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Researchers identify a 'life-and-death' molecule on chronic leukemia cells

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A new study has identified a life-and-death signaling role for a molecule on the surface of the immune cells involved in the most common form of chronic leukemia. The finding could lead to more effective therapy for chronic lymphocytic leukemia (CLL), an as yet incurable cancer that occurs in more than 16,000 Americans annually.

The study, led by researchers at the Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James), examines how an experimental drug called SMIP-016 kills CLL cells.

Earlier work by the same researchers showed that the drug targets a molecule called CD37, which is found on the surface of CLL cells. In this new study, the researchers discovered that the CD37 molecule has two regions that can concurrently activate two separate pathways in CLL cells, one that leads to cell death and another that promotes cell survival.

The findings show SMIP-016 activates the "death" part of the molecule, and they suggest that blocking the "survival" part of the molecule could improve the drug's effectiveness, the researchers say.

The study is published in the May issue of journal *Cancer Cell*.

"These findings open new possibilities for the use of immune-based therapy for treating CLL," says principal investigator Dr. John Byrd, a CLL specialist and professor of Medicine, of Medicinal Chemistry and

of Veterinary Biosciences.

"We are already targeting the cell-death pathway using SMIP-016, and we might be able to optimize the drug's effectiveness by simultaneously blocking the cell-survival region of the molecule with a second antibody," he says.

Byrd notes that drugs that can block the cell-survival pathway already exist.

"We were very surprised and excited to find that CD37 is directly involved in regulating survival and cell-death pathways," says first author Rosa Lapalombella, a research scientist in Byrd's laboratory. "That's not usually the case for molecules of this kind."

Co-principal investigator Dr. Natarajan Muthusamy, associate professor of Medicine, notes that CD37 belongs to a family of molecules called tetraspanins, which usually only facilitate signaling by bringing together other molecules that when combined issue signals.

"This work is a great example of collaborative research involving several laboratories," says researcher and co-principal investigator Dr. Michael Freitas, associate professor of molecular virology, immunology and medical genetics, whose laboratory contributed to the global proteomic work of how CD37 signals. "The support for, and emphasis on, team science is a major driving strength of Ohio State and contributed to this project's findings," he says.

Byrd hopes to begin a clinical trial soon that tests SMIP-016 combined with a drug that blocks the survival pathway.

"Overall, these findings reinforce our belief SMIP-016 could be an effective agent for treating CLL and other malignancies that sometimes

express the CD37 protein, including non-Hodgkin's lymphoma and acute lymphoblastic leukemia," says Byrd, who is the D. Warren Brown Chair of Leukemia Research.

Provided by Ohio State University Medical Center