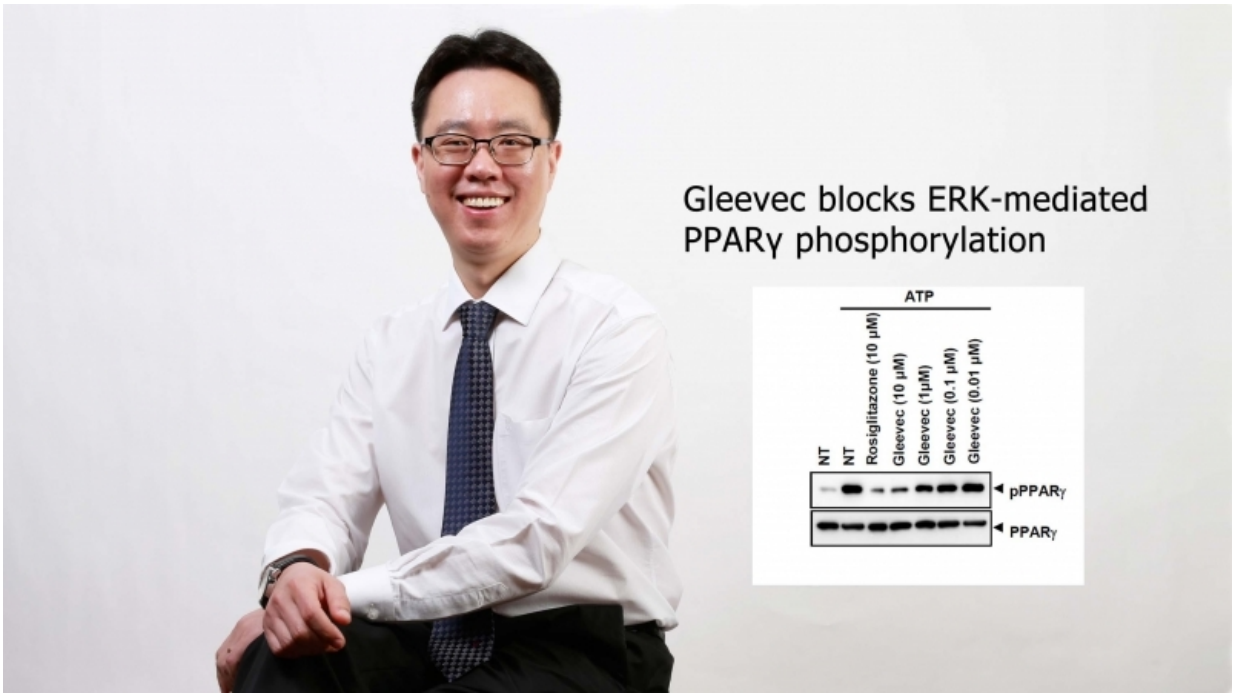
New hope for a type 2 diabetes cure

March 28 2016, by Joo Hyeon Heo



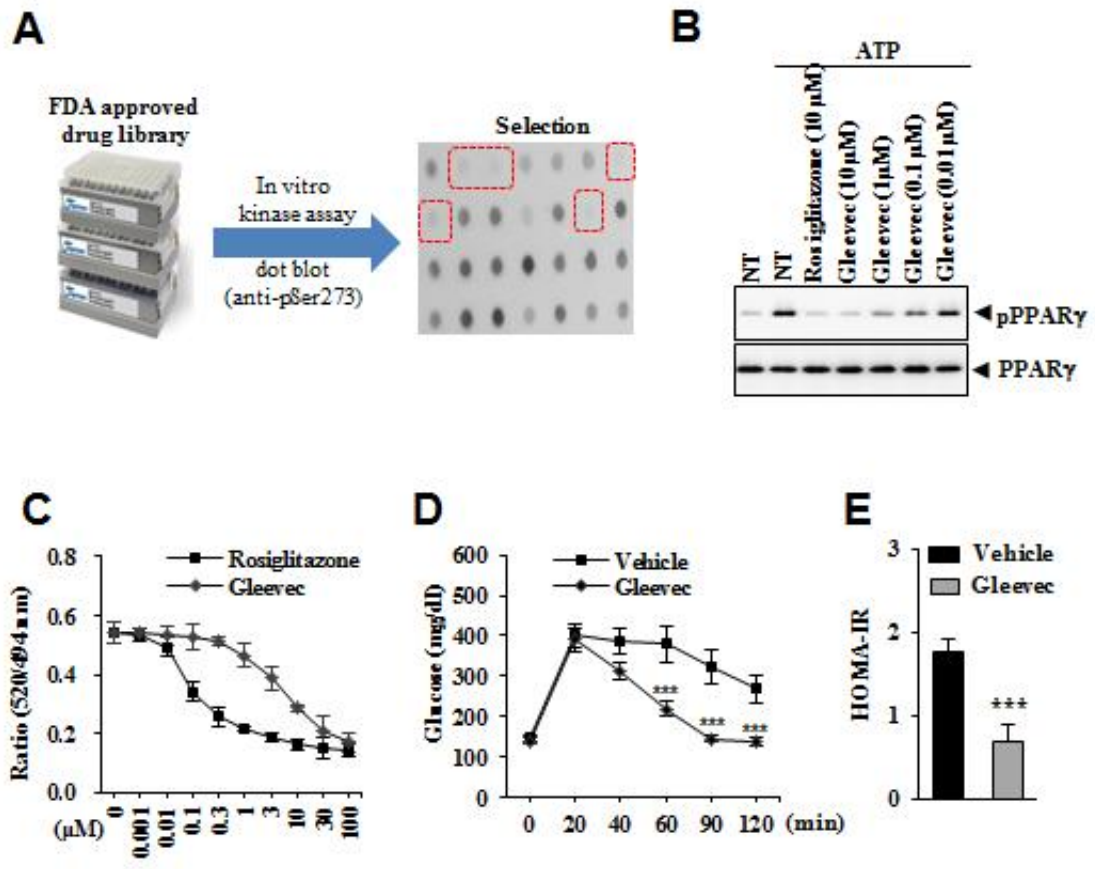
Professor Jang Hyun Choi (School of Life Sciences) of UNIST's joint research team has discovered leukemia drug holds promise for type 2 diabetic patients. Credit: UNIST

The cancer treatment drug Imatinib, otherwise known as Gleevec is approved to treat various forms of cancer, mostly notably chronic myeloid leukemia (CML). However, researchers have stumbled onto another possible use for it, curing type 2 diabetes.

The team—made up of scientists from the Scripps Research Institute in United States, South Korea-based company Hyndai Pharm Co., Ltd., the Seoul National University, and Ulsan National Institute of Science and Technology (UNIST)—has identified for the first time that, through control of PPARγ, Gleevec lowers the level of insulin resistance, thereby reducing the risk of both hyperglycemia and obesity.

Acording to the team, led by Prof. Jang Hyun Choi (School of Life Sciences) of UNIST, "Although TZD-based medicines work effectively at improving glucose uptake by skeletal muscle and other peripheral tissues, due to increased risk of adverse effects they have been withdrawn from the market ." He continues, "In order to develop new type of medication that have fewer side effects, we have have discovered a new compound that can maintain stable blood sugar levels."

Among insulin-sensitizing drugs, TZDs are a therapeutic class that are selective agonists for PPARγ, which plays a central role in how the body metabolizes glucose, stores fat, and controls immune and inflammatory responses.



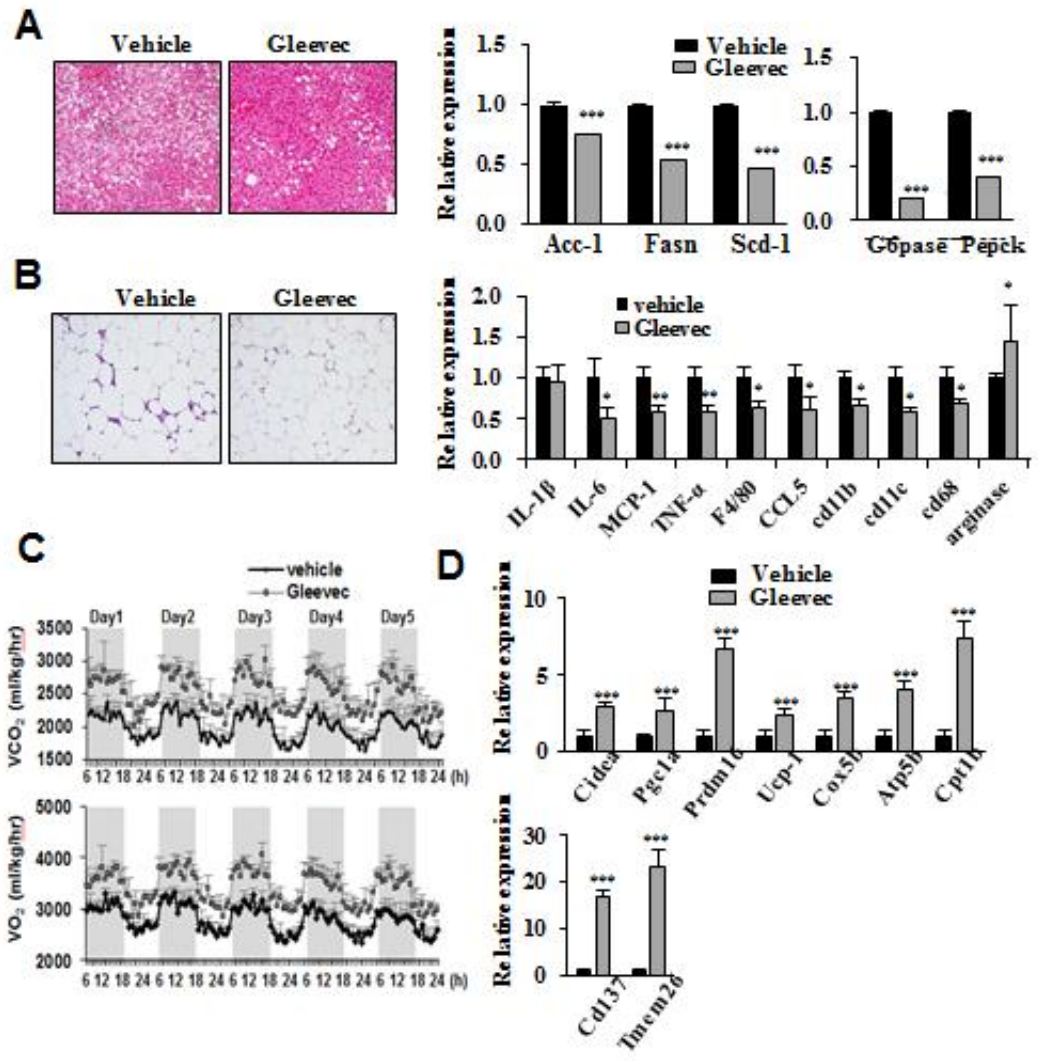
Gleevec blocks ERK-mediated PPARγ phosphorylation. Credit: UNIST

In the study, the team observed that the phosphorylation of PPARγ is closely related to developing diabetes. They also discovered that the removal of phosphoric acid from PPARγ shows anti-diabetic effects. To determine whether phosphoric acid is bound to PPARγ, the team developed a new chemical screening procedure. Using high throughput phosphorylation screening, the team discovered that Gleevec blocks CDK5-mediated PPARγ phosphorylation devoid of classical agonism as a PPARγ antagonist ligand.

Prof. Choi states, "Although studies have shown that Gleevec treatment may show improved insulin sensitivity and decrease blood glucose in

patients with known diabetes, the exact cause hasn't been proven yet." He continues, "Through this research, we discovered Gleevec, which is used in leukemia medications, can inhibit the phosphorylation of PPARγ."

Moreover, when tested with high-fat diet-fed mice, Gleevec showed improved insulin sensitivity without causing severe side effects seen with other PPARγ-targeting drugs. The researchers note that Gleevec was also found to reduce lipogenic and gluconeogenic gene expression in liver and improved inflammation in adipose tissues. Increased browning of white adipose tissue (WAT) and energy expenditure were also seen with Gleevec.



Credit: UNIST

The team notes, "Taken together, Gleevec exhibits greater beneficial effects on both glucose/lipid metabolism and energy homeostasis by blocking PPARγ phosphorylation." They continue, "These data illustrate that Gleevec could be a novel therapeutic agent for use in insulin resistance and type 2 diabetes."

The findings of the study has been published in the January edition of

the journal *Diabetes*, the most prominent publications in the field of endocrinology and metabolism with an impact factor of 8.747. The study was supported by the Bio & Medical Technology Development Program of the National Reserach Foundation (NRF) grant, funded by the Korean Ministry of Science, ICT and Future Planning (MSIP).

More information: Sunsil Choi, Eun-Sun Kim, Ji-Eun Jung, et al. "PPAR-gamma antagonist Gleevec improves insulin sensitivity and promotes the browning of white adipose tissue". *Diabetes*. (2016).

Provided by Ulsan National Institute of Science and Technology