

# Proteasome Inhibitors: A Worthy Partner to Boost Cancer Immunotherapy?

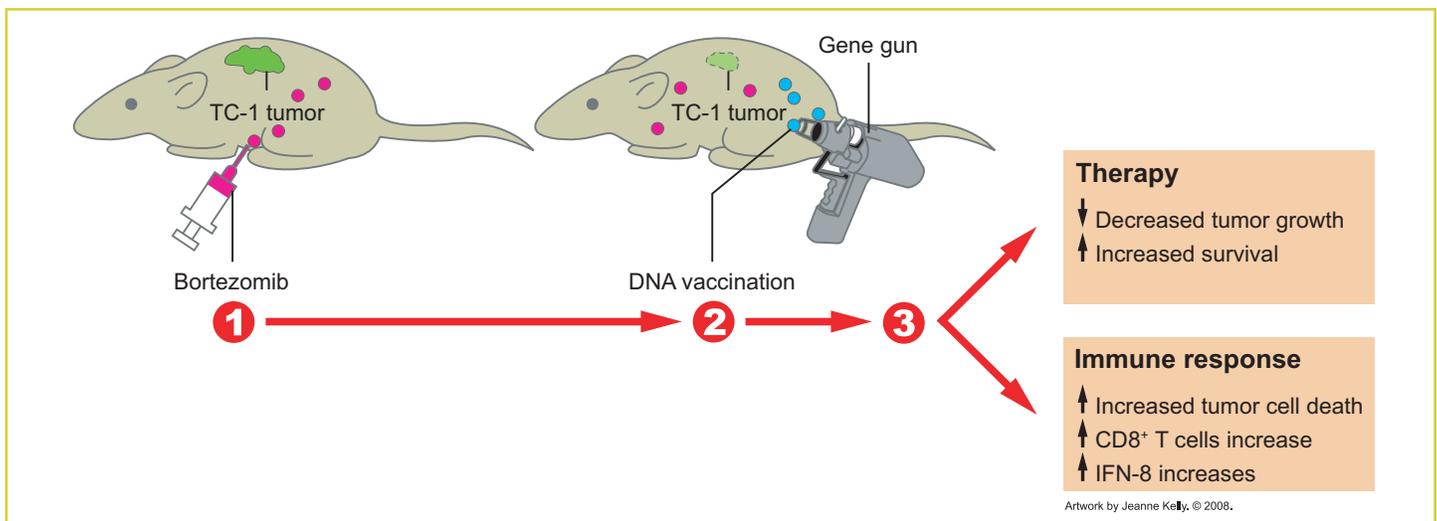
For a number of years, researchers have been frustrated by their inability to harness patients' immune systems to stem tumor growth. However, recent preclinical data involving the use of immunotherapy in combination with proteasome inhibition suggest this novel approach may be worthy of attention.

Although many clinical trials of immunotherapy have yielded only modest outcomes, promising results from a few studies indicate that if an immune response to cancer cells is elicited under the right conditions, substantial antitumor effects result. This immune response involves T cells — specifically CD8<sup>+</sup> cytotoxic T cells — that can recognize tumor antigens and destroy cancer cells. Translating

this function into effective cancer treatment, however, is not a simple task; tumors and their surrounding environment often suppress immune responses, thus prohibiting the optimal activation of T cells. One way to eliminate these immunosuppressive effects would be to drastically reduce the size of the tumor. Surgery, radiation, and traditional chemotherapy currently are the most common methods used to shrink a tumor. Unfortunately, they cause many undesirable side effects, including additional immunosuppressive activity of their own.

To effectively harness the power of the immune system, scientists are seeking better partners for immunotherapy. The ideal partner would not only be

capable of killing cancer cells and lessening the immunosuppressive effects of tumors, but it also would be capable of increasing the cancers' immunogenicity (i.e., ability to activate the immune system). Thomas Sayers, Ph.D., a Senior Investigator in the CCR Laboratory of Experimental Immunology in the Cancer and Inflammation Program, discusses one potential partner, the reversible proteasome inhibitor bortezomib, in a paper recently published in the *Journal of Molecular Medicine*. Proteasome inhibitors disrupt the turnover of proteins within cells, which can result in cell death, or apoptosis. Interestingly, some tumor cells are more sensitive to the fatal effects of proteasome inhibition than normal cells. Nontransformed cells can tolerate up to 70 percent to 80



In a mouse model of cancer, as shown above, administration of bortezomib (i.e., a reversible proteasome inhibitor) followed by DNA vaccination (i.e., a type of immunotherapy) will increase T-cell and other immune responses, resulting in increased tumor cell death and therapeutic benefit.

percent inhibition of proteasome activity without undergoing apoptosis, but certain cancer cells die under similar circumstances.

Sayers draws on a number of pre-clinical studies to build the case for bortezomib as a partner for immunotherapy. A recent study in mice showed that when bortezomib is administered prior to DNA vaccination (i.e., a type of immunotherapy), the immune response to the tumor is amplified and tumor cell death is increased. One potential explanation

is that bortezomib treatment kills many tumor cells before vaccination, thus alleviating immunosuppression associated with the tumor. It is also possible that molecular changes induced by bortezomib in the dying cells enhance the ability of the immune system to respond to the cancer cells. Research has shown that certain molecules expressed on the surface of dying tumor cells can aid in the subsequent generation of T-cell responses. Bortezomib treatment increases cell surface levels of one of these molecules, a heat shock protein

(HSP90), on apoptotic tumor cells. Although researchers do not yet know enough about the efficiency of the bortezomib immunotherapy tag-team in eliminating cancer, a possible complementary interaction between these different therapeutic approaches certainly warrants further research.

## Reference

Sayers T. Productively combining proteasome inhibition with the immunotherapy of cancer. *J Mol Med* 86: 857–60, 2008.