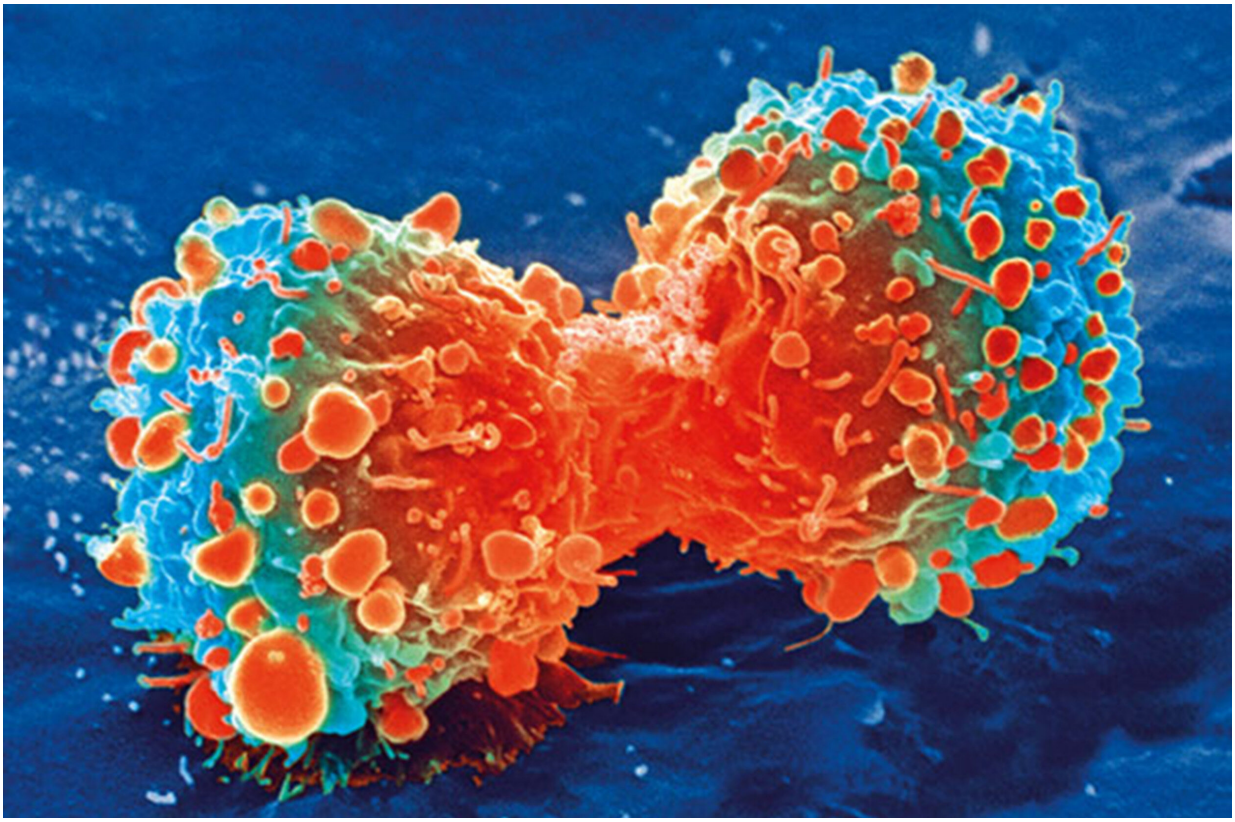
MedicalXpress

Combination of traditional chemotherapy, new drug kills rare cancer cells in mice

August 16 2017



Cancer cell during cell division. Credit: National Institutes of Health

An experimental drug combined with the traditional chemotherapy drug cisplatin, when used in mice, destroyed a rare form of salivary gland tumor and prevented a recurrence within 300 days, a University of

Michigan study found.

Called adenoid cystic carcinoma, or ACC, this rare cancer affects 3,000-4,000 people annually, and typically arises in the salivary glands. It's usually diagnosed at an advanced stage, is very resistant to therapy, and there's no cure. People may have read about ACC in the news lately, because elite professional runner Gabe Grunewald is currently undergoing her fourth round of treatment since her 2009 ACC diagnosis.

Typically, oncologists treat ACC tumors with surgery and radiation. They rarely use chemotherapy because ACC is extremely slow-growing, and chemotherapy works best on cancers where cells divide rapidly and tumors grow quickly, said Jacques Nör, a U-M professor of dentistry, otolaryngology and biomedical engineering, and principal investigator on the study.

The Nör lab treated ACC tumors with a novel drug called MI-773, and then combined MI-773 with traditional chemotherapy cisplatin. MI-773 prevents a molecular interaction that causes tumor cells to thrive by disarming the critical cancer fighting protein, p53.

Study co-author Shaomeng Wang, U-M professor of medicine, pharmacology and medicinal chemistry, discovered MI-773, which is currently licensed to Sanofi.

Researchers believe that blocking that interaction sensitized ACC cancer cells to cisplatin—a drug that under normal conditions, wouldn't work. When administered to the mice with ACC tumors, the cisplatin targeted and killed the bulk cells that form the tumor mass, while MI-773 killed the more resistant cancer stem cells that cause tumor recurrence and metastasis.

"This drug MI-773 prevents that interaction, so p53 can induce cell

death," Nör said. "In this study, when researchers activated p53 in mice with salivary gland cancer, the cancer stem cells died."

The key is that in many other types of cancer, p53 is mutated so it can't kill cancer cells, and this mutation renders the MI-773 largely ineffective. However, in most ACC tumors p53 is normal, and Nör said researchers believe this makes these tumors good candidates for this combined therapy.

Researchers performed two different types of experiments to test ACC tumor reduction and recurrence. First, they treated tumors in mice with a combination of MI-773 and cisplatin, and tumors shrank from about the size of an acorn to nearly zero.

In the second experiment, the acorn-sized tumors were surgically removed, and for one month the mice were treated with MI-773 only, with the hope of eliminating the cancer stem cells that fuel recurrence and metastasis.

"We did not observe any recurrence in the mice that were treated with this drug after 300 days (about half of mouse life expectancy), and we observed about 62 percent recurrence in the control group that had only the surgery," Nör said. "It's our belief that by combining conventional chemotherapy with MI-773, a drug that kills more cancer stem cells, we can have a more effective surgery or ablation."

One limitation of the study is that it's known that about half of all ACC tumors recur only after about 10 years, and this observational period was only 300 days.

In a typical metastasis, the cancer cells spread through the blood to other parts of the body. But ACC cancer cells like to move by "crawling" along nerves, and it's common for ACC tumor cells to follow the

prominent facial nerves to the brain—picture a mountain climber ascending a rope—where it's often fatal.

Research is still too early-stage to know how humans will respond, and the drug will work primarily in tumors where p53 is normal. If p53 is mutated, which is fairly common in other tumor types, this drug won't work as well, Nör said.

The work was funded by the Adenoid Cystic Carcinoma Research Foundation, U-M and the National Institutes of Health.

The study, "Therapeutic Inhibition of the MDM2-p53 interaction prevents recurrence of adenoid cystic carcinomas," appeared earlier this year in the journal *Clinical Cancer Research*.

More information: Felipe Nör et al. Therapeutic Inhibition of the MDM2–p53 Interaction Prevents Recurrence of Adenoid Cystic Carcinomas, *Clinical Cancer Research* (2016). DOI: 10.1158/1078-0432.CCR-16-1235

Provided by University of Michigan