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News Release

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Study Explains Why Muscles Weaken with Age and Points to Possible Therapy

(NEW YORK, NY, (August 2, 2011) – Researchers at Columbia University Medical Center have discovered the biological mechanism behind age-related loss of muscle strength and identified a drug that may help reverse this process. Their findings were published in the August 2 online edition of *Cell Metabolism*.

As we grow older, our skeletal muscles tend to wither and weaken, a phenomenon known as sarcopenia. Sarcopenia, which begins to appear at around age 40 and accelerates after 75, is a major cause of disability in the elderly. Exercise can help counter the effects of age-related muscle loss. Otherwise, there are no established treatments.

According to the new study, conducted in mice, sarcopenia occurs when calcium leaks from a group of proteins in muscle cells called the ryanodine receptor channel complex. These leaks then trigger a chain of events that ultimately limits the ability of muscle fibers to contract, reports study leader Andrew R. Marks, M.D., chairman and professor of physiology and cellular biophysics, the Clyde and Helen Wu Professor of Medicine, and director of the Wu Center for Molecular Cardiology at Columbia University Medical Center (CUMC).

Ryanodine receptors, which are calcium channels found in most body tissues, have been the focus of Dr. Marks' research since 1989. After cloning the ryanodine receptor gene, he later discovered, in studies of mice, that leaky ryanodine receptors are involved in the development of heart failure and arrhythmias. In 2009, he showed that leaks in these channels also contribute to Duchenne muscular dystrophy, a genetic disorder characterized by rapidly progressing muscle weakness and early death.

Since muscular dystrophy and sarcopenia have some commonalities, Dr. Marks suspected that ryanodine receptor leakage may also be involved in age-related muscle loss, which the present study shows is the case.

"This is a completely new concept — that the damage that occurs in aging is very similar to what happens in muscular dystrophy," says Dr. Marks, "thus as we age we essentially develop an acquired form of muscular dystrophy."

Both the aging process and the genetic defect responsible for muscular dystrophy cause an increase in the production of oxygen free radicals, highly reactive and harmful molecules. “Our data suggest that this sets up a vicious cycle, in which the free radicals cause ryanodine receptors to leak calcium into the cell. The calcium poisons mitochondria — organelles that power the cell — leading to the release of even more free radicals. This, in turn, causes more calcium leakage. With less calcium available for contraction, the muscles get weaker,” says first author Daniel C. Andersson, M.D., Ph.D., a postdoctoral fellow in physiology and cellular biophysics at CUMC.

The study also points to a possible therapy for sarcopenia: an experimental drug called S107, developed by Dr. Marks and his colleagues. The drug acts by stabilizing calstabin1, a protein that binds to ryanodine receptors and prevents calcium leakage.

In the study, 24-month-old mice (roughly the equivalent of 70-year-old humans) were given S107 for four weeks. The mice showed significant improvements in both muscle force and exercise capacity, compared with untreated controls. “The mice ran farther and faster during voluntary exercise,” says Dr. Andersson. “When we tested their muscles, they were about 50 percent stronger.” The drug had no effect on younger mice with normal ryanodine receptors.

A similar drug is now in phase II clinical trials for the treatment of heart failure.

“Most investigators in the field of aging have been saying that the way to improve muscle strength is to build muscle mass, using such therapies as testosterone, growth hormone, and insulin-like growth factor-1,” says Dr. Marks. “But an increase in muscle mass is not necessarily accompanied by an increase in muscle function. Our results suggest that you can improve muscle function by fixing leaky calcium channels. And in fact, treating aged mice with S107 enhanced muscle strength without increasing muscle size, at least during the four-week treatment period.”

Dr. Marks’ paper is titled, “Ryanodine Receptor Oxidation Causes Intracellular Calcium Leak and Muscle Weakness in Aging.” In addition to Dr. Andersson, his coauthors include Mathew J. Betzenhauser, Steven Reiken, Albano C. Meli, Alisa Umanskaya, Wenjun Xie, Takayuki Shiomi, and Ran Zalk at CUMC, and Alain Lacampagne at Universités Montpellier, Montpellier, France.

A.R. Marks is a consultant for ARMGO Pharma, Inc., a privately held biopharmaceutical company which has been awarded an exclusive, worldwide license from Columbia University for its ryanodine receptor technology. The company's proprietary drugs, known as "rycals," are a new class of oral agents that act on ryanodine receptors to repair the calcium leak associated with chronic diseases. ARMGO Pharma, Inc. is seeking to discover and develop novel small-molecule therapeutics to treat debilitating cardiac, muscular, and neurological disorders. The company's lead drug candidate is currently undergoing Phase II

clinical trials for heart failure. Other programs have not yet entered the clinical phase of development, please visit www.armgo.com for further information.

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