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New hybrid treatment forces cancer cells to starve

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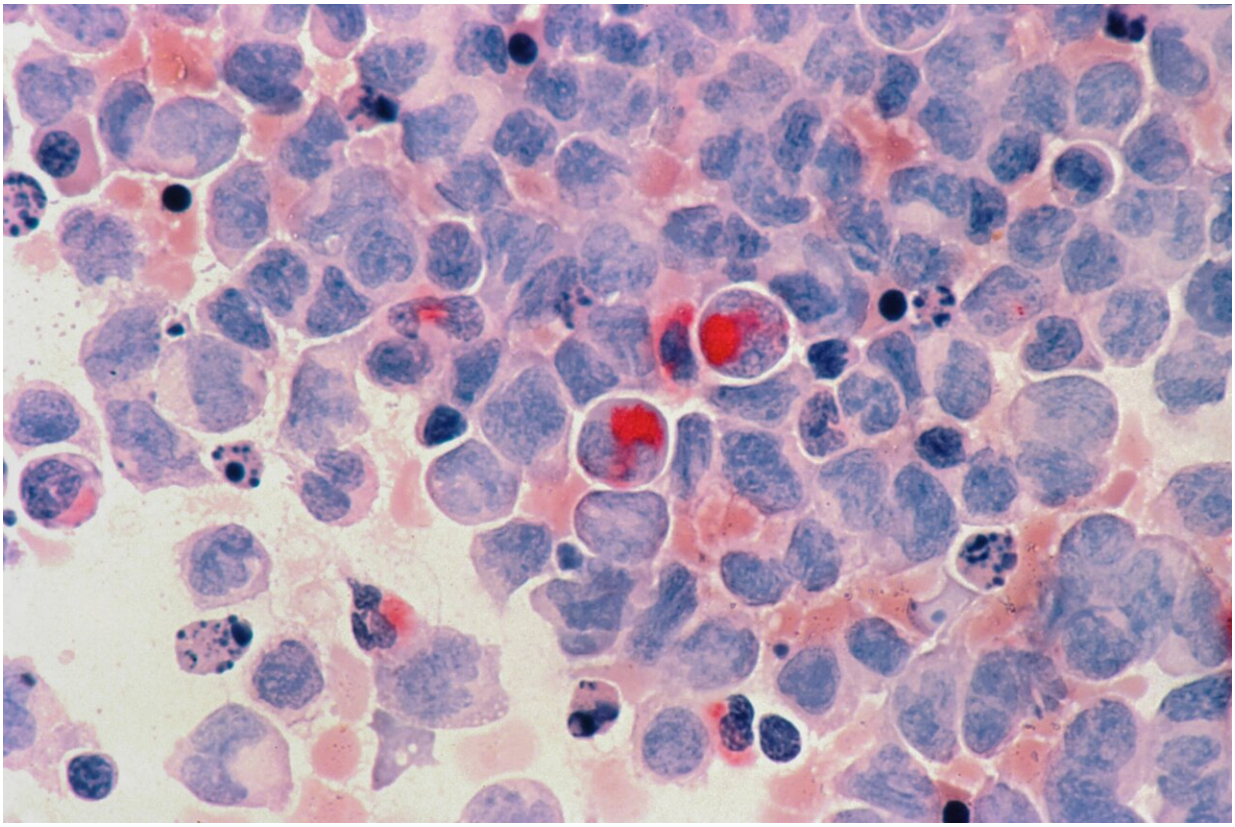

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The combination of a drug and a protein fragment prevents the growth of blood cancer cells, a new study in mice shows.

The work addressed multiple myeloma, a cancer that forms in blood cells that normally fight infections by making proteins that remove germs. The cancerous cells build up in bone marrow, crowding out healthy blood cells and making faulty proteins. There might be no symptoms at first, but many patients later experience bone pain, nausea, brain fog, fatigue, or infections.

In about half of multiple myeloma cases, changes in the DNA of the RAS gene—which encodes a switch that regulates growth—cause the related RAS protein to become "stuck in the on mode" and cause cancer, researchers say.

Currently, there are no effective treatments for multiple myeloma when patients relapse, a setting where genetic changes (mutations) in RAS become more common. This includes attempts to directly counter abnormal RAS function, which has moved the field to explore other ways of targeting RAS tumors.

Along these lines, RAS mutations also turn up a cellular pathway called macropinocytosis, which normally engulfs nutrients like proteins and fats outside of cells and pulls them inside, where they can be used as extra metabolic fuel. Cancer cells cannot multiply without these supplies, and those with RAS mutations become uniquely capable of this type of scavenging, the study authors say.

Led by researchers at NYU Grossman School of Medicine and Tezcat Biosciences, the new study found that a carefully chosen protein called a monobody, linked to a drug called MMAE that prevents cells from multiplying, was together pulled inside the cancer cells to stop abnormal growth in both cell tests and in live animals with the disease.

"Our new approach targets cancers that have been very hard to treat," said study first author Nathan Beals, Ph.D., a post-doctoral researcher in

the Department of Biochemistry and Molecular Pharmacology at NYU Langone Health. "We are taking advantage of a process that is significantly overactive in cancer cells, which focuses the treatment effect on abnormal cells."

Presented as an oral abstract on December 9 at the 2023 annual meeting of the American Society of Hematology (ASH) in San Diego, the new work was based in part on monobodies, a class of compounds originally invented by NYU Langone faculty member Shohei Koide, Ph.D. and colleagues in 1998.

The current research team designed a monobody with a simple protein framework that is engulfed by cancer cells with RAS mutations.

Once taken into cancer cells via mutant RAS-induced macropinocytosis, the monobody-MMAE conjugate blocked the action of cell skeleton components (microtubules) and so kept the cancer cells from dividing and multiplying.

Studies in isolated, human, RAS-mutant multiple myeloma cells showed that they have continual macropinocytosis underway, whereas normal cells do not. A cell-tracking technology then showed that the study monobody was taken up through macropinocytosis at a high level into multiple myeloma cells but did not enter cells when the process was not underway. Once inside, the conjugate caused up to a five-fold increase in the death of RAS cancer cells when compared to normal cells.

In studies in live mice with mutant RAS multiple myeloma tumors, treatment with the conjugate at a relatively lower (sub-optimal) dose resulted in a roughly six-fold decrease in tumor size after 21 days, while control tumors showed no significant difference in tumor volume. In a subsequent study, a larger dose of the conjugate killed mutant RAS tumors, with no relapses over 60 days, in a "dramatic improvement" over

standard care options, the authors said.

In addition, improved outcomes were seen when the conjugate was used in combination with standard anti-cancer treatments, enabling them to be effective at lower doses (with the potential for fewer side effects).

"Our conjugate improved survival in early tests and has the potential to be important clinically against multiple myeloma," said study senior author Dafna Bar-Sagi, Ph.D., senior vice president, vice dean for science, and chief scientific officer at NYU Langone.

Provided by NYU Langone Health