Towards more effective treatment for multiple myeloma

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A new study from SUNY Downstate Medical Center in Brooklyn, New York, shows that MAL3-101, a recently developed inhibitor of the heat shock protein 70 (Hsp70), appears to have potent anti-tumor effects on multiple myeloma, a bone marrow cancer. Despite aggressive modes of treatments, myeloma ultimately remains incurable. The disease has a high incidence in the communities served by SUNY Downstate.

The findings, published in a recent issue of *Journal of Oncology*, are the result of a collaborative effort among researchers working in the laboratory of Olcay Batuman, MD, at Downstate; scientists at the University of Pittsburgh, where the small molecule inhibitor MAL3-101 was developed; scientists at the University of California at San Francisco; and other collaborators at SUNY Downstate.

Multiple myeloma is characterized by an accumulation and expansion of neoplastic plasma cells in the bone marrow. Normally, these white blood cells manufacture the antibodies needed to fight infection. When plasma cells become cancerous, however, they invade the bone marrow and the skeleton, and the immune system is severely compromised. Skeletal fragility, fatigue, weight loss, kidney failure, and repeated infections are common key manifestations and causes of morbidity and mortality from multiple myeloma. The risk for developing this disease increases with age.

"Currently multiple myeloma remains an incurable disease, despite the use of stem cell transplants, high-dose chemotherapy, and radiation,"

explains Dr. Batuman, professor of medicine and cell biology at Downstate and head of the research team that conducted the study. "New treatment modalities are urgently needed," she says.

The study aimed to explore the cytotoxic effects of MAL3-101 on multiple myeloma tumor growth. The researchers found that MAL3-101 exhibited anti-myeloma effects both in vitro and in vivo on tumor cell lines, as well as on primary tumor and endothelial cells from patients. When used in animal studies with the proteasome inhibitor bortezomib, MAL3-101 significantly boosted its anti-myeloma effects. Dr. Batuman's team found that by targeting Hsp70 activity, the dosage of synergic agents such as bortezomib could be reduced without compromising their effectiveness. The ability to reduce dosage makes it possible to continue the use of drugs that are toxic at higher concentrations. The addition of new synergistic agents also enriches the treatment arsenal by reducing drug resistance.

"The results of our study are very encouraging," says Dr. Batuman. "While this is not a cure and it will be some time before the compound is developed as a drug, we believe that MAL3-101, when used synergistically with existing therapies, could reduce overall drug concentrations and avoid treatment resistance."

Dr. Batuman adds, "It is possible to speculate that MAL3-101 may also modulate development of the multiple myeloma cancer stem cell. The relapse of multiple myeloma in patients in whom complete remission had been achieved is currently thought to indicate the presence of treatment-resistant multiple myeloma cancer stem cells. At Downstate, a group effort is now geared towards identifying and targeting these cancer stem cells in multiple myeloma. The anti-myeloma effects of MAL3-101 could include inhibition of cancer stem cell development, since the Hsp-70 function is required in early plasma cell development. Our prediction is that antagonism of the Hsp-70 chaperone or

chaperones by affecting non-redundant pathways could be effective in multiple myeloma treatment."

Provided by SUNY Downstate Medical Center