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Novel compound prevents metastasis of multiple myeloma in mouse studies

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In an advance against the problem of cancer metastasis, Dana-Farber Cancer Institute scientists have shown that a specially developed compound can impede multiple myeloma from spreading to the bones in mice. The findings, published in the Sept. 25 issue of *Cell Reports*, suggest the technique can protect human patients, as well, from one of the most deadly aspects of cancer.

The research involves a new approach to the challenge of cancer metastasis, the process by which tumors spread to and colonize distant parts of the body. Whereas research has traditionally focused on cancer cells themselves, scientists are increasingly studying the interactions between tumor cells and the tissues around them – the so-called microenvironment. In the current study, researchers explored why errant myeloma cells often settle in bones, and whether the bones could be made less hospitable to such malignant homesteading.

"While cure and survival rates have increased for many types of cancers in recent decades, most of these gains have been made in patients with primary cancers – cancers that have not spread beyond their initial site," said the study's senior author, Irene Ghobrial, MD, of Dana-Farber's Center for Hematologic Oncology. "Metastasis remains one of the most formidable complications we face as cancer researchers and physicians. Improvements in the treatment of metastatic cancers have, for the most part, not been nearly as dramatic as in primary disease."

The current study focused on multiple myeloma because it is metastatic

by nature. Myeloma cells originate in the bone marrow, depart for the bloodstream, and eventually return to the bones, where they form numerous colonies – hence the name multiple myeloma.

Ghobrial and her team knew that a substance called stromal cell-derived factor-1 (SDF-1) is a kind of protein pied piper, attracting certain cells to new locations within the bone marrow. They found that mice with advanced stages of myeloma had sharply higher levels of SDF-1 at the sites in the bones where metastasis had occurred.

"We reasoned that by neutralizing SDF-1, we could change the bone marrow environment to make it less receptive for multiple myeloma cells, reduce myeloma cells' affinity for the marrow, and thereby inhibit the progression of the disease," said Aldo Roccaro, MD, PhD, the study's co-first author with Dana-Farber colleague Antonio Sacco, RN.

Working with the German biotechnology company NOXXON Pharma, the researchers tested a substance – called olaptesed pegol (a PEGylated mirror-image L-oligonucleotide) – that binds tightly and specifically to SDF-1. Laboratory experiments suggested that olaptesed pegol blocks the activity of SDF-1, making it a less alluring signal for tumor cells. In mice, the researchers found that olaptesed pegol alters the bone marrow, rendering it uninviting to myeloma cells. The result was a slowing of the disease progression and a prolonged survival of the animals.

It isn't completely clear what becomes of the blood-borne myeloma cells that are prevented from metastasizing to the bones, the researchers said. "We know that myeloma cells can't survive for long if they're circulating in the blood and can't adhere to other tissue," Ghobrial remarked. "We saw no evidence that they had metastasized and begun to grow in other tissue, either.

"Our findings clearly document a therapeutic effect of olaptesed pegol in

a mouse model of advanced myeloma," Ghobrial continued. "It is now being tested in a clinical trial of multiple myeloma patients, with more trials to come."

Provided by Dana-Farber Cancer Institute

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