IU researchers find pathway to cancer-associated muscle weakness

Oct. 12, 2015

INDIANAPOLIS – Cancer researchers at Indiana University and their colleagues have discovered how cancer-induced bone destruction causes skeletal muscle weakness.

Led by Theresa Guise, M.D., the Jerry and Peggy Throgmartin Professor of Oncology at the IU School of Medicine and a researcher at the Indiana University Melvin and Bren Simon Cancer Center, the investigators have identified the molecular pathways that lead to cancer-associated muscle weakness. They found that inhibiting TGF-β, a growth factor released from bone during cancer-induced bone destruction, improved muscle function in mouse models of human cancers.

“Advanced cancer often spreads to the bone and patients can have muscle weakness because of that. This weakness can severely reduce the quality of life in patients and increase the risk to fracture bone. We previously showed that when cancer spreads and causes bone destruction it releases growth factors into the circulation. In the present study, we found that these factors can cause muscle weakness,” Dr. Guise explained.

She added: “In mice with cancer in bone, muscle weakness could be prevented by drugs that inhibit bone destruction or block the growth factor activity or stabilize calcium in the muscle. These drugs have the potential to prevent muscle weakness in patients with cancer in the bone.”

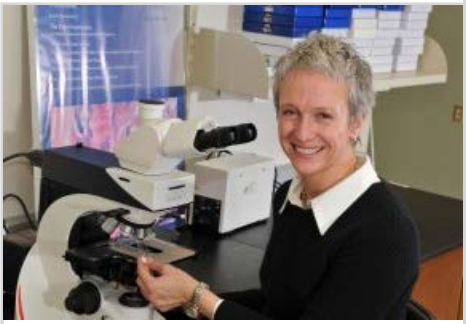
Their research was published online today in Nature Medicine.

For the study, Dr. Guise, who is also a Komen Scholar, pointed out that the same mechanisms cause muscle weakness in many different tumor types in which cancer grows in bone. Dr. Guise and her colleagues studied breast cancer, prostate cancer, lung cancer, and multiple myeloma — all cancers that typically spread to bone. Four different molecular checkpoints were identified and were successfully targeted by four different drugs, improving muscle function. In addition, the findings were confirmed in human muscle samples from patients with cancer in bone.

Once cancer spreads to bone, patients often experience bone pain, fractures, nerve compression and muscle weakness. Currently, there are no effective treatments for cancer-associated muscle weakness. “These findings should lead to new therapies to treat cancer-associated muscle weakness that could be studied in the clinic over the next few years,” Dr. Guise said.

A nationally acclaimed endocrinologist, Dr. Guise’s research focuses on understanding why some cancers spread to bone and how they affect bone, as well as the long-term effects of cancer therapies on bone. As such, she leads a team of researchers at IU School of Medicine who are investigating ways to improve treatments for bone metastases and muscle weakness.

Co-authors of the study included David Waning, Ph.D., Khalid Mohammad, M.D., Ph.D., and David Roodman, M.D., all of IU School of Medicine, and Andrew R. Marks, M.D., of Columbia University.



Theresa Guise, M.D. | PHOTO BY IU SCHOOL OF MEDICINE

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The research was supported, in part, by the National Institutes of Health (grant U01CA143057) from the National Cancer Institute, the National Institute of Arthritis, Musculoskeletal and Skin Diseases (grant R01AR060037), the American Cancer Society, the Susan G. Komen Foundation and the IU Simon Cancer Center.

Biomarker predicting transplant complications may be key to treating them

Oct. 8, 2015

INDIANAPOLIS -- A protein that can be used to predict if a stem cell transplant patient will suffer severe complications may also be the key to preventing those complications, an international research team based at the Indiana University School of Medicine reported Wednesday.

In the study, reported in the journal Science Translational Medicine, researchers said that blocking the activity of the protein called ST2 offers a potential new treatment for graft-versus host-disease, an immune problem that affects many transplant recipients.

Although transplant specialists have been able to reduce its impact, graft-versus-host disease remains a leading cause of death among patients who receive a stem cell transplant from another person, known as an allogeneic transplant. Such transplants are used to treat blood and bone marrow cancers such as leukemia, lymphoma and multiple myeloma, often as a last resort. Graft-versus-host disease occurs when immune cells from the transplant see the patient's body as foreign and attack it.

In previous research, Sophie Paczesny, M.D., Ph.D., professor of pediatrics and of microbiology and immunology, and colleagues reported that patients with a high level of ST2 were more than twice as likely to have graft-versus-host disease that resisted standard treatment with steroids; and nearly four times as likely to die within six months of the transplant.

In the new research, Paczesny and colleagues determined that the version, or isoform, of ST2 associated with graft-versus-host disease is produced at high levels in the intestines, where much of the damage from the disease occurs.

Using mouse models of the disease, the researchers found that blocking the activity of ST2 resulted in reduced severity of graft-versus-host disease and lower mortality. In addition, blocking ST2 did not reduce the effectiveness of the transplant as a treatment for leukemia.

The results, said Dr. Paczesny, "provide a proof of principle that this molecule and associated pathways are potential targets for new therapies that could provide targeted treatment for patients most at risk for severe graft-versus-host disease."

Approximately 20,000 allogeneic stem cell transplants were performed worldwide in 2012. Thirty to 40 percent of stem cell transplant recipients whose donor is related will experience graft-versus-host disease. The percentage can rise to 60 to 80 percent if the patient and donor are not related.

The researchers said the findings could also prove relevant to other immune system disorders where the same molecular pathways are involved.

The research was funded by grants from the National Cancer Institute (R01CA1688f14), the Leukemia and Lymphoma Society (Scholar Award 1293-15), the Physician Scientist Initiative grant from the Lilly

Sophie Paczesny, M.D., Ph.D.

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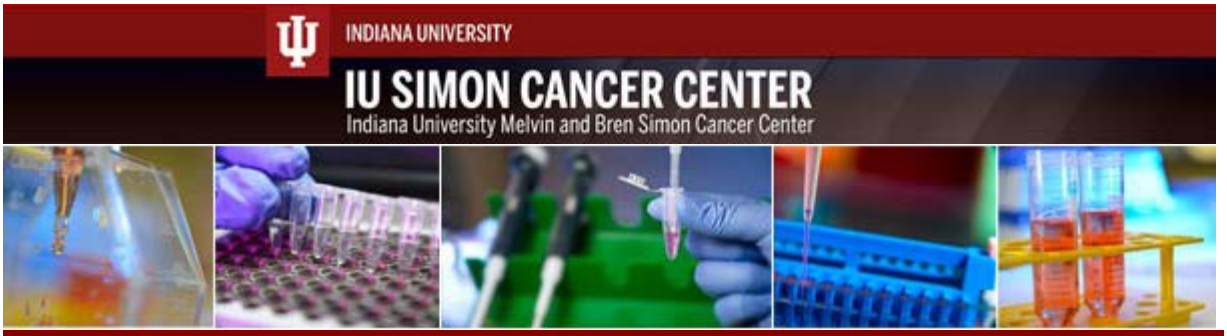
Endowment, the Senshin Medical Research Foundation, and the National Institute of Allergy and Infectious Diseases (R01AI34495).

Dr. Paczesny is a researcher with the Herman B Wells Center for Pediatric Research and the Indiana University Melvin and Bren Simon Cancer Center.

In addition to Dr. Paczesny, investigators contributing to this research were first author Jilu Zhang, Abdulraouf M. Ramadan, Brad Griesenauer, Wei Li, Matthew J. Turner, Reuben Kapur and Helmut Hanenberg of the IU School of Medicine; Chen Liu of the University of Florida College of Medicine, Bruce R. Blazar of the University of Minnesota, and Isao Tawara of Mie (Japan) University Hospital.



IUSCC news

October 2015

News briefs

New GU developing program at IUSCC

Pili

A new Genitourinary Cancer Research Program is a developing program at the IU Simon Cancer Center. Co-led by **Roberto Pili**, MD, the program's goal is to translate basic science findings into the clinical setting by identifying novel therapeutic targets and strategies for the prevention and treatment of bladder, kidney, prostate and testicular cancer. The program is a collaborative effort between the Purdue University Center for Cancer Research and the IU Simon Cancer Center.

- Learn more about the GU program.
- Learn about the five other research programs.

Core update

The Bio-Plex Core is now known as the Multiplex Analysis Core.

Christie Orschell, PhD, the core's director, explained that the core no longer houses only the BioPlex instrument, thus, the name change.

"We now also have the Aushon, another type of multiplex immunoassay platform, that can quantitate protein to the femtogram level," Dr. Orschell said.

She added: "We offer multiplex immunoassay-based technologies for quantitation of proteins and other analytes from a wide range of tissue types and large number of species."

The core is located in Walther Hall, Room 335.

Learn more.

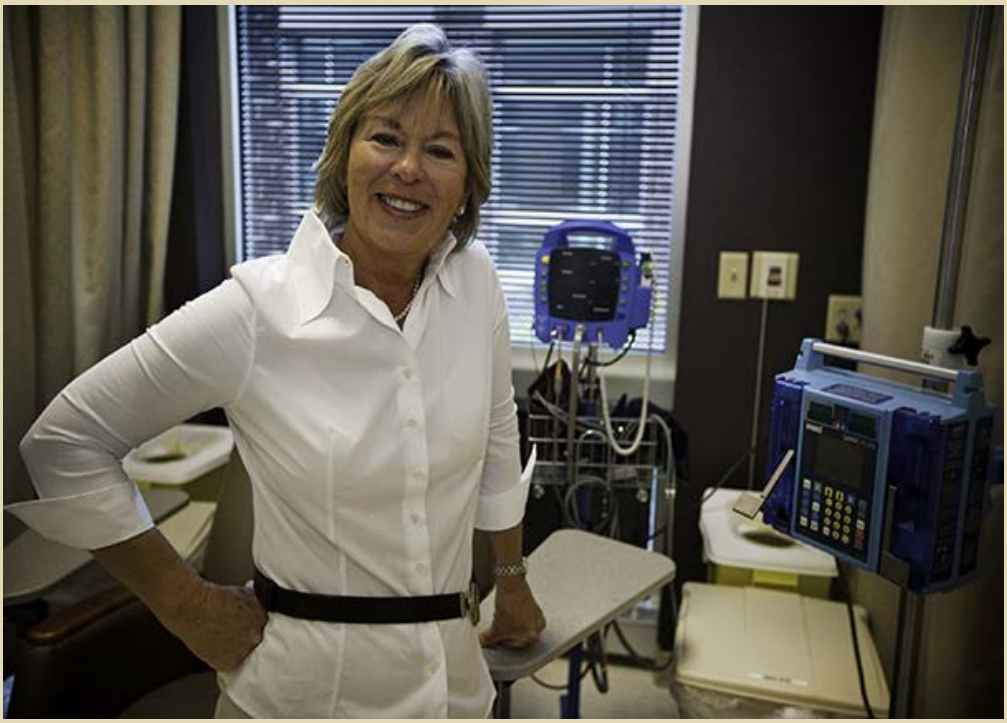
New IU Simon Cancer Center PowerPoint template available

Are you about to put together a PowerPoint presentation in which you'll be representing the IU Simon Cancer Center? If so, we invite you to use the newest cancer center template: http://cancer.iu.edu/documents/IUSCC_PowerPoint_Template_2015.pptx.

You'll find a title page and two options for subsequent pages: One page with the IU Simon

Cancer Center signature (logo), and a page without the signature. This gives you the option of either using the signature on every page or using it more sparingly, either throughout the presentation, or perhaps only for the final slide.

The new template adds consistency to the IU Simon Cancer Center's overall look. The template's design takes elements from the Website (www.cancer.iu.edu), the monthly e-letter, and internal announcements.



Mary Beth Gadus was first diagnosed with breast cancer in 1988. Twenty years later, she established 100 Voices of Hope, which has raised close to $1 million for breast cancer research at the IU Simon Cancer Center. Meet Mary Beth.

IUSM to take part in national pancreatitis research consortium

The IU School of Medicine is one of 10 members selected to take part in a national Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer, with $1.86 million in funding over five years.

This CSCPDPC award, a U01 research project, is funded by the National Institutes of Health, the National Cancer Institute and the National Institute of Diabetes and Digestive and Kidney Diseases.

The two objectives of the research consortium are to pursue clinical research on chronic pancreatitis and acute recurrent pancreatitis, and on pancreatic cancer and pancreatogenic diabetes mellitus. Through recruitment and acquisition of well-characterized patients and associated biospecimens, this research network will achieve the research objectives.

Evan Fogel, MD, is the principal investigator on this award. Other investigators include cancer center members **Stuart Sherman**, MD, and **Murray Korc**, MD.

The consortium also includes the University of Iowa, Cedars Sinai LA, the Mayo Clinic, Stanford University, Baylor University, the University of Florida, the Kaiser Foundation, and the University of Pittsburgh. The University of Texas MD Anderson Cancer Center is the consortium's data coordination and management center.

IUSM receives Transforming Clinical Practice Initiative Award

The IU School of Medicine is one of 39 health care collaborative networks selected to participate in the Transforming Clinical Practice Initiative. The school will receive up to $46.4 million to provide technical assistance support to help equip clinicians in the Midwest with tools, information, and network support needed to improve quality of care, increase patients' access to information, and spend health care dollars more wisely.

Cancer center members in the news

- **Paul Helft**, MD, was recognized with an Excellence in Faculty Mentoring Award during the IU School of Medicine's recent fall faculty meeting.

- Outside of the lab, **Theresa Guise**, MD, is an underwater photographer. You can check out her exhibit, "Beyond Jaws: An Expose on Sharks," from 6 p.m. to 9 p.m. Nov. 6 at M10 Studio in the Circle City Industrial Complex, 1124 Brookside Ave.

- **Richard Zellars**, MD, has been recommended to become the fourth holder of the William A. Mitchell Chair in Radiation Oncology with the title of William A. Mitchell Professor of Radiation Oncology, pending the president's approval. Dr. Zellars is currently chair, Department of Radiation Oncology.

Zellars

- **Timothy Corson**, PhD, has been awarded a $100,000 Research Grant Award from the St. Baldrick's Foundation to support his research on retinoblastoma, a cancer of the eye in children that can cause blindness or death. The award provides funding for year-long research projects that look to find new and better cures for childhood cancers, according to the foundation. Dr. Corson's team has developed a new chemical that blocks abnormal blood vessel growth in the eye without side effects. By blocking new blood vessel formation, they will starve a growing retinoblastoma tumor of oxygen and nutrients and stop its growth. If successful, this work will pave the way for development of a new retinoblastoma drug and also testing in other pediatric and adult cancers.

Helpful Links

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