

Sweta Girgenrath

HELPING CHILDREN with CHRONIC MUSCULAR DYSTROPHY

Can muscle cells deficient in laminin—a protein that normally helps anchor muscle cells—be manipulated to prolong life and reduce the effects of a rare form of muscular dystrophy?

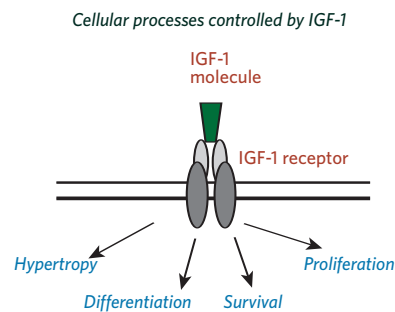
Newly hired Assistant Professor Mahasweta Girgenrath, PhD, is studying the cell biology in congenital muscular dystrophy (CMD). CMD is the term given to a group of progressive muscle-wasting diseases that affect both male and female infants at or shortly after birth. Health of muscle cells depends on proper structure function of their integral proteins, including laminin. In the muscle cells of infants with MDCIA, the most common form of CMD, laminin is missing or dysfunctional. The symptoms can range in severity from mild to extreme, and often lead to death in early childhood. CMD occurs in one out of 100,000 births.

CMD is one of nine types of muscular dystrophy, an inherited disorder caused by genetic defects that results in the weakness and degeneration of the skeletal muscles that control movement. There are no cures for any of the muscular dystrophies, only treatments for secondary symptoms.

“My major goal is to understand the pathophysiology of this and other forms of muscle degenerative diseases and prevent or ameliorate symptoms,” says Girgenrath.

She is the principal investigator on two research grants, one from the National Institutes of Health and a second from the Muscular Dystrophy Association (MDA), awarded to develop strategies to treat laminin deficiencies. The MDA grant is

part of the special translational research program designed to fast-track treatment approaches for rare neuromuscular diseases that have proven promising in initial studies, since for-profit drug companies are mostly interested in developing drugs that affect a large segment of the population. The MDA defines translational research as “preclinical activities leading up to a clinical trial.”



MDCIA is rare compared to the more common Duchenne muscular dystrophy (DMD), which isn't detectable until a child is three to five years old. DMD affects only males; boys may live as long as 25 or 30 years. In DMD, the missing protein is dystrophin. Clinical trials are already under way for DMD patients, including one with gene-compounds being injected into bicep muscles, and have shown promising results. DMD affects one in 3,500 male infants.

“MDCIA is such a devastating disease,” says Girgenrath. “And those affected are helpless infants. It's pretty scary because

there is no cure. I'd like to try to do something about it.”

Girgenrath has always been intrigued by the mechanisms that regulate skeletal muscle growth, repair, and survival in the context of muscular dystrophies. After continuing her muscle research as a post-doc at Pennsylvania State University, she switched to cardiac biology at Brigham and Women's Hospital only to realize where her passion lay and accepted a research position at Boston Biomedical Research Institute (BBRI) in Watertown, Massachusetts, an independent nonprofit lab dedicated to forging a connection between basic discovery and medical application.

“I wanted to go back to muscle research,” she recalled. “I was lucky to get into the right lab.”

At BBRI, regenerative biology is one of four program initiatives for life debilitating and deadly diseases, including muscular dystrophy. She worked with scientist Jeffrey Boone Miller, her mentor, for six years. There, she was part of a team and became the lead author on several papers in peer-reviewed journals, including an article in the *Journal of Clinical Investigation* on hampering apoptosis—a type of cell death—to prolong survival of those suffering from CMD.

Girgenrath and her colleagues found that two genetic interventions increased survival rates in laminin-deficient mice. Some mice were bred to overproduce a protein called Bcl-2, which protects against apoptosis (cell death), while others were bred not to produce another protein called Bax, a contribu-

tor to cell death. According to Girgenrath, the lack of the Bax protein improved life span growth and muscle health. The Bax-free mice were larger than those bred to replicate CMD, although not as large as healthy mice. Bax lessened the disease severity and made the muscles more resistant to cell death.

“We had noteworthy improvement in the pathology,” she says. “The mice lived 25 weeks or 175 days, instead of 28 to 42 days. That's quite significant.”

Girgenrath speculates that perhaps a combination of therapy strategies might help to prolong life for infants with CMD. For example, along with inhibiting apoptosis and facilitating muscle regeneration, using growth factors such as IGF-1 might improve the experimental outcomes.

In addition to her research, Girgenrath is in the process of developing a course on the biology of muscles in health and disease for the Spring 2009 semester. She is also excited about pursuing her muscle-stem cell research and hopes to have more undergraduate and graduate students to assist her in the lab by fall 2008.

“We're still struggling to figure out a treatment regime to benefit the quality of life and improve life expectancy,” she says. “Researchers may not find a cure in the next couple of years, but prospects of developing a successful treatment regimen are very bright.”

Left: Sweta Girgenrath, assistant professor in the Department of Health Sciences at BU Sargent College.

Below: Girgenrath in her lab at Sargent with her research assistants and graduate students.

