

HCI Clinical Trials Lead to Improved Treatment for Lentigo Maligna

A combination drug and surgical therapy for lentigo maligna (LM), a non-invasive form of melanoma, has led to recurrence rates 10 times lower than with surgery alone, and a two-thirds reduction in the size of the necessary surgical area.

Presurgery drug treatment reduces tumor size and recurrence rate

Clinical trials led by Glen Bowen, MD, co-director of the Multidisciplinary Melanoma Clinic, had such positive results that the study protocol has become the standard of care for LM at Huntsman Cancer Institute (HCI). The studies used imiquimod in patients with LM to reduce the number of tumor cells before surgery. Imiquimod is an FDA-approved drug in cream form used to treat superficial basal cell and squamous cell carcinomas, less threatening tumors than melanoma.

LM is commonly found in sun-exposed areas of the head, neck, ears, and nose, and it generally remains contained in the outer skin layer called the epidermis. The large area and irregular shape characteristic of LM create two problems in surgical treatment. First, the tumor edge is difficult to discern with the naked eye; under the microscope, the area of tumor involvement is often larger than predicted. Second, because LM commonly occurs on the face, surgery to remove it frequently leaves behind substantial disfigurement close to the eyelids, nostrils, or lips.

The standard of care for LM has been “staged” surgical excisions where the surgeon removes the LM with a five-millimeter margin of normal-appearing tissue. It takes 24 hours for slides to be prepared before a pathologist can determine whether the tumor was completely removed. If not, the patient returns the next day for another “stage” of surgery, and the process is repeated until the pathologist confirms that the tumor was completely removed. Only

then is the surgical defect repaired. With this method, only 48 percent of cancers were completely removed at the first stage, so most patients were subjected to two or more stages of surgery.

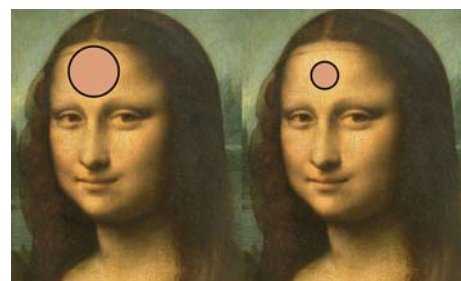
However, since adding a 12-week presurgery regimen of the cream, surgeries start with only a two-millimeter margin, and more than 70 percent of cases have no evidence of residual tumor at the first stage. This has reduced the size of post-operative defects by two-thirds.

Before staged excisions, with surgery alone, half of the removed cancers would eventually grow back (also called recurrence) and need to be removed again. With staged excisions, the recurrence rate dropped to five percent. When patients are pretreated with imiquimod, the recurrence rate has been 0.5 percent for three years after surgery, even though the tumors are being removed with a much smaller surgery. Five years of follow-up is necessary for full confirmation that pretreatment leads to smaller surgeries and a greatly reduced risk of the cancer’s return.

Improved pathology methods reduce surgical procedure time

Improved methods of analyzing pathology specimens also played a part in reducing the defect size, as well as making LM surgery less taxing on patients. Previously, LM surgery was performed in stages that required overnight tissue processing. Patients would often be required to return to HCI for surgical stages over several consecutive days. They would have to return yet again for repair of the defect, often requiring general anesthesia and extensive surgical reconstruction in the operating room.

Working closely with HCI pathologists, Anneli Bowen, MD, Scott Florell, MD, and Ron Harris, MD, Bowen devised a protocol using frozen tissue specimens. The specimens are tagged with an

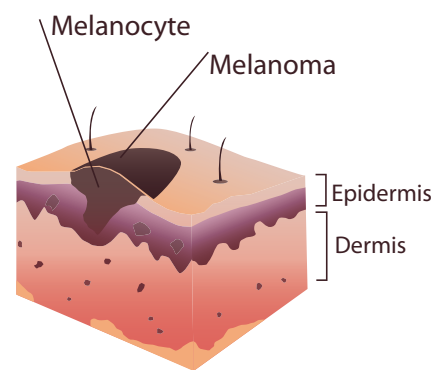


Because lentigo maligna commonly occurs on the face, surgery to remove it frequently leaves behind substantial disfigurement. A combination drug and surgical therapy has led to a two-thirds reduction in the size of the necessary surgical area and recurrence rates 10 times lower than with surgery alone.

antibody that adheres to the melanoma cells, making them easy to see under the microscope. The procedure is similar to Mohs micrographic surgery (see Melanoma Program newsletter, Winter 2004, page 5). The analysis, done with the patient still in the office, gives results at least as accurate as with overnight methods, and the results are available in one or two hours. Currently, HCI patients can have their LM tumors removed and the surgical defects repaired under local anesthesia in the outpatient Mohs clinic—in a single one-day visit.

Further trials, further improvements

Bowen is currently preparing a study to evaluate whether the addition of a second anticancer topical cream can shorten the course of imiquimod treatment from 12 to six weeks followed by the one-day surgery. Ultimately, he would like to find a specific topical therapy for LM that eliminates the need for surgery altogether in this cancer that can disfigure the face.



Lentigo maligna is a non-invasive form of melanoma commonly found in sun-exposed areas of the head, neck, ears, and nose. It generally remains contained in the outer skin layer called the epidermis.

Elementary Students Learn to “Slip, Slop, Slap, Wrap”!

Slip on a shirt, slop on sunscreen, slap on a hat, wrap on sunglasses!

Students at Jeremy Ranch Elementary School near Park City had fun learning essential sun protection lessons of the “slip, slop, slap, wrap” chant in January, led by two medical students from the University of Utah

Stephen Squires, a third-year student, and Tracy Hamblin, a second-year student, conducted two days of assemblies at the school for children in kindergarten through fifth grades. Their presentation included facts about the sun, how its light both helps and harms, and the importance of protecting the skin from ultraviolet (UV) radiation.

“To make the learning experience more fun, we held races to see who could put on the shirt, sunscreen, hat, and sunglasses quickest,” said Hamblin. “And the kids made bracelets from beads that change color when exposed to UV rays.”

Lana Pho, MD, who worked with Huntsman Cancer Institute’s Tom C. Mathews Jr. Familial Melanoma Research Clinic for several years, was a resident at University Hospital when she helped initiate this educational outreach program. Squires and Hamblin would like to see the program expand to include more medical students and other volunteers who could take “Slip, Slop, Slap, Wrap” to more schools throughout the state.



Students at Jeremy Ranch Elementary School raced to “Slip, Slop, Slap, Wrap” last January.

Remember to get your full-body skin cancer screening!



The Melanoma Program at Huntsman Cancer Institute

THE MELANOMA PROGRAM NEWSLETTER – SUMMER 2008



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Pilot Studies Power Melanoma Prevention Research

An ounce of prevention is worth a pound of cure. Ben Franklin said that about 250 years ago, and scientists in the Melanoma Program at Huntsman Cancer Institute (HCI) have been following up on his advice with studies focused on stopping melanoma, the deadliest form of skin cancer, before it happens.

The laboratory-based research takes several related approaches. HCI investigator Douglas Grossman, MD, PhD, is studying an antioxidant called N-acetylcysteine (NAC) that, taken orally, may protect the skin against damage from ultraviolet (UV) radiation and delay the onset of melanoma. Another HCI scientist, Pamela Cassidy, PhD, a research assistant professor in the Leachman lab, is looking at the trace element selenium as a possible melanoma prevention agent.



Douglas Grossman, MD, PhD



Pamela Cassidy, PhD

Both Grossman and Cassidy were awarded a series of pilot study grants from the National Cancer Institute (NCI) and the University of Utah to pursue these lines of investigation. Pilot studies are usually short-term projects that take an initial look at a specific scientific or therapeutic question. They check whether the idea offers enough potential for success to justify undertaking a larger, more expensive study.

In the spring 2007 Melanoma Program newsletter, we reported on studies by Grossman and Cassidy that received funding for pilot studies on NAC and selenium. Last October, a paper by Grossman (with Cassidy and Sancy Leachman, MD, PhD, director of HCI’s Melanoma and Cutaneous Oncology program, listed as a co-authors) was published in the journal *Clinical Cancer Research*. Their results highlighted the potential importance of

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December Symposium Highlighted Melanoma Program Research

Melanoma patients, research participants, and family members learned about recent progress the Huntsman Cancer Institute (HCI) Melanoma Program has made in research, prevention, diagnosis, and treatment. The approximately 250 attendees heard presentations on topics including *p16* genetic testing and counseling, mole mapping, and clinical trials for a new lentigo maligna treatment. Several HCI physicians, a genetic counselor, and a representative from Huntsman Cancer Foundation were among the presenters. Future similar events will keep HCI’s community updated with the latest melanoma discoveries.

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Pilot Studies Power Melanoma Prevention Research

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oxidative stress in melanoma's development and suggested that NAC might indeed be useful in preventing the disease.

Since that publication, Cassidy and Grossman, in collaboration with Leachman, have received funding for the next step: a pilot study to develop a mouse model deficient in *p16*, the gene that, when mutated, causes melanoma. With this mouse model, they can test the hypothesis that one way these *p16* gene mutations lead to melanoma is by disrupting the way skin cells respond to oxidative stress. Another phase will compare oxidative damage and responses in normal human skin cells and cells with *p16* deficiencies and mutations.

Another new study funded by HCI's Cancer Center Support Grant (CCSG) examines the role of selenium-containing proteins in melanoma genesis. Using human melanoma cells, this study will provide valuable information to help formulate the recommendations physicians make to their melanoma patients regarding selenium supplements. Philip Moos, PhD, assistant professor in the University of Utah's Department of Pharmacology and Toxicology and a CCSG member, collaborates on this research with Cassidy and Leachman.

In the newspapers and on TV, research is all about the big breakthrough. In scientific reality, breakthroughs stand on the foundation of small pilot studies like these—detailed and painstaking investigations to build the body of evidence.

This article began with a quote from Ben Franklin, and to close, another of his famous sayings applies: Little strokes fell great oaks. To solve the big problems of cancer, scientists must continue to take the little strokes from every possible angle—until the tree falls.

More New Faces in the Melanoma Program

Kristina Heintz, RN, BSN, is the research nurse for the High Risk Melanoma Study (HRMS) and the GenoMEL study. She also oversees and coordinates clinical and support aspects of HRMS, GenoMEL, Melanoma Research Registry (MRR), and Hair Color Studies. A graduate of the University of Florida, Heintz was a Mohs surgery nurse at Yale and has also worked in Connecticut and Arizona.

Emily Bullough is registrar for the Melanoma Research Registry (MRR). She coordinates the *p16* Genetic Testing Study and provides clinic support for the HRMS as well as research administration support for the Melanoma Program. Bullough graduated from the University of Utah in 2007.



(from left) Emily Bullough, Kristina Heintz, and Wendy McKenney

Wendy McKenney joined the Melanoma Program in 2005 as a work-study student; in 2007 she began full-time as a clinical study assistant for HRMS. She helps recruit and coordinate research participants. McKenney is a University of Utah graduate.

Can Cholesterol Medicine Help Prevent Melanoma?

A new clinical trial at Huntsman Cancer Institute (HCI) will investigate whether a drug that lowers cholesterol might also keep atypical moles from turning into melanoma.

The multicenter trial, led by principal investigator Sancy Leachman, MD, PhD, will explore the potential of the lipid-lowering drug lovastatin as a melanoma chemopreventive (a drug that can prevent melanoma from developing). In this study, researchers will test whether the drug can reverse precancerous changes in atypical moles. Depending on the results, larger clinical trials could follow to examine whether lovastatin actually decreases the incidence of melanoma.

Researchers want to learn more about the drug's potential because two large

cardiovascular clinical trials showed significantly fewer melanomas in people taking a lipid-lowering drug than in people not taking it. Although studies in cell culture suggest lovastatin might have an effect on melanoma cells, no clinical trials to date have confirmed this finding in humans.

Melanoma is the most common serious form of skin cancer, expected to be diagnosed in about 62,480 people in the United States this year. It is usually deadly when it has metastasized (spread). Little previous research has been done on chemoprevention of melanoma.

The trial is open to people with a personal history of non-metastatic melanoma and multiple atypical moles on the back. For more information, please call Amber Lamph in the HCI Clinical Trials Office at 801-585-0601.

Help Advance Melanoma Research

Federal funding cuts have negatively affected Huntsman Cancer Institute's Melanoma Program. Agencies such as the National Cancer Institute usually fund research after preliminary studies have shown that the line of inquiry is promising.

Gifts from private donors can help support preliminary (or pilot) studies such as one currently enrolling Huntsman Cancer Institute (HCI) patients that examines the potential of a skin cream containing selenium to prevent melanoma. Another pilot study might look at an oral antioxidant as a possible melanoma prevention agent. These studies exemplify new, leading-edge ideas in melanoma research.

If you are interested in donating to research efforts at HCI, contact Huntsman Cancer Foundation at 801-584-5800 or huntsmanfoundation.org. You can earmark your gift for the Melanoma Program.

Clinical Trials Update

Clinical trials help doctors discover the best treatments possible. Patients may or may not directly benefit from participating in a research trial. Melanoma clinical trials currently open are listed below. If you have questions, please talk to your doctors or call the Clinical Trials Office at 801-581-4477 for more information.

HCI #12920 – John Ward, MD
Phase II – Compares results of treatment with a new drug alone, a melanoma vaccine alone, and a combination of the two, in a double-blind study among a group of patients with previously treated Stage III or IV melanoma for whom surgery was not an option.

HCI #13298 – John Ward, MD
Phase II – Evaluates results of treating metastatic malignant melanoma with the chemotherapy agents docetaxel and vinorelbine plus sargramostim, a drug that stimulates the body's production of the white blood cells which fight infection.

HCI #25699 – Wallace Akerley, MD
Phase I – Investigates dosages of a new drug in combination with temozolomide (an agent already approved for certain types of brain tumors) for treatment of melanoma that has spread to the brain.

HCI #15179 – Sancy Leachman, MD, PhD
Phase II – Explores the potential of the lipid-lowering drug lovastatin as a melanoma chemopreventive, testing whether the drug can reverse precancerous

changes in atypical moles in people with a history of nonmetastatic melanoma and multiple atypical moles on the back.

MSLT II – HCI #14227 – Dirk Noyes, MD
Phase III – Compares sentinel lymphadenectomy and complete lymph node dissection versus sentinel lymphadenectomy alone in cutaneous melanoma patients.

HCI #15461 – Lisa Hazard, MD
Phase II – Tests the hypothesis that the response rate achieved with cisplatin chemotherapy delivered concurrent with radiation therapy in locally advanced or metastatic melanoma will increase 10 percent or more over the response rate of cisplatin alone.

HCI #22960 – Robert Andtbacka, MD
Phase III – Compares the efficacy and safety of treatment with the immunotherapy agent Allovectin-7® with DTIC or TMZ (chemotherapy drugs) in people with recurrent metastatic melanoma. The immunologic effects of Allovectin-7® will be characterized in some people.

HCI #26818 – Robert Andtbacka, MD
Pilot Phase II – Evaluates the ability of fluorescein injected into the skin to detect sentinel lymph nodes in patients with stage I and stage II melanoma.

HCI #28862 – Wallace Akerley, MD
Phase II – Compares effects of two different drug combinations—sorafenib plus temsirolimus and sorafenib plus tipifarnib—for their antitumor effects.

Evaluating Your Family History

Melanoma took the lives of an estimated 60,000 people in the United States last year. Approximately two percent of Americans will develop melanoma during their lifetimes. Risk factors for this skin cancer include fair skin, red hair, a personal history of melanoma or nonmelanoma skin cancer, numerous or abnormal moles, ultraviolet light exposure, and family history.

Having one close family member (such as a parent, sibling, or child) with melanoma nearly doubles the risk for developing the disease. Some people have a greater risk for developing melanoma due to inherited factors passed down in the family. In some families, a risk for pancreatic cancer also appears to be inherited along with a risk for melanoma.

Red flags that suggest an inherited melanoma risk in a family include the following:

- Individuals with multiple primary melanomas
- Individuals with a personal history of melanoma and any one of the following features in the family history:
 - One or more first-degree relatives (parents, siblings, children) with melanoma
 - Two or more second-degree relatives (uncles, aunts, grandparents, grandchildren) with melanoma

also committed to opening new clinical trials.”

Samlowski now heads the Melanoma, Renal Cancer, and Immunotherapy section at Nevada Cancer Institute in Las Vegas.

Huntsman Cancer Institute huntsmancancer.org/publicweb/content/fcacMedHist.html
U.S. Surgeon General: My Family Health Portrait https://familyhistory.hhs.gov
National Society of Genetic Counselors: Your Family History—Your Future http://www.nsgc.org/consumer/familytree/index.cfm

- Any family member with pancreatic cancer
- Unaffected individuals with two or more first- or second-degree relatives with melanoma and/or pancreatic cancer

Researchers are learning more about the inherited basis of many diseases, including melanoma. That is why it is increasingly important that you be aware of your family history and that you communicate with your relatives about health issues.

Here are important questions to ask family members about their health history.

- Have you been diagnosed with cancer?
- What was the specific type of cancer?
- How old were you when diagnosed?
- Do you get cancer screening examinations such as mammograms, colon examinations, and skin exams?
- Have you ever been a smoker?

Family medical history is always changing, so touch base with your relatives regularly to update information, and make sure to tell your doctor of any new developments.

You can find tools to help you with your family health history at the websites shown in the box above.

Families who have any of the red flags for inherited cancer risk are good candidates for a genetic risk assessment. Family members might benefit from increased cancer screening and may be eligible to participate in research studies. Huntsman Cancer Institute offers genetic risk assessment for individuals and families concerned about inherited melanoma risk. For more information, contact the Family Cancer Assessment Clinic at 801-587-9555.



It's important to be aware of your family medical history and communicate with your relatives about health issues.

Continuing Care for Melanoma Patients

Wallace Akerley, MD, Huntsman Cancer Institute (HCI) senior director of clinical research and co-director of HCI's Thoracic Cancer Program, and Julie Smit, NP, have stepped in to ensure that melanoma patients formerly seen by Wolfram Samlowski, MD, receive uninterrupted care.

Akerley and Smit will also see all new melanoma referrals.

“We continue our work to enhance HCI's Melanoma and Cutaneous Oncology Program,” said Smit, who previously worked with Samlowski and his former patients. Amber

Lamph, clinical research coordinator, helped melanoma clinical trial participants to assure a smooth transition.

“HCI continues to conduct several melanoma clinical trials for which Dr. Samlowski was the original principal investigator,” said Akerley. “We are

also committed to opening new clinical trials.”

Samlowski now heads the Melanoma, Renal Cancer, and Immunotherapy section at Nevada Cancer Institute in Las Vegas.

For more information about HCI's current melanoma clinical trials, call Amber Lamph at 801-585-0601.



Wallace Akerley, MD



Julie Smit, NP