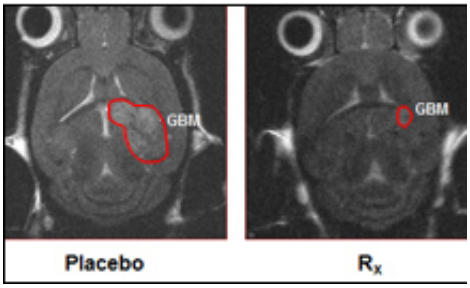
Researchers 'turn off' most notorious cancer-causing protein

December 2 2015



Mouse tumour

It's known as the most common cancer-causing protein, directly responsible for 30 per cent of all cancers and indirectly involved in virtually all cancers. For over 30 years, scientists have failed to successfully target it, but now researchers from U of T can turn this protein off with an experimental drug.

"For several decades, scientists have tried to turn off a protein called Ras," said Michael Ohh, a professor in the Faculty of Medicine's Department of Laboratory Medicine and Pathobiology. "But despite their efforts, we ultimately haven't seen much progress. In fact, it's been coined the 'undruggable' protein."

Normally, Ras promotes cell growth, but it can also cause uncontrolled cell growth when mutated or deregulated. As a result, this protein is a

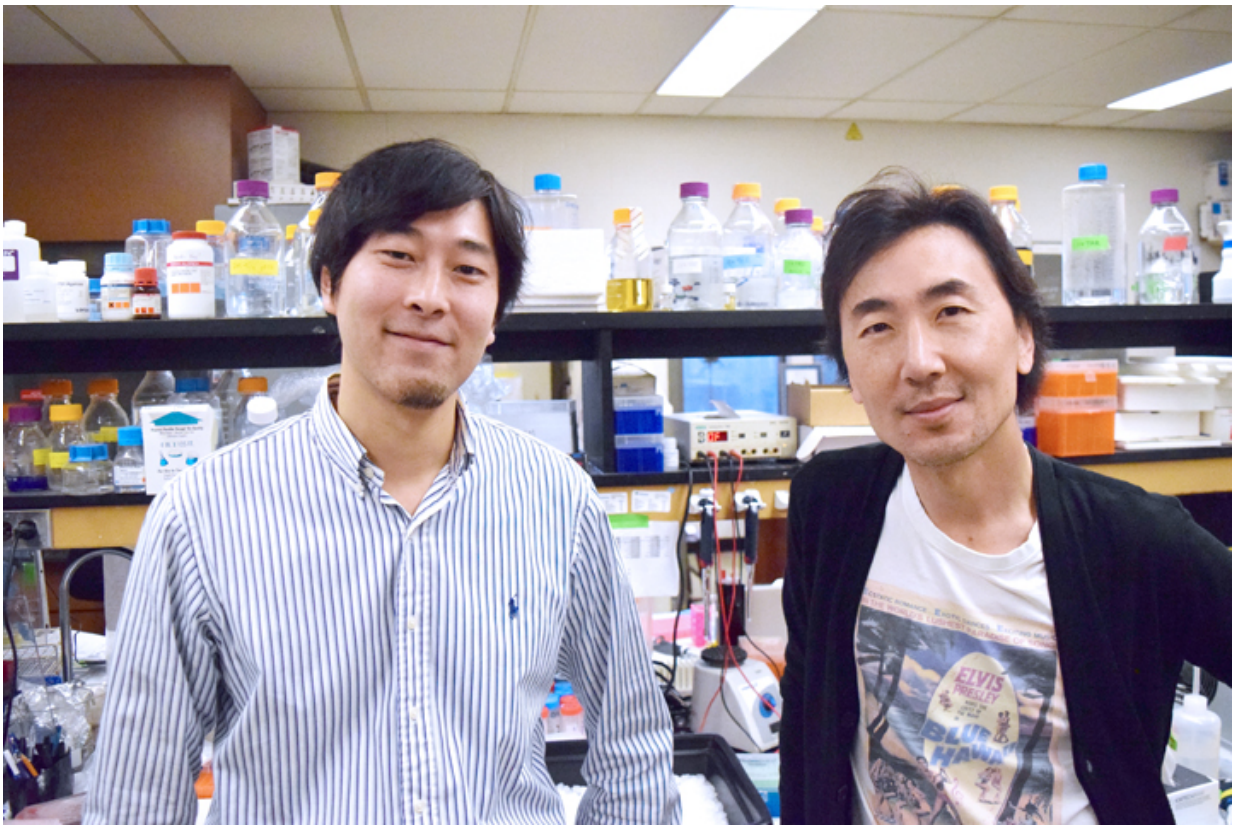
key player in many forms of cancer and is mutated in over 90 per cent of pancreatic tumours—one of the deadliest forms of cancer.

The researchers discovered that another protein, called SHP2, turns Ras off. "Our lab is known for another area of cancer biology. But on the request from a colleague, we entered the Ras field about five years ago to study mutations in a rare form of childhood leukemia," said Ohh. "We were surprised to find that nobody had identified SHP2 as a switch that regulates Ras that it could be targeted."

Working with researchers from Indiana University and Toronto's University Health Network, the team tested a SHP2 inhibitor on mice with glioblastoma, the most common and aggressive type of brain cancer. Remarkably, the inhibitor reduced these tumours by over 80 per cent.

"The inhibitors' results were incredible—we were shocked," said Ohh. "Nothing has had the same effect."

The researchers' findings were recently published in *Nature Communications*.



Dr. Yoshihito Kano (left) and Professor Michael Ohh

Next, the team will work with a cancer surgeon at the University of North Carolina to treat mice that have human pancreatic tumours. If the SHP2 inhibitor is effective, the

researchers will use this evidence to support future human clinical trials.

"In addition to being a researcher, I'm also a gastroenterologist and I see a lot of patients with pancreatic cancer," said Yoshihito Kano, co-author of the publication along with Severa Bunda, the primary author. "These patients usually die within one year, even with chemotherapy, so this drug could potentially change my patients' lives."

While their research is still in its early stages, Ohh and his team hope that their discovery will open up new perspectives in the field and potentially change cancer treatment.

"By better understanding how this cancer-causing protein works, we hope to target it much more precisely than before," said Ohh. "At the end of the day, we want other researchers to build on our fundamental discovery, providing more options for patients."

More information: Severa Bunda et al. Inhibition of SHP2-mediated dephosphorylation of Ras suppresses oncogenesis, *Nature Communications* (2015). DOI: 10.1038/ncomms9859

Provided by University of Toronto