

HEALTH

Monday, April 28, 2008

MEDICINE

IN THE LAB

Moles' split personality

One mole stays healthy while another turns malignant. Scientists are starting to understand why.

By JENNIFER CUTRARO
Special to The Times

WE'VE long been told to keep an eye on our moles lest they progress to melanoma, a form of skin cancer that's treatable if caught early, deadly if not. But not all moles are equal — some are risky; others can be safely left alone. The biological roots of those differences are not really understood. However, scientists are making progress on several fronts.

A study reported in February found a key biological difference between moles that progress to melanomas and moles that do not. One day, the knowledge might be used to shrink moles that have become cancerous, rendering them harmless.

Another finding, published this month, reported striking improvements in people with certain types of melanoma, but not others, after treatment with a drug called Gleevec, and researchers think they know why.

Though far from offering cures, these studies open doors to improved diagnosis and therapies tailored to match different types of melanoma, scientists say. "You can make ... therapy much more effective by personalizing it towards that patient's individual cancer," says Dr. Sam Hwang, a senior investigator at the National Cancer Institute in Bethesda, Md. "This will be a big trend in medicine in the next 10 to 20 years."

Melanoma is the rarest type of skin cancer but far more dangerous than the more common kinds, basal cell carcinoma and squamous cell carcinoma, which arise from other types of cells in the skin and are less likely to spread through the body. Many melanomas arise out of the blue, but some come from existing moles, which is why it's important to monitor moles in addition to checking for new lesions.

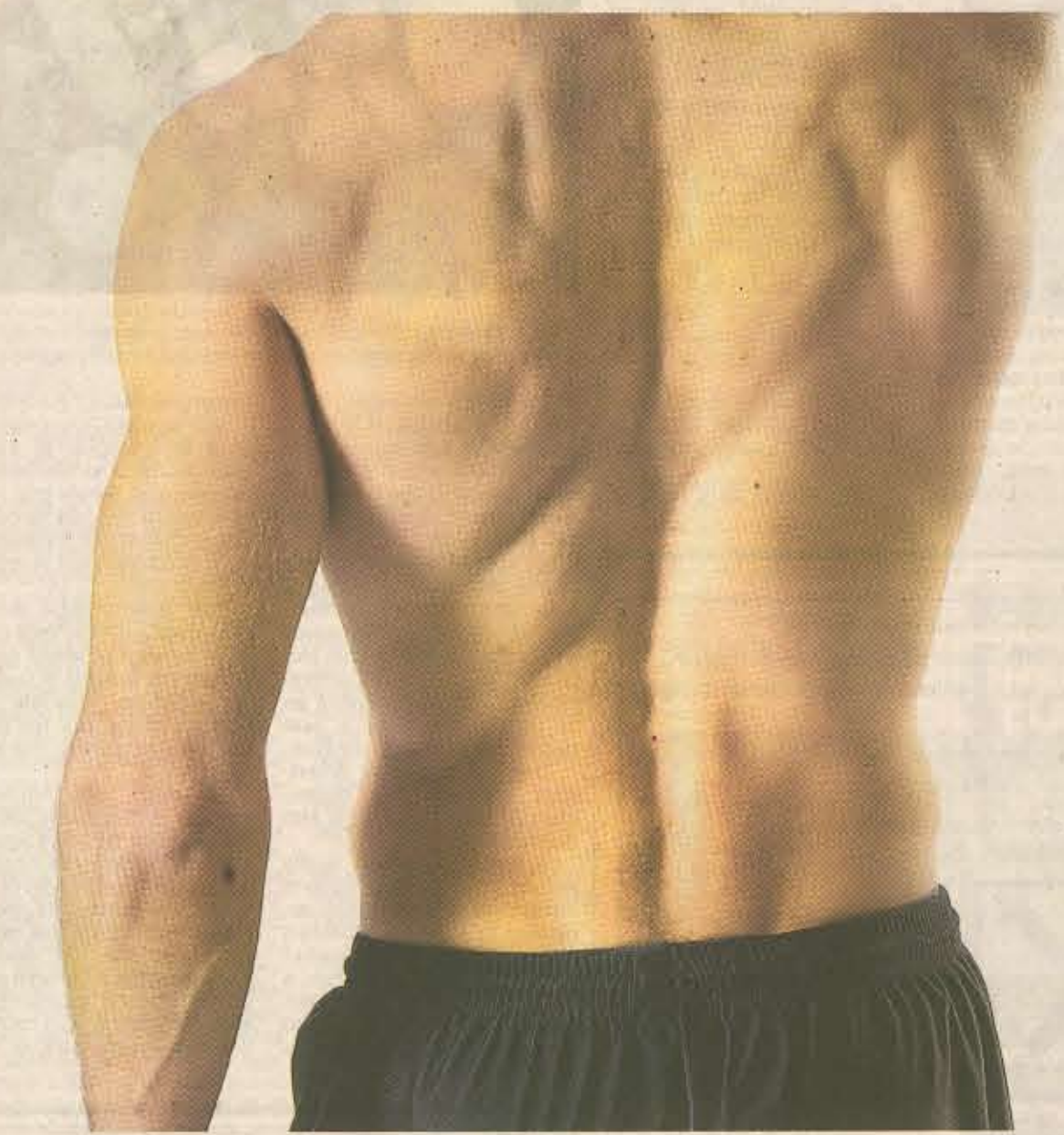
Like moles, melanomas are abnormal clusters of pigment-containing cells. There's a key difference, however. In moles, the pigment cells rest in a state of hibernation; the ones in a melanoma reproduce with abandon. This is the case even though the same genetic change in a pigment cell causes both.

One thing that sets the two apart was reported in February by Dr. Michael Green at the University of Massachusetts, Amherst, in the journal *Cell*: Normal moles constantly release an inhibitory substance, IGFBP7, that causes the pigment-containing skin cells to shut down and stop reproducing.

Green says the pigment cells seem to start making the protein when they sense the formation of a mole. "It's a very powerful mechanism," he says. "When one cell detects something is wrong, not only does it prevent itself from further development into cancer by secreting this protein, but it also protects neighboring cells by shutting them down, too."

It's possible that IGFBP7 may one day be useful as a treatment. Green and colleagues have added it to human melanoma cells growing in culture and found that this stopped the cells from growing. They've also stopped melanoma tumors from growing in mice after injecting animals with the protein.

"The study definitely has a potential clinical application in humans," says Dr. David Fisher, chief of der-



KEN HIVELY Los Angeles Times

WATCH YOUR BACK: Everyone has at least a mole or two. It's key to monitor these abnormal clusters of pigment-containing cells, because while most melanomas spring out of the blue, some come from existing moles.

matology and director of the Melanoma Center at Massachusetts General Hospital in Boston. But, he cautions, more studies will be needed to show it could work in the clinic.

A key unanswered question is why mole cells sometimes stop or slow down IGFBP7 production, allowing pigment cells to proliferate unchecked, progressing as a melanoma tumor. Green and colleagues don't yet know the answer to that.

Another study, reported April 20, suggests that a drug previously thought to be ineffective against melanoma can, in fact, reverse the spread of some melanomas that have a specific genetic signature.

The drug, imatinib, is currently manufactured by Basel, Switzerland-based Novartis International AG under the trade name Gleevec and is used to treat chronic myeloid leukemia and gastrointestinal stromal tumors.

Earlier, large-scale trials in the U.S. and Germany failed to show any response of melanoma to imatinib. But a closer look at those trials showed that a handful of patients had dramatic responses to the therapy. Scientists suspect that those who benefited had melanomas containing a genetic mutation in a gene called KIT, activating the gene inappropriately in skin. A small subset of melanomas are of this type.

"That research raised our eyebrows," says Dr. F. Stephen Hodi, director of the melanoma program at the Dana-Farber Cancer Institute in Boston, and lead author of the new *Journal of Clinical Oncology* study. He and his colleagues knew that there are a number of drugs that inhibit KIT action, including Gleevec.

Hodi and colleagues have launched a clinical trial focusing only on melanoma patients whose cancers have the KIT mutation. Their

Tracking melanoma's deadly route

Like most cancers, melanoma becomes far more dangerous when it moves from its site of origin to other locations in the body. This movement, called metastasis, occurs when cancer cells enter the bloodstream and invade new organs.

Melanoma frequently metastasizes to the small intestine — a phenomenon that until recently has left investigators puzzled. But a growing body of research suggests a protein in the small intestine may act like a homing beacon to some melanoma cells; ones that carry a corresponding protein on their surfaces.

In February, researchers at the John Wayne Cancer Institute in Santa Monica and the Sydney Cancer Centre in Camperdown, Australia, reported that melanoma cells migrating to the small intestine contain high levels of a protein called CCR9. This protein, which also is found on some white blood cells, is attracted to a protein on the surface of the small intestine, called CCL25.

"We think this is one of the mechanisms how, whether it starts on your toe or on your head, melanoma ends up on your small intestine," says senior author Dave Hoon, molecular oncology director at John Wayne.

Therapies that interrupt this connection could be promising drug targets, says Dr. Sam Hwang, a senior investigator at the National Cancer Institute, whose research has shown that a different type of protein causes cancer cells to migrate to the lymph nodes. "If you can understand why they metastasize, you can presumably block that metastasis by blocking the mechanism that is important in that process," he says.

— JENNIFER CUTRARO

reports so far are on just one of the trial members: a 70-year-old woman with an advanced stage of melanoma whose tumors decreased by up to 90% after four weeks of treatment with Gleevec. (Three other patients are also enrolled in the trial, with more to be added — but there are no results for them yet.)

Hwang of the National Cancer Institute (who was not an author of the study) says that these preliminary findings are impressive — but he adds that the oncogene is present in only a very small minority of patients, limiting the population that Gleevec treatment would help.

Though preliminary, these findings underscore the importance of

taking into account genetic differences between patients during drug trials, says Dr. Boris Bastian, associate professor of dermatology and pathology at UC San Francisco. If that's not done, "very dramatic effects of certain drugs become washed out and overlooked," he says.

Indeed, melanoma holds the dubious distinction of being one of the most difficult cancers to treat once it has spread — perhaps in part, Hwang says, because scientists and clinicians have traditionally looked at it as one specific disease.

"We lump everything into 'melanoma,' but clearly there are different molecular triggers," he says.

Monitor your moles, and look for the warning signs

Is one different from the others? Has a new one appeared? Some tips to help you decide when to see a dermatologist.

By JENNIFER CUTRARO
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Wondering if you should have that mole on your arm checked out? There have been a few updates on what you should look out for. Most dermatologists now recommend the following:

■ **Look for "ugly ducklings."** The Skin Cancer Foundation recently promoted this simple screen for identifying potentially cancerous lesions: Just look at the moles on your body and note any that look significantly different from the others — the ugly ducklings. The ugly-duckling approach is based on the fact that most people have stereotypical mole patterns. In some people, they may all appear light brown and flat. In others, they may be darker and raised. Any mole that looks different from the others should be examined by a dermatologist.



BAD MARKS AND GOOD: The three moles above are malignant, whereas the one at left is benign. And don't look to color as a guide to whether a mole is harmless — in citing which characteristics to watch, dermatologists emphasize irregularities and changes.

Photographs by Skin Cancer Foundation

■ **Look for changes.** Most melanomas arise out of the blue, not from already-existing moles. Any new skin lesion is reason to head for the dermatologist's office. But some melanomas come from moles gone bad. Any change in the shape, size or color of an existing mole should also

be examined.
■ **Remember the alphabet.** Dermatologists recommend patients consider the letters ABCDE as a guide for self-screening, and have moles exhibiting any of the following characteristics checked out: Asymmetrical shape; border that is irreg-

ular; color that is inconsistent within the mole; diameter greater than one-fourth inch; and evolving, or changing in any of the criteria above, or in any other way.

■ **Pay attention to concerns of those who are close to you.** That tip comes from Dr. Donald Morton, chief of the melanoma program at the John Wayne Cancer Institute in Santa Monica, whose wife, he says, diagnosed his melanoma years ago.

"I had a mole she didn't like the looks of," he says. "I said, 'But I'm a melanoma doctor! How could I have melanoma and not know it?'" On her insistence, he had a small, black mark biopsied, and it was a melanoma.

"That was 17 years ago," he says. "She may have saved my life."