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"Holy grail" molecule kills all types of solid cancer tumors

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A team of scientists at the City of Hope Hospital – one of the largest cancer research and treatment organizations in the United States – has recently developed what could potentially be a “holy grail” molecule that can effectively eradicate all solid cancer tumors while leaving healthy cells unaffected.

In preclinical trials, this molecule – called AOH1996 – was found to target and eradicate the proliferating cell nuclear antigen (PCNA) protein, which usually contributes to the growth and repair of a variety of cancer tumors.

Studying the cancer killing molecule

Most of the previous targeted anti-cancer therapies focus on a single pathway, enabling cancers to mutate and eventually become resistant. By contrast, since AOH1996 targets a cancerous variant of PCNA, a protein that in its mutated form is crucial in DNA replication and repair of all types of tumors, its effectiveness is higher and its range of action significantly broader.

“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 senior author Linda Malkas, a professor of Molecular Diagnostics and Experimental Therapeutics at City of Hope.

“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.”

What the researchers discovered

By testing AOH1996 in over 70 cancer cell lines and several normal control cells, Malkas and her team found that this molecule selectively kills cancer cells by disrupting the normal cell reproductive cycle.

More specifically, it targets the so-called “transcription replication conflicts” which occur when mechanisms responsible for gene expression and genome duplication collide.

By preventing cells with damaged DNA from dividing in the G2/M phase and making a copy of faulty DNA in S phase, this molecule leads to cancer cell death (apoptosis), but does not affect the reproductive cycle of healthy stem cells.

Highly effective treatment

The preclinical studies found it highly effective in treating cells derived from breast, prostate, brain, ovarian, cervical, skin, and lung cancers.

“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 lead author Long Gu, an associate research professor in the Department of Molecular Diagnostics and Experimental Therapeutics at the 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. 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.”

World leaders in cancer research

Since experiments have also shown that AOH1996 made cells more susceptible to chemical agents causing DNA or chromosomal damage (such as the chemotherapy drug cisplatin), this groundbreaking molecule could become a useful tool in combination therapies, as well as for the future development of novel 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 study co-author Daniel Von Hoff, a professor of Translational Genomics at City of Hope.

This institute’s groundbreaking translational research includes the development of the technology underlying synthetic human insulin (a major breakthrough in the management of diabetes), and of monoclonal antibodies that play a major part in widely used cancer drugs such as trastuzumab, rituximab, and cetuximab.

In future research, the scientists aim to clarify the AOH1996’s mechanisms of action to further improve the ongoing clinical trials in humans. Individuals interested to participate in the Phase 1 clinical trial can review the eligibility requirements at clinicaltrials.gov and, if eligible, call 626-218-1133 or visit City of Hope’s clinical trials webpage.

The study is published in the journal *Cell Chemical Biology*.

More about PCNA

Proliferating Cell Nuclear Antigen (PCNA) is a fundamental protein that performs an essential role in DNA replication and repair within eukaryotic cells. Known as the ‘DNA clamp,’ it plays a pivotal part in cell proliferation and DNA repair, safeguarding genomic stability and integrity.

Structure

The structure of PCNA is trimeric and ring-like. This enables it to encircle DNA and act as a scaffold during replication and repair processes.

Each of the three identical subunits combines to form this distinct ring-shaped structure with a central cavity. This central channel allows the DNA strand to pass through, offering an efficient setup for the replication and repair machinery.

Function

PCNA is a key player in the DNA replication process where it serves as a processivity factor for DNA polymerase δ and ε, essentially acting as a sliding clamp. This role enhances the capacity of the polymerases to synthesize long fragments of DNA without dissociating from the template strand.

In addition to DNA replication, PCNA partakes in the DNA repair process and cell-cycle regulation. Its interaction with proteins involved in the cell cycle, such as cyclins and cyclin-dependent kinases, is crucial for controlling cell division and ensuring genomic stability.

During DNA damage events, PCNA coordinates with various DNA repair enzymes to enable accurate and effective repair.

PCNA and cancer

The significance of PCNA in cell proliferation naturally implicates it in conditions characterized by abnormal cell growth, such as cancer. High levels of PCNA often accompany a wide range of cancers.

They act as an indicator of unregulated cell proliferation and signifying a poor prognosis. Therefore, researchers frequently use PCNA as a biomarker for cancer progression and patient outcomes.

PCNA as a therapeutic target

The central role of PCNA in cell proliferation and DNA repair has led scientists to investigate its potential as a therapeutic target.

The focus of ongoing research is to develop inhibitors that can block the functionality of PCNA. This would put a stop to unchecked cell division characteristic of cancerous growth.

While these investigations are in the early stages, the potential for PCNA-targeted therapies promises significant advancements in cancer treatment strategies.

PCNA is a crucial player in various cellular processes, most notably DNA replication and repair. Its critical involvement in cell cycle regulation and its associations with cancer make it a significant focus of numerous scientific studies.

Future breakthroughs in understanding PCNA’s role and ways to manipulate its functionality may lead to significant advancements in cancer treatment and other fields of biomedical research.