Researchers develop new potential drug for rare leukemia

30 March 2015

Tomasz Cierpicki, Ph.D., and Jolanta Grembecka, Ph.D. at the University of Michigan. Credit: University of Michigan Health System

Researchers at the University of Michigan Comprehensive Cancer Center have developed a new drug that shows potential in laboratory studies against a rare type of acute leukemia. And additional studies suggest the same compound could play a role in prostate cancer treatment as well.

The compound was developed in the labs of Jolanta Grembecka, Ph.D., and Tomasz Cierpicki, Ph.D., who have been working for several years to identify a small-molecule inhibitor that would block the interaction between the protein menin and MLL fusion proteins that cause a rare type of acute leukemia.

So-called MLL fusion leukemia can occur in both adults and children. It represents up to 10 percent of acute leukemia in adults, and about 70 percent of acute leukemia in infants. Current treatments are not very effective, with just over a third of patients surviving five years.

Protein-protein interactions such as the menin-MLL fusion protein interactions in leukemia are generally considered "undruggable," meaning it can be particularly challenging to develop drugs that target those interactions. Despite the difficulty, Grembecka says that the MLL-menin interaction remained tempting.

"In many types of cancer, you see multiple interactions and mutations that trigger the cancer. The MLL-menin interaction is a good drug target because it's the primary driver in this type of leukemia. By blocking this interaction, it's very likely to stop the cancer," says Grembecka, assistant professor of pathology at the University of Michigan Medical School.

In a study published in *Cancer Cell*, the researchers tested two compounds they developed, MI-463 and MI-503, in cell lines and in mice with MLL leukemia. They found the compounds blocked the MLL-menin interaction without harming normal blood cells. The compounds were delivered into the blood and metabolized at a good rate, both of which are key issues in developing new drugs.

The researchers had previously tested an earlier version of the compound, which showed promise. Here, they substantially improved the drug's potency and many of its pharmacologic properties, making it more attractive for potential use in humans.

"Against all odds, we decided to explore finding a way to block the MLL-menin interaction with small molecules. From nothing, we have been able to identify and greatly improve a compound and show that it's got valuable potential in blocking MLL fusion leukemia in animal models," says Cierpicki, assistant professor of pathology at the U-M Medical School.

Meanwhile, prostate cancer researchers at U-M discovered that menin and MLL play a role in

androgen receptor signaling, which is a key driver of prostate cancer. In a study published in *Nature Medicine*, the researchers tested the same MLL-menin inhibitors against castration resistant prostate cancer cells and mice models.

"Our study suggests that this MLL-menin inhibitor might also have a potential role in a more common solid tumor, in this case prostate cancer," says Arul M. Chinnaiyan, M.D., Ph.D., director of the Michigan Center for Translational Pathology and the senior author on the *Nature Medicine* paper.

The compounds must be tested further in the laboratory before any clinical trials could be considered. Grembecka and Cierpicki's labs are looking at further refinements and more advanced testing of their inhibitors. Chinnaiyan's team will continue to investigate the role of MLL in castration resistant prostate cancer.

No treatments or trials are currently available using an MLL-menin inhibitor. To learn more about available treatment options or clinical trials for MLL leukemia or prostate cancer, call the Cancer AnswerLine nurses at 800-865-1125.

More information: Targeting the MLL complex in castration-resistant prostate cancer, DOI: 10.1038/nm.3830

Provided by University of Michigan Health System