

## Compound from marine bacteria shows potential as multiple myeloma therapy

Kills blood cancer cells with low toxicity in preclinical studies

11/14/2005 An anti-cancer compound derived from bacteria dwelling in ocean-bottom sediments appears in laboratory tests to be a potent killer of drug-resistant multiple myeloma cells, and potentially with less toxicity than current treatments, report Dana-Farber Cancer Institute researchers in the November issue of *Cancer Cell*.

The experimental compound, NPI-0052, has been found to block or inhibit cancer cells' proteasomes from working effectively. The proteasome work as a cell's "garbage disposal," chewing up and disposing of old, unwanted proteins. With their proteasome jammed, cells die from the backup of damaged proteins.

"Proteasome inhibition is a key therapeutic target and bortezomib (Velcade tm) was the first in a new class of compounds in multiple myeloma. NPI-0052 is a novel proteasome inhibitor with a chemical structure and action that is distinct from bortezomib, and has the promise of being even more effective for patients," says Kenneth Anderson, MD, director of the Jerome Lipper Multiple Myeloma Center at Dana-Farber, and senior author of the report.

The compound will be moved into Phase I clinical trials in early 2006, say officials of Nereus Pharmaceuticals in San Diego, the developer of NPI-0052. The compound will be tested as a single agent and subsequently in combination with other treatments.

Multiple myeloma is a currently incurable cancer of the bone marrow that causes a plunge in the production of vital red and white blood cells. Although relatively rare, it is the second most common type of blood cancer and accounts for 11,000 deaths annually in the United States. Bortezomib, approved by the Food and Drug Administration in 2003 for relapsed myeloma patients and subsequently for patients who have received at least one prior treatment, demonstrated in clinical trials that it extended the time to disease progression and also improved survival.

Though less toxic than conventional chemotherapy, bortezomib does have significant side effects in some myeloma patients, including altered blood counts and nerve pain. In some patients, the disease can be resistant or become resistant to bortezomib.

Because NPI-0052 and bortezomib attack the same intracellular target in different ways, the Dana-Farber researchers contend that combining these two agents might be more effective than using either therapy alone and be better tolerated by patients as well.

In preclinical studies, NPI-0052 blocks a wider range of proteasome activities than bortezomib, say the researchers, and works at lower doses. NPI-0052 also appears to be less toxic to normal cells. Bortezomib is currently given by intravenous infusion. "NPI-0052 can be given orally, although the first clinical trials will be using the intravenous route," says Paul Richardson, M.D, who is also a co-author in this study and will be leading the Phase-I clinical trial in myeloma at Dana-Farber.

NPI-0052 was discovered by William Fenical, PhD, and his collaborators at The Scripps Institute of Oceanography during the fermentation of *Salinispora*, a new class of marine gram-positive bacteria identified in sediment samples from the ocean floor. The substance has shown strong anticancer properties in laboratory tests. Nereus Pharmaceuticals holds an exclusive license to the compound for drug development.

Experiments with NPI-0052 began at Dana-Farber in 2003, said Dharminder Chauhan, PhD, lead author of the paper along with Laurence Catley, PhD. When added to cells from patients whose disease was resistant to both standard drugs and bortezomib, the compound efficiently killed the cells. Analyses showed that NPI-0052 and bortezomib express different profiles for inhibiting the three major proteasome activities.

In mice implanted with human myeloma tumor cells, NPI-0052 was well tolerated, prolonged survival and significantly reduced the rate of cancer recurrences. Because NPI-0052 and bortezomib block the proteasome in different ways, the researchers tested them together on myeloma cells. They found that the cancer cells were killed more effectively by the combination than either compound alone without additional toxicity to normal cells.

"This is a laboratory advance that shows clinical promise," says Dr. Chauhan. "We think this is going to be the '2006 Model' of proteasome inhibitors."

Michael Palladino, Jr., PhD, chief technical officer of Nereus Pharmaceuticals, said that the company plans to file an investigational new drug (IND) application by the end of the year, with trials at several centers including Dana-Farber starting in early 2006.

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Dana-Farber Cancer Institute ([www.dana-farber.org](http://www.dana-farber.org)) is a principal teaching affiliate of the Harvard Medical School and is among the leading cancer research and care centers in the United States. It is a founding member of the Dana-Farber/Harvard Cancer Center (DF/HCC), designated a comprehensive cancer center by the National Cancer Institute.