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First demonstration of muscle restoration in an animal model of Duchenne muscular dystrophy

Implications for treating many types of genetic diseases

PHILADELPHIA -- Using a new type of drug that targets a specific genetic defect, researchers at the University of Pennsylvania School of Medicine, along with colleagues at PTC Therapeutics Inc. and the University of Massachusetts Medical School, have for the first time demonstrated restoration of muscle function in a mouse model of Duchenne's muscular dystrophy (DMD). The research appears ahead of print in an advanced online publication of Nature.

"This new class of treatment has the potential to help a large number of patients with different genetic diseases that have the same type of mutation," says senior author H. Lee Sweeney, PhD, chair of the Department of Physiology at Penn. This genetic flaw causes from 5 to 15 percent (and in a few instances up to 70 percent) of individual cases of most inherited diseases, including DMD, cystic fibrosis, and hemophilia.

The new drug, developed by the South Plainfield, NJ-biotech firm and called PTC124, binds to the ribosome, a cellular component where the genetic code is translated into proteins, one amino acid at a time. The drug allows the ribosome to read through a mistake in the genetic code called a premature stop codon in order to properly make whole proteins.

In DMD, patients are missing dystrophin, a protein that helps keep muscle cells intact. About 15 percent of DMD patients do not make dystrophin because of the mutation. DMD eventually affects all voluntary muscles, as well as heart and breathing muscles.

PTC124 attaches to ribosomes in all cell types within the MD mouse model, overriding the mutation in the dystrophin gene that tells it to halt production of the protein. Instead of stopping, the full-length dystrophin protein is made. The drug enables enough protein to be made to correct defects in the muscle of the DMD mouse, and at the same time the drug does

not prevent the ribosome from reading correct "stop" signals in the genetic code to make other necessary proteins.

"Enough dystrophin accumulated in the muscles of the MD mice so that we could no longer find defects in the muscles when we examined them," says Sweeney. "For all intents and purposes the disease was corrected by treatment with PTC124." The drug allowed dystrophin to be made in cells in which it was previously absent, to be delivered to the proper location at the cell membrane, and to induce restoration of muscle function in rodent muscles.

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Co-first author Elisabeth Barton, PhD, worked on this project as a postdoctoral fellow in the Sweeney lab, and continued as a collaborator when she became an Assistant Professor in Penn 痴 School of Dental Medicine.

The study was supported in part by the Muscular Dystrophy Association and the Parent Project Muscular Dystrophy.

PTC124 is presently nearing the end of a Phase II multi-center clinical trial in DMD patients, of which Children's Hospital of Philadelphia is a major accruing site.

Dr. Sweeney directs a Paul Wellstone Muscular Dystrophy Cooperative Center, sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases. He is also on the Scientific Advisory Board of PTC Therapeutics Inc.

This release can be viewed at www.pennhealth.com/news.

PENN Medicine is a $2.9 billion enterprise dedicated to the related missions of medical education, biomedical research, and high-quality patient care. PENN Medicine consists of the University of Pennsylvania School of Medicine (founded in 1765 as the nation's first medical school) and the University of Pennsylvania Health System.

Penn's School of Medicine is ranked #2 in the nation for receipt of NIH research funds; and ranked #3 in the nation in U.S. News & World Report's most recent ranking of top research-oriented medical schools. Supporting 1,400 fulltime faculty and 700 students, the School of Medicine is recognized worldwide for its superior education and training of the next generation of physician-scientists and leaders of academic medicine.

The University of Pennsylvania Health System includes three hospitals, all of which have received numerous national patient-care honors [Hospital of the University of Pennsylvania; Pennsylvania Hospital, the nation's first hospital; and Penn Presbyterian Medical Center]; a faculty practice; a primary-care provider network; two multispecialty satellite facilities; and home care and hospice.