

# TEAMING UP TO COMBAT MELANOMA:

SEVERAL RESOURCEFUL PHYSICIANS and researchers are speeding up the attack on the deadliest form of skin cancer by pooling their expertise.

FOR MONTHS, RESEARCHER WEIMING GAI KEPT HITTING A WALL. In the laboratory run by two physician-scientists, Drs. Iman Osman and David Polsky, she had been trying to grow and manipulate skin cells a certain way to better study the deadliest of skin cancers, melanoma. But the cells had been too finicky. Now, after 10 months of effort, her luck has shifted and she wears a beaming smile.

David Polsky, M.D., Ph.D., Assistant Professor of Dermatology and Associate Director of the Pigmented Lesions Section in the Ronald O. Perleman Department of Dermatology, peers through the microscope at the cells. He, too, is pleased, and will share the good news with his colleague, Dr. Osman, Associate Professor of Dermatology, Urology, and Medicine.

The ability to grow and tinker with cancer cells genetically is crucial. Yet melanoma cells are particularly difficult to manipulate, hampering the ability of researchers to understand the malignant behavior of these cells. Viewed through the fluorescent microscope, the large green glowing cluster of cells looks like shingles on a rooftop. The test that Gai applied involved a short electrical jolt to the cells, and it worked. A gene, one that causes the fluorescent green, has been successfully delivered to the cells. Such a method can now be used to study the genes that seem to transform a healthy cell into a cancerous one.

This successful day in the lab is a minute step forward in the race to understand and, ultimately, treat melanoma. The progress is important not only for Drs. Osman and Polsky, but for other colleagues with whom they have decided to join forces. They are part of a growing trend toward translational research, an approach that the National Institutes of Health (NIH) advocates as a “powerful process that drives the clinical research engine” in the NIH Roadmap for Biomedical Research, a large-scale program launched in 2002.

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**ONCOLOGIST**  
Iman Osman, M.D.

In that same year, seven NYU physicians and researchers, including Drs. Osman and Polsky, banded together in a translational effort to improve the odds for patients afflicted by melanoma. They come from diverse disciplines: dermatology, molecular biology, medical and surgical oncology, and pathology. Their joint effort builds on the extensive expertise in melanoma that NYU Medical Center has maintained for decades. As individuals, each shines a flashlight on the melanoma puzzle. With the synergy of a group, the light shines brighter.

The progress in the labs of Drs. Osman and Polsky helped another group member, oncologist Anna C. Pavlick, D.O., Assistant Professor of Medicine and Dermatology, land a National Cancer Institute (NCI) drug trial that emphasizes translational research. "None of our activities would be possible without great collaboration between dermatologists, basic scientists, and surgeons," says Dr. Pavlick. To shorten the journey from lab bench to bedside, the group seeks to find better

ways to detect melanoma, enhance responses to therapy, and contribute to developing effective drugs. Information flows in a loop, beginning and ending with the patient. Insights from the molecular biology of tumors are scrutinized in the lab and taken to the clinic. Clinical results are compiled and analyzed, and that knowledge circles back to the lab for further evaluation.

Separately, they all treat patients and pursue individual avenues of research. However, at monthly and sometimes



**DERMATOLOGIST**  
David Polsky, M.D., Ph.D.

weekly intervals in the evenings after their busy workday, they depart from their individual routines and come together as members of what they call the Interdisciplinary Melanoma Cooperative Group (IMCG). They meet to think, brainstorm, and share results and methods with a singular mission. They review one another's projects and results, design experiments, and co-publish their findings in academic journals. They sometimes squabble. They praise and support and even harshly criticize each other.

"Many researchers want to work this

collaboratively," says Dr. Iman Osman,, the group's co-founder. "We actually do it; we complement one another and understand each person's strengths." Dr. Osman is the IMCG principal investigator and organizer. As her colleagues say, she is the glue that holds the group together. "It is becoming clearer that collaborative efforts are going to make a difference in cancer," says Steven J. Burakoff, M.D., the Laura and Isaac Perlmutter Professor of Pathology and Director of the NYU Cancer Institute and the Skirball Institute of Biomolecular Medicine. He sees the IMCG as "a fantastic model program" with "a marvel of interaction." Recently, the IMCG received additional funding from the NYU Cancer Institute and has also been supported by the Department of Dermatology and by private donations.

Patients and the IMCG team face the harsh reality that advanced melanoma does not respond well to the few available drugs. Some patients call themselves "melanoma warriors" as they battle the disease and undergo treatment. And with good reason; the foe they face is formidable.

More than other forms of skin cancer, advanced melanoma has the hideous ability to spread beyond the skin to other organs. The five-year survival rates for patients with advanced melanoma that has metastasized lie between 10 and 20 percent, says Dr. Polsky. Surgery is the therapeutic mainstay. In fact, when melanoma is detected early enough, surgery can cure the patient. Early detection is crucial.

Alfred W. Kopf, M.D., (55) Head of the Oncology Section of the Skin &

Cancer Unit of NYU Medical Center, is a pioneer in the study of melanoma. He developed a widely adopted mnemonic device used to help diagnose the disease (see page 29). He celebrated his 80th birthday this year, and still sees patients twice a week with Dr. Polsky.

Dr. Kopf is troubled by the lack of medications for melanoma patients, particularly for people with metastatic disease. “We really need to find better treatment,” he says. The hopes are that scientific discoveries at the bench can find their way into drug development, and that clinical observations can stimulate new approaches in the lab. “I am very hopeful about all the new information coming from molecular biology; I think that is absolutely the right direction,” he says.

Skin cancer is not well understood. It forms in various cell types found in the skin, such as squamous cells and basal cells. Both of these cell types can give rise to skin cancers, but the deadliest skin cancer is melanoma, which accounts for the majority of skin cancer deaths.

Melanoma forms in melanocytes, the cells that make, store, and transport pigment to surrounding skin cells. Why melanocytes transform into cancerous versions of themselves is not known. There is, however, a combination of genetic and environmental risk factors, such as family history of melanoma, light skin, and excessive exposure to ultraviolet rays, including the artificial ones of tanning salons.

In the U.S., says Dr. Polsky, melanoma is more frequent in men than in women: one in 58 men and one in 82 women develop melanoma. Many scientists say



**IMMUNOLOGIST**  
**Nina Bhardwaj, M.D., Ph.D.**

the incidence of melanoma is growing faster than any other cancer in the U.S., although researchers differ in their assessments of why. “Some of the increased incidence may be due to better detection of early stage disease and more screening,” says Dr. Polsky. “But there is also an overall increase in deaths from melanoma.”

There is little debate about how deadly melanoma can be. One form that evolves rapidly—nodular melanoma—is very hard to detect early, and accounts for a large proportion of melanoma deaths, says Dr. Polsky. Only 4 percent of all skin cancers are melanoma, he says, yet melanoma causes some 80 percent of skin cancer deaths. According to the American Cancer Society, in 2006 an estimated 62,190 new cases of melanoma and 7,910 deaths are expected.

Besides the pressures of treating patients with a daunting disease, the collaborative effort faces plenty of logistical challenges. Tumor specimens are evaluated in the course of treatment. Specimens also need to travel in a timely fashion to the labs of various group members. In addition, information must jump over the hedges and walls that traditionally separate disciplines.



**ONCOLOGIST**  
**Anna C. Pavlick, D.O.**

The IMCG has a comprehensive database that tracks patients, their treatments, and characteristics of their disease. That means careful data collection and analysis. It also means plenty of miles walked by IMCG Clinical Coordinator Joanna Spira.

With the patient’s consent, she sees to it that a small amount of patient tumor tissue is taken from the operating room of IMCG member Richard L. Shapiro, M.D. (’88), Associate Professor of Surgery at the NYU Clinical Cancer Center, or that of his colleague and IMCG member Russell S. Berman, M.D. (’90), Assistant Professor of Surgery at the NYU Clinical Cancer Center. Spira makes certain that fresh



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tumor specimens reach the lab of group member Nina Bhardwaj, M.D., Ph.D., (81) Professor of Medicine, Pathology and Dermatology. Speed is important because the researchers need to study tissue in a state that best approximates that of the body.

Among other projects, Dr. Bhardwaj and her colleagues are trying to capture a snapshot of genetic patterns in the tumor tissue to better understand what makes a growing tumor so deadly. With the aid of microarrays—tools that let scientists examine patterns of activity in hundreds of genes at the same time—gene activity in metastasized tumors can be compared to non-diseased tissue. One early finding is that thicker, more aggressive melanomas show higher levels of a protein called NY-ESO-1. This protein may offer insight into melanoma. “We are still busy characterizing what we are seeing,” Dr. Bhardwaj says.

Spira also ensures that samples reach Drs. Polsky and Osman, who study the role of individual genes and proteins. A small amount of blood is used by Leonard F. Liebes, Ph.D., another IMCG member, who is Director of the Oncopharmacology Laboratory and Associate Professor of Medicine, as he strives to develop a test that can help in establishing a patient’s chemotherapeutic regimen.

Clinical oncologist Anna Pavlick, an IMCG member, is seeing an increasing number of patients referred to NYU because of its expertise in melanoma. She is in charge of administering clinical trials of chemotherapy and, in collaboration with Dr. Bhardwaj, two trials of vaccines to melanoma patients.

Clinical information and data about the molecular biology of the patient’s tumors are compiled in the IMCG database and evaluated by Molly Yancovitz, M.D., the current Melanoma Translational Research Fellow working with the IMCG.

The group not only organizes clinical and research efforts—it sleuths collectively, following specific hunches about tumor biology. Somewhere, somehow, as pigment-producing melanocytes go about their normal business of dividing, differentiating, aging, and dying, a conversion occurs. Networks of interacting pathways of enzymes that regulate the cellular goings-on are hijacked for cancerous purposes.

“Melanoma is quite complicated and I would say we are just beginning to figure out how to short-circuit it,” says Dr. Polsky. Some newer cancer drugs—a class of targeted drugs that build on insights from molecular biology—manage to intervene in those pathways, sometimes brightening the outlook for patients. There is no such drug for melanoma. Not yet. “If you could find a drug that cures even 10 percent of metastatic melanoma patients, it would be a major breakthrough,” says Dr.

Polsky. To do so, researchers hunt for vulnerable spots in pathways, looking at the molecular cast of characters involved. “There’s not really one key player in melanoma,” says Dr. Polsky. “It is more like an ensemble.”

One of the enzyme families that make up a pathway of interest is called the mitogen-activated protein kinase signaling cascade, MAPK for short. “One interesting thing is that this pathway is turned on in the vast majority of melanomas,” says Dr. Polsky. There are different ways to activate this pathway and a number of players in it. One is an enzyme called BRAF. In patients with metastatic melanoma, Dr. Polsky and his colleagues found a high percentage

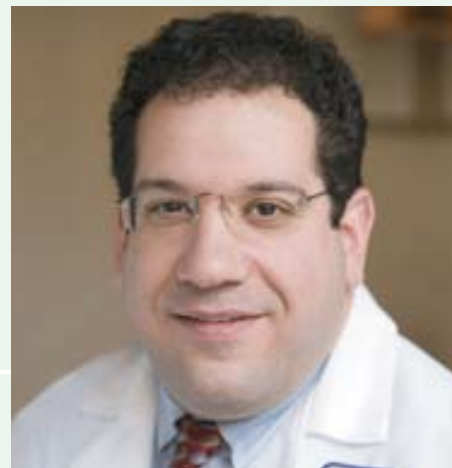
## **SURGEON** Richard L. Shapiro, M.D.



of a mutated form of this enzyme. Could its presence indicate malignancy? His team is studying a large number of tumor samples to pursue this question.

“BRAF is confusing because it is also found in a mutated form in moles, which are benign lesions,” he says. He and his colleagues believe that this enzyme is basically a good guy that can

## **SURGEON** Russell Berman, M.D.





**PHARMACOLOGIST**  
**Leonard F. Liebes, Ph.D.**

turn bad. When other bad guys are added to the mix, and when the pathway goes haywire in a number of crucial spots, melanoma may result. Some information in melanoma research derives from studies of families predisposed to melanoma. About 25 percent of these persons appear to have a mutation in a gatekeeper enzyme called p16. When both BRAF and p16 mutate, the risk of melanoma appears to rise substantially, Dr. Polsky explains. That is another reason to watch BRAF closely.

At the 2005 World Congress on Melanoma, Dr. Polsky and his colleagues presented a sensitive blood test to detect this enzyme in patients. The test has potential in the clinic, Dr. Polsky says. For example, it could be used to monitor a patient's response to a drug that inhibits this enzyme.

BRAF has also caught the eye of commercial drug developers, and clinical trials are underway with inhibitors, one of which is called sorafenib. A clinical trial with this drug run by Dr. Pavlick began at NYU last year. The trial also has a molecular dimension: patients not only receive the drug, they are screened for mutations. "Do you need mutant BRAF to have a response to this drug?" Dr. Pavlick asks. "That is a question we are pursuing in this trial."

The tumor specimens from patients in the trial are analyzed in the lab of Drs. Osman and Polsky to determine if the tumor has the mutation. That analysis can help reveal whether the presence of the mutation affects the response to the treatment.

This enzyme BRAF is a good example of the translational approach of the IMCG, says Dr. Polsky. Publishing their studies on the subject put the group on the map. A grant was then approved to develop the BRAF blood test. As Dr. Pavlick explains, the molecular biology findings by Drs. Osman and Polsky enabled her to land a special drug trial contract with the National Cancer Institute (NCI). The program that emphasizes translational research is called Cancer Therapy Evaluation Program (CTEP) and targets new anti-cancer agents and molecular biology.

As the group members probe melanoma with the tools and insight of their respective medical sub-specialties, they believe in the cross-disciplinary synergy that comes from joining forces. At the same time they are keenly aware that their group includes a larger community. And a key component of that community is patients facing a difficult disease, patients who may not see a cure come through in their lifetime. "We are so very grateful to patients," Dr. Osman says, "who let us use their blood and tissue and permit us to poll them for our research."

*For a physician referral, please call the NYU Physician Referral Service at 888-7NYUMED (888-769-8633)*

## GROUP MUSCLE

The Interdisciplinary Melanoma Cooperative Group (IMCG) builds on efforts by NYU clinicians to collect, in a database from 1972 onward, the diagnostic workup, pathology reports, tumor characteristics and measurements, treatment, and follow-up care of their patients. Among those contributing to this endeavor over the years are Drs. Alfred W. Kopf ('55), Head of the Oncology Section of the Skin & Cancer Unit, Matthew Harris, Professor of Surgery, and Daniel F. Roses ('69), the Jules Leonard Whitehill Professor of Surgery and Oncology.

The IMCG is vigorously expanding this database, linking more complex clinical and research data to tissue specimens, explains Dr. Polsky. Since 2002, when the group was formed, 463 patients have agreed to participate in the program and 150 patients are being added each year. "We are not aware of any institution in the U.S. with a collection like this or a group like the IMCG," says Dr. Polsky.

Other institutions have tissue banks with patient samples; still others have complete records about patient care. "This is not just tissue banking," says Dr. Osman. "We collect specimens and we know what is going on with each of these patients."

Following diagnosis or treatment, patients who have given their consent, get a call at regular intervals from Clinical Coordinator Joanna Spira and her colleagues to chronicle their health. Biopsy samples, if they are collected at other medical centers, are sent to NYU where they are evaluated and tracked.

The upkeep of this collection is critical, the scientists say.

### MELANOMA LOOKS LIKE...

- A** = asymmetrical lesion.
- B** = lesion with irregular borders. **C** = multiple colors unevenly distributed.
- D** = diameter larger than 0.2 inches or 6 millimeters (the size of a pencil eraser).
- E** = evolving, changing size, color or symptoms such as itching and oozing over time.

