“In order to develop new and effective treatments for diabetes, researchers need to understand the complex and delicate biology behind human metabolism as well as the disorders that develop when this finely tuned system is out of balance.”

When a person’s blood sugar level is high even when the person hasn’t recently eaten—known as an “elevated fasting glucose level”—it provides a first clue that he or she is at risk of developing type 2 diabetes.

Finding ways to lower blood glucose offers great promise for diabetes treatment because doing so reduces the risk of the many diabetes complications that substantially affect the quality of life. The need for new drugs is accelerating as almost 26 million Americans have type 2 diabetes, and an estimated 79 million people are at risk of developing the condition.

During the day, when we feed, we use high-octane glucose from the food we take in to get around. And at night, when we fast, our body shifts to burning the fat from adipose stores, which provide a lower-power but longer-lasting source of energy.

Although most organs in the body can use glucose or fat as a source of energy, the brain requires glucose during both night and day. The liver assumes this task during fasting, when it becomes a glucose-producing organ. Obese individuals with insulin resistance produce too much glucose, leading to elevated glucose levels in the bloodstream that contribute to the development of type 2 diabetes.

The Montminy lab identified the function of a genetic switch, called CRTC2, which controls the production of glucose by the liver during fasting and in diabetes. The researchers found that the CRTC2 switch is turned on in liver cells during fasting in response to a hormone called glucagon. Glucagon flips the CRTC2 switch on in liver cells by causing a chemical change in CRTC2 known as de-phosphorylation. The group showed that inactivating the CRTC2 switch blocked the hormone’s ability to stimulate glucose production by the liver during fasting.

In recent studies, the Montminy lab has determined that the CRTC2 switch controls glucose production through an enzyme that associates with the switch. Inactivating this enzyme with a small molecule inhibitor was sufficient to lower blood glucose levels in obese, insulin-resistant mice. These findings may offer new targets for drug development and provide effective therapies for the treatment of type 2 diabetic individuals.

For more information, please visit www.salk.edu/faculty/montminy

From left to right: Wolfgang Fischer, Sandra Guerra, Talitha Van der Meulen, Emilie Blanchett, Jose Paz, Dandan Chen, Run Shen, Young-Sil Yoon, Wenwei Tsai, Jeong Ho Kim, Marc Montminy, Biao Wang, Ezra Wiater, Hongbo Wang, Susie Hedrick, Kim Ravenskjaer, Meghan Hogan, Jeniffer Hernandez, Sam Van de Velde, Debbie Doan, Vera Nies