The concept of a cancer stem-cell model has been one of the most promising—though controversial—advances in cancer-related research in recent years. The model is based on a belief that a handful of rogue stem cells drive the formation and growth of malignant tumors in many cancers. Based on this model, researchers have been pursuing treatments that target the rare stem cells instead of trying to kill every cancer cell in a patient's body.

But new research, which appeared in a cover story in the journal Nature, suggests that the model is flawed when applied to melanoma. In a series of experiments involving human melanoma cells transplanted into mice, the research team found that tumor-forming cells aren't rare at all. They're quite common, in fact, but standard laboratory tests failed to detect most of them.

The research likely will lead to dramatic changes in the way that researchers approach new treatments for the deadliest form of skin cancer.

“People were looking to the cancer stem-cell model as an exciting new source for the development of life-saving cures for advanced melanoma,” said Timothy M. Johnson, M.D., Director of the U-M Health System’s Melanoma Program and a co-author of the Nature paper. “Unfortunately, our results show that melanoma does not strictly follow this model.”

“So we'll need to redirect our scientific efforts and remain focused on the fundamental biological processes underlying the growth of melanomas in humans,” said Dr. Johnson. “And as we pursue new treatments for advanced melanoma, we’ll have to consider that a high proportion of cancer cells may need to be killed.”

Melanoma kills more than 8,000 Americans each year. The human melanoma cells used in the mouse experiments were provided—with the patients’ consent—by a team from the U-M’s Multidisciplinary Melanoma Program, one of the country’s largest melanoma programs and part of the U-M Comprehensive Cancer Center.

In spite of the new findings, the cancer stem-cell model may hold some promise for other types of cancer, said co-author Sean Morrison, Ph.D., Director of the Center for Stem Cell Biology at the U-M Life Sciences Institute.

“I think the cancer stem-cell model will, in the end, hold up for some cancers,” Morrison said. “But other cancers, like melanoma, probably won't follow a cancer stem-cell model at all. The field will have to be reassessed after more time is spent to optimize the methods used to detect cancer stem cells.”

Scientists previously estimated that only one in 1 million melanoma cells has the ability to run wild, exhibiting the kind of unchecked proliferation that leads to new tumors. These aggressive interlopers are the cancer stem cells, according to backers of the model.

But after updating and improving the laboratory tests used to detect these aberrant cells, Morrison’s team determined that at least one-quarter of melanoma cells have the ability to form new tumors.
Sentinel lymph node biopsy has spared a portion of melanoma patients from having to undergo further surgery. But now researchers think they can carve out a larger portion of patients who can avoid this extra treatment step.

A team of researchers from the University of Michigan were able to develop a decision-tree that could help physicians determine which patients with a positive sentinel lymph node biopsy are least likely to have additional regional disease.

The findings are preliminary and do not represent a shift in practice at this time. A multi-site randomized, controlled trial is underway at U-M and other institutions to look at whether a complete node dissection can be avoided for some patients.

“Not all patients who have a full lymph node dissection benefit from that. This research is very promising and may change the way we treat patients in the future. For now, however, we cannot stop doing the dissection when it is indicated,” says senior study author Michael Sabel, M.D., associate professor of surgery at the U-M Medical School.

Sentinel lymph node biopsy is often recommended for patients with melanomas greater than 1 millimeter who have a higher risk of cancer having spread to the lymph nodes. If the sentinel node is positive, it is highly recommended the patient undergo a completion lymph node dissection. Only about 20 percent of patients with a positive sentinel node will have further cancer in other lymph nodes.

In this study, the researchers looked at data from a comprehensive prospective melanoma database begun in 2004 to track the size and location of sentinel lymph node metastases. The database included 136 samples that could be analyzed for this study. The researchers found factors such as the tumor location, Breslow thickness, and the number and size of positive sentinel nodes impacted whether cancer had spread to non-sentinel nodes. The researchers then used these factors to create a decision tree to stratify risk.

“Our goal was to identify patients who may avoid completion node dissection. We attempted to create a decision tree to identify the lowest risk group,” says lead study author Timothy Frankel, M.D., a house officer in the U-M Department of Surgery.

The researchers identified a subset of patients for whom there is an extremely low risk of finding additional disease when they return to the OR for a completion dissection. The researchers found that for the 46 cases where the volume of the metastasis represented less than...
1 percent of the surface area of a single sentinel lymph node, the risk of a positive non-sentinel node was 4 percent, compared to 29 percent when more nodes were involved or more disease was present. Further, of 31 patients who also had a Breslow thickness less than 2 millimeters, none had additional positive nodes. This group represents about one-fifth of the study population.

“We could potentially be talking about a significant number of patients who could be spared the risk and side effects of additional surgery. We hope that the randomized trial now underway will reinforce these findings,” Dr. Sabel says.

For now, the tool could help physicians and patients better understand the likelihood for additional regional disease in patients with positive sentinel nodes.

Some 62,480 Americans will be diagnosed with melanoma this year, according to the American Cancer Society.

Other authors were Sandra L. Wong, M.D., Alfred E. Chang, M.D., Vincent M. Cimmino, M.D., and Riley S. Rees, M.D., all from the U-M Department of Surgery; Lori Lowe, M.D., from the departments of Dermatology and Pathology; Christopher K. Bichakjian, M.D., from the Department of Dermatology; Carol R. Bradford, M.D., from the Department of Otolaryngology; and Timothy M. Johnson, M.D., from the departments of Surgery, Dermatology and Otolaryngology.

Reference: *Annals of Surgical Oncology*, DOI: 10.1245/s10434-008-0024-x

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“*This research is very promising and may change the way we treat patients in the future...*”
After Bill Martin was diagnosed with and treated for melanoma a few years ago, the University of Michigan Athletic Director had an epiphany. “I remember thinking, ‘I’m responsible for 300 people here,’” Martin says. If this could happen to me, he thought, then surely it could happen to many of the coaches and staff members who spent hour after hour, day after day in the sun.

He guessed correctly. Martin asked his physician—Timothy M. Johnson, M.D., Director, Multidisciplinary Melanoma Program, University of Michigan Comprehensive Cancer Center—to hold a skin cancer screening at the Athletic Department’s facilities. The third of these screenings was held this summer, and to date, physicians have identified dozens of people with melanomas, basal cell or squamous cell carcinomas, or pre-cancerous skin lesions.

Among the other members of the Athletics staff who have been diagnosed with melanoma, and successfully treated for it, are Head Hockey Coach Red Berenson, and former Head Football Coach and current Senior Associate Athletic Director Lloyd Carr.

“I’m so thankful to Bill that he had this screening, because had he not had it, I probably would not have gone in. Had I not gone in, I would have been in serious trouble,” said Berenson.

Their experience provides some guidance for primary care physicians:

1. Pay particular attention to middle-aged men during their annual check-ups. They tend to be less aware than their spouses about the need to be tested for skin cancer. But remember that both genders and all age groups are at risk; U-M, for example, sees at least one teenage patient a month who has melanoma.

2. Hold a screening in a location that is convenient for patients because it may increase the likelihood that they will attend. Several people at the Athletic Department screening said they attended in part because it was held so close to their workplace.

3. Since many people need an extra push to get tested for skin cancer, encourage your patients who have had skin cancer diagnoses to become advocates. They can suggest to their friends, coworkers and family members that they also get screened.

Carr is one person who has become an advocate after his diagnosis and treatment. “Do something about it. Don’t wait and hope that it goes away, because it’s not going away,” he advised viewers during a recent television news interview.

Nationwide, athletic organizations are doing more and more to help raise awareness about skin cancer. Major League Baseball and the American Academy of Dermatology, for example, started a “Play Sun Smart™” program, and more than 19,000 skin cancer screenings of MLB players, trainers, coaches...
and staff have been conducted. The AAD’s “Be Sun Smart℠” sun safety messages encourage athletes to increase awareness on ways to protect themselves from excessive exposure to the sun, especially midday between 10 a.m. and 4 p.m. In addition, studies from the University of Cincinnati and elsewhere have indicated that young athletes, marathon runners and others are at increased risk of skin cancer. (See self-screening education card provided with this newsletter.)

- Key Points

- All age groups are susceptible to skin cancer, with cases among teenagers and other young people on the rise.
- Athletes, coaches and others who spend a lot of time in the sun should be educated about the early signs and symptoms of skin cancer and in particular melanoma, and checked regularly for skin cancer. (See self-screening education card provided with this newsletter.)
- Friends, family members and co-workers can be powerful advocates for the importance of skin cancer screenings.

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Coach Berenson and some of the Michigan hockey team.
On any given day, the University of Michigan Health System is engaged in more than a hundred clinical trials, greatly increasing options for the prevention, treatment, care and possibly cure of disease. When the diagnosis is melanoma, clinical trials provide a source of hope for patient and physician alike.

“Because treatment for melanoma is so limited, the best two options for treatment are a clinical trial or High Dose Interleukin-2 (IL-2),” says Christopher D. Lao, M.D., M.P.H. “Unfortunately, receiving IL-2 or some other medications might exclude the patient from a clinical trial. That’s why it’s good to refer them to a large tertiary care center such as the University of Michigan, where experience can help with all of these decisions. And that’s why it’s good to have U-M providing a venue for crucial national clinical trials.”

Dr. Lao is clinical assistant professor in the U-M Department of Internal Medicine and is currently directing for U-M the first national non-chemotherapy, multi-agent trial in metastatic melanoma that uses a combination of targeted agents to stem or abate the disease. (See SWOG S0438). “This non-chemo targeted approach we hope will shut down the growth of the cancer cells, specifically in melanoma, and allow the cells to die,” says Dr. Lao.

Dr. Lao also is exploring chemoprevention as a new strategy against the development of melanoma based on the principle that melanoma carcinogenesis is a multi-step process, and that molecular events and pathways associated with these steps can be targeted. With chemoprevention, he plans to use drugs, vitamins and other natural products to try to reduce the risk of, or delay the development or recurrence of, melanoma.

The University of Michigan Health System is home to the Comprehensive Cancer Center, one of only 39 U.S. centers to earn the National Cancer Institute’s “comprehensive” designation by meeting strict guidelines, including participation in National Cancer Institute testing of new therapies. In addition, UMHS is an active member of SWOG (Southwest Oncology Group), the largest National Cancer Institute-supported clinical trials cooperative group in the U.S. Bruce G. Redman, D.O., says these particular affiliations are two of the reasons that UMHS is awarded so many clinical trials for skin cancer and melanoma.

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“We’re also one of the largest melanoma referral centers in the country,” says Dr. Redman. “Our aggressive clinical trials program is a resource for community physicians, for example, who may primarily see breast, lung and colon cancer but may not see as much skin cancer.”

Dr. Redman is U-M professor of medicine and executive officer of SWOG.

“We are a resource not only to actively treat patients but to render options for care,” Dr. Redman says of the dozens of U-M researchers involved in melanoma and skin cancer research.

The results of Dr. Redman’s work on a randomized Phase 1b trial assessing autologous, tumor-pulsed dendritic cells as a vaccine administered with—or without—IL-2 in patients with metastatic melanoma appeared in the July-August 2008 issue of *Immunotherapy*. While the vaccine made from the patients’ own tumor failed to induce a clinical response, the vaccine was well tolerated and immunogenic—providing one more crucial step forward in autologous vaccine research.

“We spend a lot of time on the phone with referring physicians,” says Dr. Redman. “That’s what we’re here for. And that’s all a part of the clinical trials process.”
MELANOMA CLINICAL TRIALS

UMHS is currently engaged in clinical trials of all forms of skin cancer, from squamous and basal cell skin cancers to melanoma and Merkel cell carcinoma.

Following are clinical trials currently—or soon—accepting patients. New clinical trials are opening all the time. Check with us to find out more. Referring physicians should call M-LINE at 800-962-3555 or search our clinical trial database at www.med.umich.edu/engage.

Pilot, Feasibility Study of Serial Biopsies of Dysplastic Nevi

The prevention study will evaluate patients who are at risk for melanoma or who have raised dysplastic nevi. (UMCC 2007.136)

Phase I Study of Topical Curcumin

The study will evaluate a topical agent in cancer therapy called curcumin. Chemoprevention. Opening Spring 2009

Phase II Trial of BAY 43-9006 (Sorafenib)

A Phase II Trial of BAY 43-9006 in combination with Carboplatin and Paclitaxel in patients with metastatic uveal melanoma. (SWOG S0512)

Multi-Center Selective Lymphadenectomy for Melanoma Trial II

A Phase III multi-center randomized trial of sentinel lymphadenectomy and complete lymph node dissection versus sentinel lymphadenectomy alone in cutaneous melanoma patients with molecular or histopathological evidence of metastases in the sentinel node. (UMCC 2005.130)

Phase II Trial, Effect a Combination of Drugs Will Have on Melanoma

This randomized Phase II trial will study the effects of the combination of BAY 43 9006 (sorafenib) and either CCI-779 (temsirolimus) or R115777 (tipifarnib) on melanoma. CCI-779 is given by IV at U-M; the other medications are taken by mouth. (SWOG S0438)

Please visit the clinical trials database (engage) at www.umengage.org for the most up-to-date information on clinical trials.

RESOURCES

Skin Cancer Program Web Site

We have developed a dedicated Web site that offers an array of information for you and your patients. Below is some helpful information that you will find:

For patients
- Patient testimonials
- Meet the Director
- Frequently asked questions (FAQ)

For physicians and their staff
- Downloadable version of FAQs
- Toll-free number for consults, appointment scheduling, patient information and test results
- Web links to other valuable information such as: services, consult guidelines, CME, clinical trial information and educational resources

Cancer Genetics Registry

The U-M Cancer Genetics Registry enrolls people with personal and/or family histories of cancer, and encourages people with hereditary melanoma to enroll. Registry participants may be eligible for testing for a specific gene called CDKN2A (also known as p16) associated with hereditary melanoma. Participants consent to share medical and family history information and donate three tubes of blood. This is an open, ongoing study. Researchers anticipate that they will be able to share test results with participants over time. (UMCC 2-79)

FOR MORE INFORMATION OR ASSISTANCE

call M-LINE at 800-962-3555
Dr. Morrison and Johnson stressed that the team’s findings do not broadly invalidate the cancer stem-cell model. Cancer stem cells likely do exist in some forms of cancer but are “probably much more common than people have been estimating,” Dr. Morrison said.

Co-lead authors of the Nature paper are Life Sciences Institute research fellows Elsa Quintana, Ph.D., and Mark Shackleton, Ph.D. In addition to Drs. Morrison and Johnson, other co-authors are surgical oncologist Michael Sabel, M.D., and dermatopathologist Douglas Fullen, M.D. The work was supported by the Howard Hughes Medical Institute, the Allen H. Blondy Research Fellowship and the Lewis and Lillian Becker gift.

**KEY POINTS**

- The cancer stem-cell model does not apply to melanoma. Malignant melanomas are formed by a large number of cancer cells—possibly up to 25 percent of cells—rather than a small number of rogue stem cells, as once thought.

- Future treatments of advanced melanoma will have to kill a higher portion of cancer cells than previously believed.

- A quarter of patients with melanoma are younger than 45 years old.

**FIND MORE ON THE WEB**

U-M Health System Skin Cancer Program  
www.umskincancer.org/

U-M Multidisciplinary Melanoma Program  
www.cancer.med.umich.edu/cancertreat/skinancer/the_clinic.shtml

U-M Stem Cell Research  
www.umich.edu/stemcell/

U-M Center for Stem Cell Biology  
www.lsi.umich.edu/facultyresearch/centers/stemcellbiology/

U-M Comprehensive Cancer Center’s cancer stem cell research  
www.cancer.med.umich.edu/research/stemcells.shtml