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Researchers find pathway to cancer-associated muscle weakness

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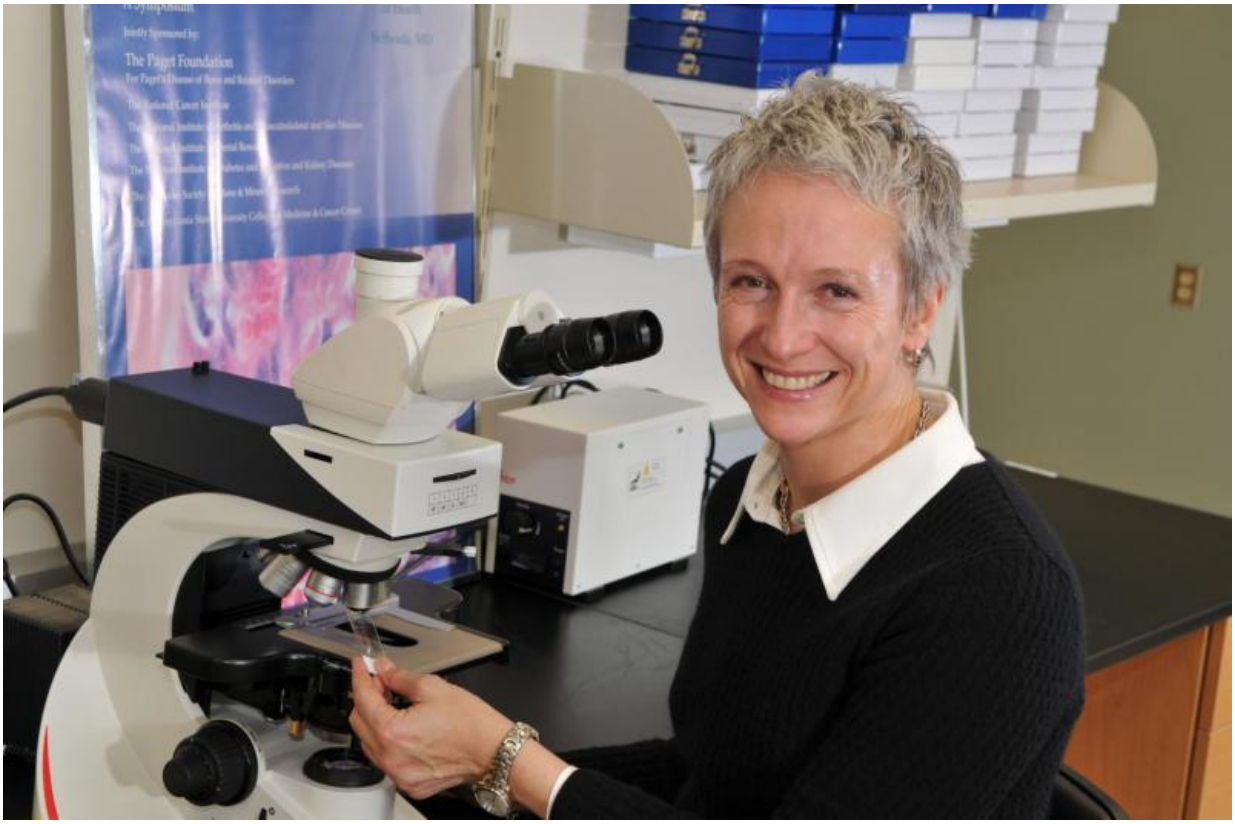

Theresa Guise. Credit: Indiana University School of Medicine

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.

More information: Excess TGF-β mediates muscle weakness associated with bone metastases in mice, DOI: 10.1038/nm.3961

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