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Partnership may soon lead to clinical trials of metabolic syndrome drug

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University of Utah researchers have discovered that an enzyme involved in intracellular signaling plays a crucial role in developing metabolic syndrome, a finding that has a U of U spinoff company developing a drug to potentially treat the condition.

The researchers, led by Jared Rutter, Ph.D., professor of biochemistry, hope to begin human clinical trials of a drug in the next couple of years.

"The approved drug therapies do not treat or prevent this condition in most people," says Rutter, senior author of a study describing the research published July 3, 2014, in *Cell Reports*. "But given the results of our research with mouse and rat models, we are hopeful that metabolic syndrome can be effectively treated with drug therapy someday soon."

Metabolic syndrome, a group of conditions that increases the risk for developing heart disease, diabetes and stroke, is estimated to affect up to 25 percent of adults. Public health officials believe metabolic syndrome has reached epidemic proportions in the United States and elsewhere.

Metabolic syndrome includes disorders such as high blood pressure, high blood sugar levels, abnormal cholesterol readings, and obesity. One of the prominent features of the syndrome is the excessive production and storage of fatty acids and triglycerides.

In research with rodents, Rutter, doctoral student and first author on the Cell Reports study Xiaoying Wu, and Allen Nickols of BioEnergenix, a

company Rutter co-founded in 2009, discovered that an enzyme known as PASK stimulates the overproduction of fatty acids and triglycerides. PASK works by chemically modifying other proteins in order to alter their specific functions. One of the proteins it modifies is SREBP-1c, which functions as the master regulator of all of the enzymes that make fat.

Using a drug candidate being developed by the University of Utah spinoff company BioEnergenix, the researchers prevented PASK from modifying SREBP-1c. This, in turn, prevented SREBP-1c from increasing the production of enzymes that make fat, resulting in a drop in the levels of fatty acids and triglycerides in mouse and rat livers. Insulin resistance and diabetes were also partially reversed in diabetes-prone animals.

"We hope that this is an example where science leads us not only to a better understanding of how the body works, but also to the discovery of approaches that we can use to treat human disease," Rutter says.

Researchers don't know what causes fatty acids and triglycerides to be overproduced, and that will be a focus of Rutter's ongoing research as well as trying to understand how PASK activates SREBP-1c.

This study is a prime example of a public/private partnership to advance research and health care, a model becoming more common in medical and other scientific research. In this case, a U of U spinoff company is using a University of Utah-developed technology to improve the knowledge and clinical treatment of an issue with a major impact on U.S. health. To address this health issue, the University of Utah recently established the Center for Diabetes and Metabolism, which pairs researchers and clinicians who work side by side to develop treatment and prevention options. Rutter serves as co-director of this center.