CRISPR-Cas9 technique exploits pancreatic cancer cells' vulnerabilities to develop new treatments

November 22 2016, by Jef Ekins

Researchers at the University of Toronto have developed a process that dramatically cuts the amount of time it takes to create new cancer treatments. Using a new breakthrough technology, their study, published today in *Nature Medicine*, identified a new potential target for the treatment of a class of pancreatic cancer, and unveiled a new treatment option that exploits genetic faults to destroy cancer cells.

Associate Professor Stephane Angers and PhD student Zachary Steinhart from the Leslie Dan Faculty of Pharmacy, along with Drs. Jason Moffat and Sachdev Sidhu from the Donnelly Centre for Cellular and Biomolecular Research, the Department of Molecular Genetics, and the Centre for the Commercialization of Antibodies and Biologics, made this discovery using the cutting-edge CRISPR-Cas9 genome editing technology.

Using this revolutionary tool, the team of researchers probed the function of every single gene expressed by pancreatic cancer cells to determine that one of the receptors (Frizzled-5) is essential for the growth of mutant pancreatic cancer cells. Normally, the signaling pathways activated by Frizzled-5 tell cells when to divide, what types of cells to become, and when they should die. When mutated or deregulated, however, they can initiate tumour growth.

Having identified the key role that the Frizzled-5 receptor plays in

promoting pancreatic cancer growth, the team rapidly developed an antibody drug to inhibit the growth of these cells. The study showed that the antibody proved highly effective in killing the cancer cells in patient-derived samples and shrank tumours in mice without damaging the surrounding healthy cells.

Leveraging the Donnelly Centre's state-of-the-art platform for custom antibody design, the team was able to create a targeted antibody in months – a fraction of the time it would normally take to develop a safe and effective treatment for a specific cancer.

As part of this study, the team also explored the role of this receptor in colorectal cancer, a form of cancer that shares common features with pancreatic cancer. The results of this study indicate that Frizzled-5 may be a factor across multiple cancer types, broadening the potential use of anti-Frizzled-5 antibodies as a targeted cancer therapy.

"Ultimately, this study revealed genetic vulnerabilities in pancreatic cancer cells that could be exploited through the development of new targeted antibodies to inhibit tumor growth," noted Dr. Angers of the Centre for Pharmaceutical Oncology. "By targeting the exact signaling circuit activated in these tumors, these rapidly developed antibodies have shown considerable promise as a cancer treatment. Moreover, the state-of-the-art antibody development platform developed at U of T is a transformational leap forward in our ability to rapidly create exciting new treatments to combat various cancers."

More information: Zachary Steinhart et al. Genome-wide CRISPR screens reveal a Wnt–FZD5 signaling circuit as a druggable vulnerability of RNF43-mutant pancreatic tumors, *Nature Medicine* (2016). DOI: 10.1038/nm.4219

Provided by University of Toronto