

Targeted chemotherapy kills all tumor cells in preclinical research

Zen Logsdon | Aug 07, 2023
Patient Stories Research

A cancer-killing pill targeting the PCNA protein appears to have destroyed solid tumor cells in recent preclinical research. Read how it works and next steps

Could a new molecule targeting a protein called PCNA help scientists develop a cancer-stopping pill? New preclinical research suggests it may be possible.

Researchers aimed at a protein once thought to be too challenging for targeted therapy, proliferating cell nuclear antigen (PCNA). They developed a chemotherapy called AOH1996 to specifically target that protein, which appears to destroy all solid tumor cells in preclinical research. The early outcomes of the research conducted by City of Hope scientists were published on Aug. 1 in the journal [Cell Chemical Biology](#).

Testing Drug in Humans

As the scientists continue to investigate the foundational mechanisms that make this cancer-stopping pill work in animal models, they note that there is an ongoing Phase 1 clinical trial testing the therapeutic in humans.

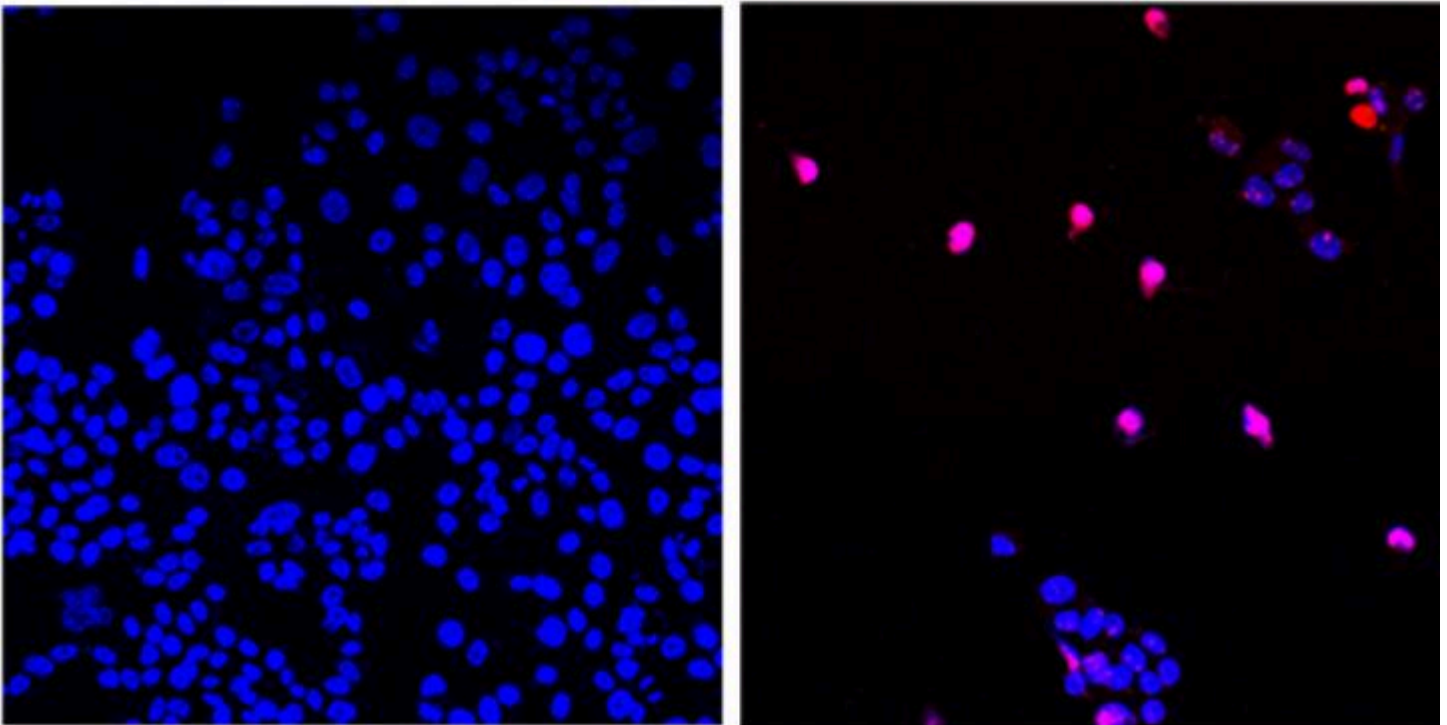


Linda Malkas, M.D.

Most targeted therapies focus on a single pathway, which enables wily cancer to mutate and eventually become resistant, said [Linda Malkas](#), Ph.D., professor in City of Hope's Department of Molecular Diagnostics and Experimental Therapeutics and the M.T. & B.A. Ahmadinia Professor in Molecular Oncology. However, the cancer-killing pill Malkas has been developing over the last two decades, [AOH1996](#), targets a cancerous variant of PCNA, a protein that in its mutated form is critical in DNA replication and repair in all expanding tumors.

“PCNA is like a major airline terminal hub containing multiple plane gates. Data suggests PCNA is uniquely altered in cancer cells, and this fact allowed us to design a drug that targeted only the form of PCNA in cancer cells. Our cancer-killing pill is like a snowstorm that closes a key airline hub, shutting down all flights in and out only in planes carrying cancer cells,” said Malkas, senior author of the new study. “Results have been promising. AOH1996 can suppress tumor growth as a monotherapy or combination treatment in cell and animal models without resulting in toxicity. The investigational chemotherapeutic is currently in a Phase 1 clinical trial in humans at City of Hope.”

AOH1996 has been effective in preclinical research treating cells derived from breast, prostate, brain, ovarian, cervical, skin and lung cancers and is exclusively licensed by City of Hope to RLL, LLC, a biotechnology company that Malkas co-founded and holds financial interest in.



City of Hope-developed small molecule AOH1996 targets a cancerous variant of the protein PCNA. In its mutated form, PCNA is critical in DNA replication and repair of all expanding tumors. Here we see untreated cancer cells (left) and cancer cells treated with AOH1996 (right) undergoing programmed cell death (violet). (Photo credit: City of Hope)

Scientists tested AOH1996, a small molecule PCNA inhibitor, in more than 70 cancer cell lines and several healthy control cells. They found that AOH1996 selectively kills cancer cells by disrupting the normal cell reproductive cycle. It targets something called transcription replication conflicts, which occur when mechanisms responsible for gene expression and genome duplication collide.

The study authors found that investigational therapy prevented cells with damaged DNA from dividing and from making a copy of their faulty DNA, which is what causes cancer to grow and spread. As a result, AOH1996 caused cancer cell death (apoptosis), but it did not interrupt the reproductive cycle of healthy stem cells.

Targeted Cancer Treatment

“No one has ever targeted PCNA as a therapeutic because it was viewed as ‘undruggable,’ but clearly City of Hope was able to develop an investigational medicine for a challenging protein target,” said [Long Gu](#), Ph.D., lead author of the study and an associate research professor in the Department of Molecular Diagnostics and Experimental Therapeutics at Beckman Research Institute of City of Hope.

“We discovered that PCNA is one of the potential causes of increased nucleic acid replication errors in cancer cells,” Gu said. “Now that we know the problem area and can inhibit it, we will dig deeper to understand the process to develop more personalized, targeted cancer medicines.”

During experiments, the study authors found that the investigational pill made cancer cells more susceptible to chemical agents that cause DNA or chromosome damage, such as the chemotherapy drug cisplatin. This may suggest that AOH1996 could become a useful tool in combination therapies as well as for the development of new chemotherapeutics.

“City of Hope has world leaders in cancer research. They also have the infrastructure to drive [translational drug discovery](#) from the laboratory into the clinic for patients in need,” said [Daniel Von Hoff](#), M.D., study co-author and a distinguished professor at Translational Genomics Research Institute, part of City of Hope.

The researchers are now aiming to better understand the mechanism of action to further improve the ongoing clinical trial in humans.