New drug shows promise slowing tumor growth in some hard-to-treat cancers

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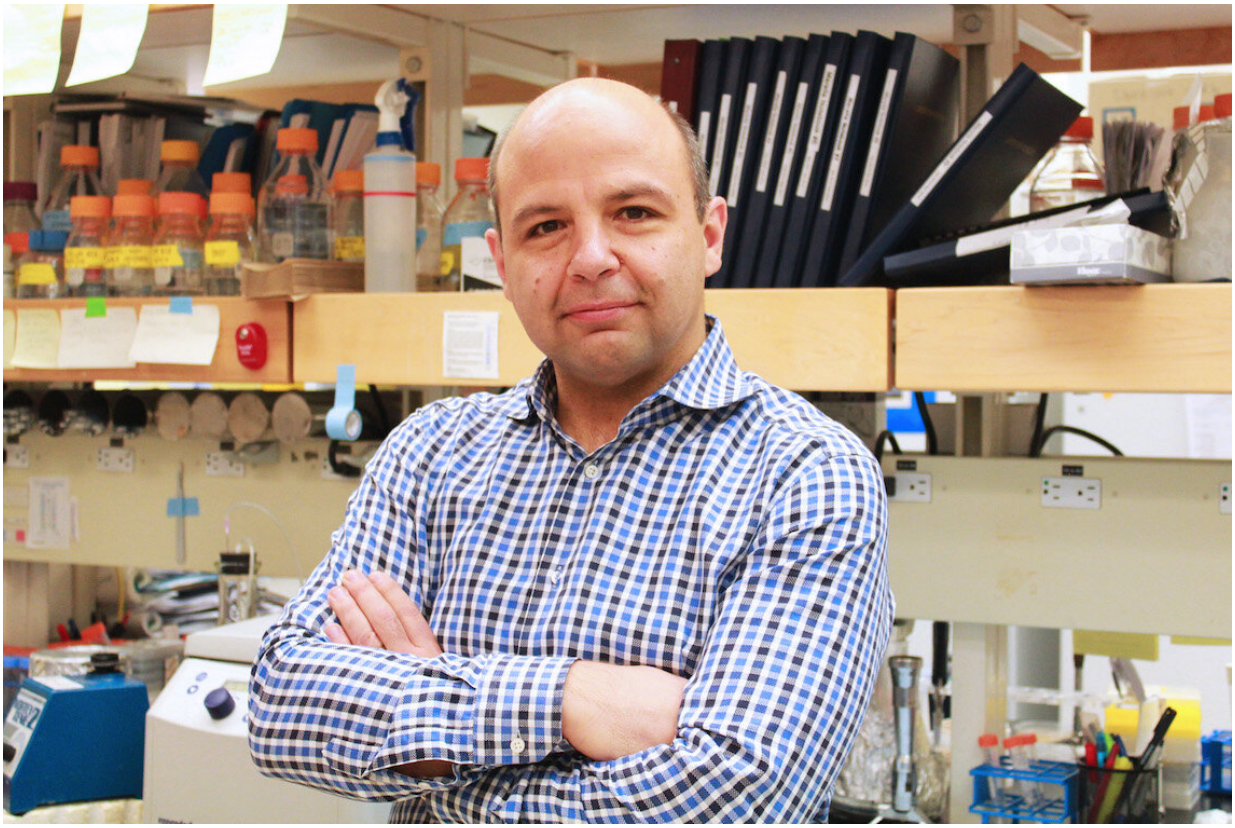

Daniel Durocher's lab designed a new drug with CRISPR-Cas9 gene-editing technology that blocks an enzyme essential for the survival of certain cancer cells (photo courtesy of Sinai Health

Scientists at Sinai Health and the University of Toronto say a new drug

designed to block an enzyme essential for the survival of certain cancer cells shows promise in curbing tumor growth.

The preclinical findings, published this month in the journal *Nature*, describe a new drug designed with CRISPR-Cas9 gene-editing technology in the lab of Daniel Durocher, a senior investigator at Sinai Health's Lunenfeld-Tanenbaum Research Institute (LTRI) and a professor of molecular genetics in U of T's Temerty Faculty of Medicine.

The researchers identified genes that are essential for the viability of CCNE1 amplified cancer cells, which are characteristic of some hard-to-treat ovarian, endometrial and bladder cancers. They found the enzyme PKMYT1 is essential in CCNE1 amplified cells, but not in otherwise healthy cells. In collaboration with precision oncology company Repare Therapeutics, the team developed a drug called RP-6306, which blocks PKMYT1 activity and effectively kills the cancer cell.

"These cancer cells depend on the PKMYT1 enzyme to survive," said Durocher. "Our preclinical data show enormous promise in the drug RP-6306's ability to target these types of tumors and profoundly inhibit tumor growth."

Currently, tumors with CCNE1 amplification have very few therapeutic options. David Gallo, a senior scientist at Repare Therapeutics, said they've been able to demonstrate that RP-6306 is both potent and selective for oral use in humans.

"Gynecological and other solid tumors with amplifications of CCNE1 are notoriously resistant to current standard-of-care treatments," said Gallo, co-first author on the Nature paper. "There is a dire need to find new options for these patients."

The work was a close collaboration between the Durocher lab and Repare Therapeutics. Durocher founded Repare Therapeutics in 2016 alongside Frank Sicheri, also a Lunenfeld-Tanenbaum Research Institute senior investigator who is a professor of molecular genetics and biochemistry at U of T.

The company is built on the concept of synthetic lethality, a process that incorporates functional genomics to discover genetic vulnerabilities to specific cancer mutations.

"This close collaboration between our group and Repare highlights how industry and academia can work together to discover new treatment options for cancer patients," said Durocher. "It's rare that a new target is published alongside a launched clinical trial. This speaks volumes about the innovative capacity of the LTRI and its collaborators."

Repare Therapeutics has initiated Phase I clinical trials in patients with CCNE1 amplified solid tumors, with initial results expected in late 2022.

More information: David Gallo et al, CCNE1 amplification is synthetic lethal with PKMYT1 kinase inhibition, *Nature* (2022). DOI: 10.1038/s41586-022-04638-9

Provided by University of Toronto

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