Cachexia in Cancer: Is It Treatable at the Molecular Level?

By Cori Vanchieri

Cachexia—the wasting of skeletal muscle, with or without fat loss—is often considered inevitable in patients with advanced cancer. But for more than a decade, basic biologists have been saying that cancer cachexia deserves a closer look. Two recent studies in mice suggest that the biologists are right and raise the possibility that the condition will someday be preventable or even reversible.

Amgen researchers led by HQ Han, M.D., Ph.D., reported in Cell in August that a new compound that inhibits the action of myostatin and activin, two proteins that block muscle development, not only reversed muscle wasting in mice with several types of advanced cancer but also increased their lifespan. University of Miami researchers reported similar results on muscle-wasting reversal earlier in the year.

The Amgen and Miami scientists are just two of the groups working on cachexia. Many in the field are focusing on diseases other than cancer, such as sarcopenia (severe muscle depletion) and muscular dystrophy. But cachexia affects a large number of patients with advanced cancers—up to 80% by some estimates—and has been estimated to be the immediate cause of death in 20-40% of patients. Exact figures are unknown, partly because there is no agreement on the definition of cachexia (see statbite).

Clinicians do agree, though, that the condition limits the ability to treat cancer. Vickie E. Baracos, Ph.D., at the University of Alberta in
Edmonton said that for patients with severe muscle wasting, standard doses of chemotherapy are toxic. That means the dose has to be reduced or the patient switched to a possibly less-effective regimen.

Muscle-Blocking Proteins

Previous studies have tackled cachexia at the molecular level without success, but targeting the myostatin pathway shows more promise, according to Michael Tisdale, a professor at Aston University, Birmingham, UK, who wrote a commentary accompanying the Cell study. The myostatin gene and its role in regulating skeletal muscle mass first came to light in 1997, when Se-Jin Lee, M.D., Ph.D., and colleagues found that mice engineered to lack myostatin, part of the transforming growth factor β family, exhibit dramatic increases in skeletal muscle mass throughout the body.

“From the get-go, the potential applications in a wide variety of disease settings were pretty obvious to everybody,” said Lee, professor of molecular biology and genetics at the Johns Hopkins University School of Medicine, Baltimore.
Muscle-wasting diseases such as muscular dystrophy were of obvious interest, as was muscle loss in aging and cachexia-causing conditions such as cancer, AIDS, and sepsis. The bodybuilding community took note as well. But whether myostatin had effects beyond muscle development wasn’t clear.

Then in 2002, Wyeth (now part of Pfizer) developed a neutralizing monoclonal antibody against myostatin and showed that it caused muscle growth in healthy adult mice. That finding showed that myostatin’s effects went beyond development, Lee said. Other drug companies began developing their own compounds.

Amgen focused on ActRIIB, a receptor that controls signaling of several ligands in the transforming growth factor β family, including myostatin and activin. Han’s team found that many cancers produce a large amount of activin A. When the researchers overexpressed activin A in mice, severe muscle wasting and cachexia occurred.

They then devised a decoy receptor to block ActRIIB signals to see what effect it would have on cachexia in several mouse models of cancer. In a colon 26 mouse model, it prevented and reversed the muscle loss that cancer caused. Proinflammatory cytokines, such as interleukin 6 and tumor necrosis factor α, which were considered important players in muscle loss, remained elevated. So without affecting these cytokines, the inhibitor was still able to completely reverse muscle loss. “These data argue that the ActRIIB signaling pathway is dominant,” Han said.

Most striking was the apparent effect of blocking ActRIIB on survival. In the colon 26 model, when all the untreated mice had died, more than half of the treated animals had been rescued. The researchers saw an even greater survival benefit with the treatment in inhibin-deficient mice bearing gonadal tumors.

“Our most important finding,” said Han, who is scientific executive director of metabolic disorders at Amgen, “is the unequivocal demonstration that muscle mass is an important determinant of survival in cancer conditions.”

The decoy receptor also reversed atrophy of the heart. Cardiac muscle loss in cancer cachexia has been overlooked, Han said, although heart failure is a major medical issue in cancer.

“I hope this finding will stimulate more interest by oncologists and cardiologists.”

In the earlier study with the myostatin pathway, University of Miami researchers, led by Teresa A. Zimmers, Ph.D., a former student of Lee at Hopkins, tested a different activin receptor inhibitor that reduced muscle wasting and protected fat stores in both colon 26 and Lewis lung cancer mouse models. They published the results in *Biochemical and Biophysical Research Communications* last January.

Clinical trials of several inhibitors of the myostatin pathway are under way but mainly in noncancerous conditions, such as age-related sarcopenia and muscular dystrophy. Lee said companies have run or are running clinical trials of their own inhibitors, including Wyeth, Acceleron, Eli Lilly, and Novartis. Amgen ran a phase I trial of a myostatin inhibitor but hasn’t gone forward with that or with human trials of its ActRIIB decoy receptor. Virtually every pharmaceutical company has some program targeting this pathway, mostly in sarcopenia.

The aim is to get through the short term while getting therapy for the cancer.”

Lee is not convinced that the myostatin pathway is the central player. He said no one has determined whether the pathway activated in cancer cachexia is causing wasting. But a second question is in some ways more important: “Can interfering with the pathway provide clinical benefit? We have every reason to be optimistic.”

### Other Pathways

The myostatin pathway is not the only target of cachexia researchers. Other mechanisms of interest include fat metabolism, the androgen receptors on muscle, and proteins that block muscle development.

Joanna Brell, M.D., program director for symptom management and drug development at the National Cancer Institute, said she’d like to see more work to understand a protein involved in muscle differentiation, called myo-D, which is highly expressed in pancreatic cancer. Other researchers are studying genetic polymorphisms associated with cytokine production to see whether any are associated with risk of cachexia.

Fat is an exciting area as well, Brell added. An abundance of metabolic activity in fat might offer clues to cachexia and the hypermetabolic rate seen in patients with cachexia.

Selective androgen receptor modulators (SARMs) hold promise, according to Baracos. These small molecules are designed to fit the active site of the androgen receptor in muscle. Because they don’t latch on to androgen receptors outside muscle, they don’t have masculinizing effects.

Early work with SARMs in cancer is in progress at several companies. Memphis-based GTx has an oral agent that, as reported at this year’s American Society of Clinical Oncology meeting, increased muscle mass and improved muscle strength and performance in postmenopausal women, elderly men, and men and women with cancer cachexia in phase IIb studies. And Ligand Pharmaceuticals, in LaJolla, Calif., has a SARM in phase I testing in healthy volunteers.

### Treat Sooner

Regardless of the treatment approach, researchers seem to agree that cachexia treatment often comes too late. “Many interventions
fail because they are focused on late cachexia,” said Mary E. Platek, Ph.D., R.D., a postdoctoral fellow at Roswell Park Cancer Institute studying markers for cachexia. “We might not be looking at the right timeline. Can we intervene earlier?”

Baracos agrees and calls for better measures of muscle loss. Using computed tomography, she and colleagues have documented the dramatic degree to which cancer patients lose muscle. “In oncology, we have access to the highest-quality diagnostic images,” she added. “We usually look at them for different purposes—to follow the disease—but it’s possible to take any cancer patient’s diagnostic image and find out exactly how much muscle they have.” This approach would also allow starting treatments earlier.

According to Han, the first step may be changing expectations. People used to think that osteoporosis was inevitable and irreversible, he noted, but today there are drugs to prevent it. “Now we’re recognizing that cachexia is part of a serious disease process, and we need a drug to change it.”

Dr. Lee is the scientific founder of Metamorphix, Inc., and a consultant to the company. Under a licensing agreement with MMI, he is entitled to a share of royalties received by Johns Hopkins on sales of products related to myostatin. Dr. Han is an employee of Amgen.