRF sees many promising new treatment opportunities including novel combination immunotherapies, triple combination of BRAF/MEK and anti-PD1 regimens and moving effective treatments for advanced disease into the adjuvant high risk setting.

[Read this article](https://www.realworldhealthcare.com) on Real World Health Care.