SHH-MB tumors revealed that the location of genetic alterations along the SHH pathway plays a role: Loss-of-function mutations in \textit{PTCH1}, which inhibits vismodegib sensitivity, as did alterations in \textit{p53}. However, tumors with pathway mutations downstream of \textit{SMO}, including \textit{GLI2} and \textit{SUFU}, were nonresponsive.

“These results validate findings from larger genomics studies that showed substantial numbers of SHH-MB patients had varying mutations predictive of vismodegib response,” says Yoon-Jae Cho, MD, a pediatric neuro-oncologist at California’s Stanford University School of Medicine. There have been no previous pediatric trials with vismodegib, he adds, so these studies “open up our ability to combine vismodegib with other targeted therapies, or with some of the backbone chemotherapies regimens for kids, for more durable responses.”

Clinicians at St. Jude have now incorporated vismodegib into treatment regimens after patients with SHH-MB complete standard-of-care therapy. This could reduce recurrence, Robinson says; if not, new therapeutic targets may be uncovered by analyzing the molecular features of recurrent tumors.

“The idea is to look at vismodegib responses in a larger population of patients with SHH-MB,” Robinson explains. “The more specific our drugs, the better we need to understand the tumors we’re targeting.”

**Hedgehog Inhibitor Approved for BCC**

The FDA has approved a second targeted treatment for locally advanced basal cell carcinoma (BCC). Sonidegib (Odomzo; Novartis) inhibits a key step in the Hedgehog pathway, a developmental regulatory cascade that is aberrantly activated in the majority of BCCs.

BCC is the most common form of skin cancer, accounting for 80% of skin cancers in the United States. Most cases can be cured with surgery, radiation, or topical medications, but until recently there was no effective treatment for the small number (1%-10%) of inoperable, recurrent, and metastatic tumors. That changed in 2012 with the approval of vismodegib (Erivedge; Genentech), an inhibitor of the smoothened (SMO) protein, a component of the Hedgehog pathway.

The FDA approved sonidegib, another SMO inhibitor, based on results from the phase II BOLT study, which compared two doses (200 mg and 800 mg per day, given orally) in 194 patients with locally advanced BCC who were ineligible for surgery or radiation. Sonidegib showed durable antitumor activity, with 58% of the patients given the 200 mg dose achieving an objective response. Most side effects were mild to moderate, including muscle spasms, loss of sense of taste, and alopecia. Severe side effects included elevated creatine kinase levels and breakdown of muscle tissue. Because there was no evidence of better tumor response in the patients receiving the 800 mg dose of sonidegib, and adverse events were more common, the FDA approved the 200 mg dose.

“The clinical activity and side effect profile of sonidegib appear similar to vismodegib’s. Due to the importance of the Hedgehog pathway in fetal development, both drugs carry a black box warning about significant fetal toxicity.”

With the approval of sonidegib, “we have two drugs that are very effective,” says William Sharfman, MD, director of cutaneous oncology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore, MD. “The challenge now is to figure out which patients with locally advanced disease can best benefit from the drug,” he says.

Sharfman notes that the drugs might be useful to shrink tumors before disfiguring surgery or delay the need for surgery, and studies of these neoadjuvant applications are under way.

The downfall of many molecularly targeted therapies is the development of resistance. Clinical experience suggests that about 20% of patients taking vismodegib develop resistance within a year, mainly through acquired mutations in \textit{SMO}. Whether sonidegib will perform better remains unknown, says Jean Y. Tang, MD, PhD, a dermatologist and physician-scientist at California’s Stanford University. Preliminary experience with the drugs suggests that cross-resistance does occur, says Tang.

Studies of sonidegib and other SMO inhibitors are also under way in medulloblastoma, another cancer caused by \textit{SMO} mutations, as well as other tumors with Hedgehog pathway activation.

“The hope is that this pathway or target is relevant for other cancers and that one can expand the treatment options for other deadly cancers,” says Tang.

**Pinpointing Melanoma’s Invasive Trigger**

In its earliest stage, melanoma proliferates within a basal skin layer that separates the outer epidermis and inner dermis, but the disease is \textit{in situ}, meaning melanoma cells aren’t yet invasive or metastatic. What provokes their aggression hasn’t been well understood; however, a recent study suggests that the surrounding microenvironment, along with Notch signaling, may be key (\textit{Mel Cell} 2015;59:664–76).

“To metastasize, melanoma cells need to invade the dermis, which contains blood vessels,” explains senior author Carmit Levy, PhD, an investigator at Tel Aviv University’s Sackler School of Medicine in Israel. “Oddly, before heading deeper [into the dermis], they first extend upward, to the top of the epidermis. I wondered why they were apparently starting out in the wrong direction, and it occurred to me that our skin’s outermost layer might contain the trigger for invasion.”

Levy and her group explored their hunch by co-culturing noninvasive melanoma cells with different types of normal human skin cells, including differentiated and basal keratinocytes from the epidermis. Only melanoma cells interacting with differentiated keratinocytes became highly invasive—measured via a gel-based infiltration assay—and displayed reduced pigmentation, another marker of invasive capability. Mice treated with this combination of melanoma cells and...
differentiated keratinocytes also had significant numbers of lung metastases. Aware that melanoma cells express the Notch receptor, and that one of its ligands, DLL1, is expressed in differentiated keratinocytes, the researchers were not surprised to observe significant Notch activity when both cell types were co-cultured. Analyses of patient samples showed that melanoma cells far from DLL1-expressing differentiated keratinocytes remained noninvasive; on the other hand, direct contact between these cells induced Notch signaling and dermal invasion.

“Melanoma cells have to reach a particular microenvironment within the epidermis where Notch ligand–expressing cells reside,” Levy says. “Once contact is made, it triggers an entire cascade of events, leading to metastasis.”

Next, the researchers investigated this cascade in greater molecular detail. They found that in noninvasive melanoma cells, the proteins MITF and RBPKJ cooperatively bind to and repress miR-222/221, two microRNAs in close proximity to each other. The Notch receptor’s intracellular domain—cleaved when direct interaction of melanoma cells with differentiated keratinocytes activates Notch signaling—interferes with this repression by removing MITF; subsequently, miR-222/221 is activated and precipitates melanoma cells’ ability to invade the dermis.

“This study sheds significant light on the complex relationships between malignant and nonmalignant cells in tumor microenvironments,” says Marc Ernstoff, MD, director of the melanoma program at Cleveland Clinic’s Taussig Cancer Institute, OH. “Understanding the pathways by which melanoma turns invasive, and how normal cells nearby contribute, will allow us to develop therapeutic strategies that can change the biological behavior of primary tumors.”

For instance, Levy envisions delivering Notch inhibitors directly to the epidermis—perhaps via a skin cream. Then “patients with atypical moles could receive anti-Notch treatment, even while being monitored,” she says.

“Melanoma’s gestation is a lengthy one,” Levy adds, “and as we uncover more of this disease’s early events, we may someday be able to prevent metastasis altogether.”

Five New Experts Appointed to NCAB

Five new cancer experts were appointed in June by President Barack Obama to serve on the National Cancer Advisory Board (NCAB).

Established in 1971, the NCAB consists of 18 members, including 12 distinguished leaders from health and scientific disciplines, and six representatives of the general public, including experts in the fields of public policy, law, health policy, economics, and management. Members serve overlapping 6-year terms. The group advises the NCI director, the secretary of the U.S. Department of Health and Human Services, and the president on issues related to the NCI’s operations, including its programs and future direction. According to its charter, the NCAB may also review applications for grants and cooperative agreements for research and training, and recommend the approval of “projects that show promise of making valuable contributions to human knowledge.”

The NCAB’s newest members are:

• Peter C. Adamson, MD, chair of the Children’s Oncology Group at The Children’s Hospital of Philadelphia, PA;
• Max S. Wicha, MD, deputy director of research at the University of Michigan’s Taubman Medical Research Institute in Ann Arbor, MI;
• Randall C. Tepper, MD, chief of the Gynecologic Oncology Branch at the National Cancer Institute, NIH, Bethesda, MD;
• Timothy J. Ley, MD, director of stem cell biology at the Washington University School of Medicine in St. Louis, MO;
• Max E. Chawla, MD, PhD, director of the National Heart, Lung, and Blood Institute’s Cardiovascular Genetics Program;
• Deborah Watkins Bruner, RN, PhD, associate director for outcomes research at Emory University’s Winship Cancer Institute in Atlanta, GA;
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The registry would allow researchers, health care professionals, and patients to search information about diagnosis, disease trends, risk factors, treatment availability, and outcomes.

• Bristol-Myers Squibb launched its Immuno-Oncology Rare Population Malignancy Program in the United States. The program is a multi-institutional initiative with academic-based cancer centers to investigate immunotherapies for high-risk, poor-prognosis cancers, defined as a rare population malignancy. A rare population malignancy is a subpopulation within a higher-incidence disease population, such as BRCA1 and BRCA2 breast cancers.

• The FDA approved carfilzomib (Kyprolis; Onyx Pharmaceuticals) in combination with lenalidomide and dexamethasone for the treatment of patients with relapsed multiple myeloma who have received one to three prior lines of therapy. The drug was previously approved as a monotherapy for a subset of patients with multiple myeloma.

• A proposed rule in Massachusetts would limit prices on drugs, especially very high-priced agents such as newer, targeted therapies for cancer. In addition, the law would “force biotechnology and pharmaceutical companies to justify their prices,” The Boston Globe reported.

• A recent study found that about 10% of serious and unexpected complications are not reported to the FDA by drug manufacturers within 15 days, as directed by federal regulations, a delay that could compromise the safety of other patients (JAMA Intern Med 2015 July 27 [Epub ahead of print]).