"Mighty mouse" makes headlines

Red Sox fans may have noticed something more about pitcher Jason Johnson last summer than his spotty performance—the insulin pump on his belt. Johnson, like many other professional athletes with type 1 diabetes, uses an insulin pump to regulate his blood sugar. Why is such careful monitoring necessary? It's because exercise can cause overall blood sugar levels to plummet, explains DMS biochemist Lee Witters, M.D. Muscles burn glucose more quickly during physical activity. This process recently inspired Witters, a sports fan, to look for a new way to treat diabetes without insulin.

The question that Witters and his team began pursuing is whether boosting glucose uptake in skeletal muscle can sufficiently lower overall blood sugar levels. They came close to answering that question with a study that was published a few months ago in the *American Journal of Physiology: Endocrinology and Metabolism*.

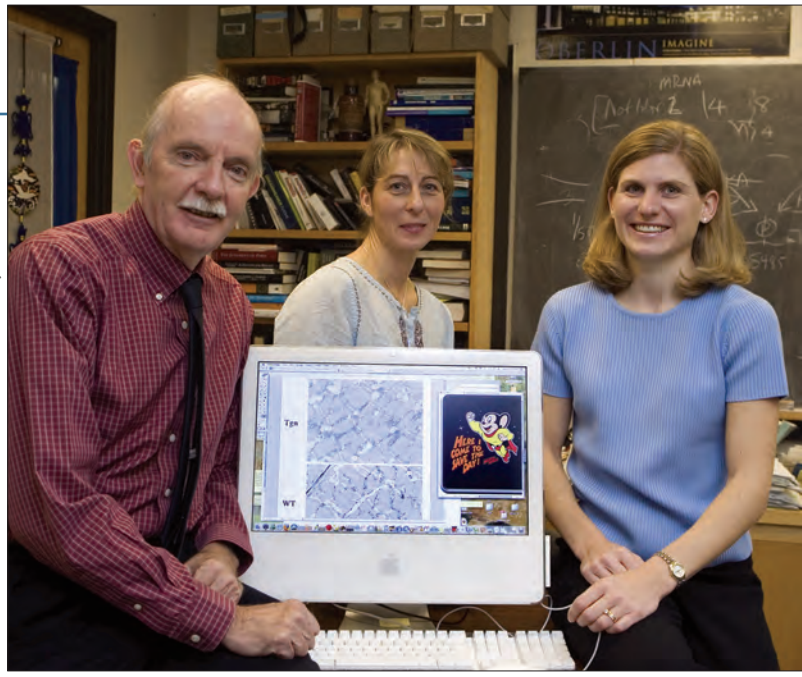
In the study, the researchers turned on a usually silent gene in the skeletal muscle of mice. The resulting mice stored two to three times as much glucose in their skeletal muscle as normal. And, much to the surprise of Witters, they were able to run three times as long as a normal mouse before reaching the point of exhaustion.

"We weren't trying to make super-athletes," says Witters. "This is really one of those serendipitous things that happens in research where you set off to do one thing and suddenly you find something else."

Mighty: Nevertheless, a number of media outlets, including *Sports Illustrated*, reported on Witters's "mighty mouse," not for its potential benefits for treating diabetics but for its potential to lead to "gene doping"—the manipulation of genes to enhance athletic performance.

"I don't know this for a fact," says Witters, "but manipulating this particular gene, just one gene, might in fact create a human who has enhanced exercise capacity." But gene doping, as well as gene therapy (altering gene expression to treat a disease), is still "a good ways off," Witters observes. Even finding a full answer to his initial question—whether boosting glucose storage can be used to treat diabetes—will require more research.

Much of that work will be conducted by the Dartmouth team's collaborators at the Joslin Diabetes Center in Boston. "We're a biochemistry lab," Witters points out, and therefore not equipped to do the physiological tests necessary to further the research. Their collaborators at Joslin, however, "have treadmills to run the mice on and lots of other ways to measure things like oxygen consumption and carbon dioxide generation."



JOSEPH MEHLING

Lee Witters, left, parlayed an observation during a baseball game into a study on glucose uptake. Christine Richardson, center, a research assistant, and Laura Kersting Barré, right, a 2001 DMS graduate, were coauthors on the paper.

Target: Although the team's *American Journal of Physiology (AJP)* study failed to answer the initial question, it did reveal a "druggable target"—the gene and corresponding enzyme that cause increased glucose storage. In other words, a medicine could be designed to mimic or enhance the action of that enzyme and perhaps help people with muscle weaknesses caused by aging or various diseases. (Witters has been studying this enzyme, called AMPK, for more than a decade. See **dartmed.dartmouth.edu/winter05/html/disc_enzyme.php** for more on his work in this area.)

The *AJP* paper revealed some other important findings, too. For example, many genes, such as the one manipulated in the study, are thought to be active in just one tissue. But Witters's team was able to turn on a gene in skeletal muscle that is usually active only in the liver. This "raises a lot of very interesting issues about tissue-specific enzyme function," he explains, "and the rather arbitrary definitions we have" for some enzymes. The finding also "offers the opportunity," he adds, "of creating mice in which the [AMPK] gene would be selectively turned on in the liver or the heart or areas of the brain or in fat tissues" to treat certain conditions.

As he and other researchers have shown, AMPK helps regulate energy levels in cells and therefore plays an important role in cancer and appetite control, as well as in diabetes. "We had to show at least in one line of mice that our genetic manipulation . . . would actually play out at a physiologic level," Witters says. "Now that we've done that, that offers a world of opportunities for using the same general strategy to genetically activate the enzyme selectively in other tissues."

So what began as a single hypothesis, sparked by the world of professional sports, has unleashed a slew of new findings and research opportunities. Witters and his collaborators plan to present some of these findings, currently unpublished, at the annual scientific meeting of the American Diabetes Association in June. JENNIFER DURGIN