Research

How a drug derived from an antiparasitic might combat blood cancer

by Angus Liu | Oct 22, 2020 9:55am

Scientists at the University of Alberta found an NMT inhibitor derived from an antiparasitic drug cleared blood cancer in mice. (PDPics/Pixabay)

Cancer cells rely on different signaling pathways to promote their survival. Now, scientists at the University of Alberta have promising preclinical evidence that a new drug could work in blood cancers by targeting B-cell signaling.

The compound, called PCLX-001, led to significant tumor regression in mouse models, including completely clearing out lymphoma that had stopped responding to the standard therapies CHOP and Roche's Rituxan, according to results published in **Nature Communications**.

PCLX-001 is an inhibitor of the enzyme NMT. Because NMTs are essential for the viability of parasites, small-molecule NMT inhibitors have been developed. PCLX-001 is derived from such a drug, which is being studied for treating African sleeping sickness.

NMTs have also been proposed as anti-cancer targets because their expression is often increased in cancer cells. In the current study, the University of Alberta team screened PCLX-001 against 300 cells lines and found that the drug inhibits growth at far higher levels in blood cancers like lymphoma, leukemia and myeloma than it does in other cancer cell types.

How does the drug work?

In humans, NMTs mediate myristoylation, a process by which the fatty acid myristate is added to proteins. This cellular process is important, as it allows proteins to interact with cell membranes and become part of the cell signaling system.

Blood cancers have fewer copies of NMTs, making them more sensitive to PCLX-001, the team found. As a result, the drug affects myristoylation in malignant lymphoma cells more so than it does in normal B cells.

PCLX-001 is a potent inhibitor of B-cell receptor (BCR) signaling, which is a main pathway lymphoma cells leverage to avoid normal programmed cell death. PCLX-001 reduced the levels of Src-family tyrosine kinases (SFKs), as well as other downstream BCR signaling proteins, the team found.

The drug's ability to suppress BCR signaling appeared superior to that of Bristol Myers Squibb's SFK inhibitor Sprycel and Johnson & Johnson and AbbVie's BTK inhibitor Imbruvica, according to the scientists.

In testing PCLX-001's effect in two mouse models of lymphoma, the researchers found that it significantly reduced tumor cell growth, including inducing complete remission when given at a high dose. In addition, in the models of diffuse large B-cell lymphoma that was refractory to common regimens CHOP, RICE and DHAP, the high-dose drug also led to complete tumor regression in six of eight mice, the team reported.

RELATED: New insights into cancer cell escape mechanisms could boost immuno-oncology treatments

Scientists have been investigating pro-survival signaling in cancer cells for inspiration in developing new therapies. A group of Chinese researchers recently found that Merck's AKT inhibitor MK-2206 blocked the Wnt and EGF signaling pathways, which are responsible for activating a gene that contributes to the crippling of the immune system's T cells.

A Spanish research team identified a non-coding RNA called ALA-1, which is upregulated in lung cancer and reduces signals that activate cancer-killing immune cells.

Luc Berthiaume, the senior author of the new study on PCLX-001, hopes Pacylex will move the drug into clinical testing by the end of this year. "We think PCLX-001 is a compound with a large therapeutic window that can kill the cancer cells at a much lower concentration than what is needed to kill normal cells," he **said** in a statement.

Read More On

non-Hodgkin lymphoma lymphoma blood cancer leukemia B cells academic research

Pacylex Pharmaceuticals University of Alberta Merck

About the Author

Angus Liu
Associate Editor