Monoclonal antibodies primed to become potent immune weapons against cancer

March 20 2009

New research suggests that monoclonal antibody therapy of cancer can be improved to be much more powerful than it is today, says a researcher at Georgetown University Medical Center's Lombardi Comprehensive Cancer Center in the March 21 issue of the *Lancet*.

"We believe that antibody therapy has the capacity to immunize people against cancer," says Louis Weiner, MD, director of the cancer center at GUMC and an internationally recognized expert in development and use of monoclonal antibodies. "Treatment modifications might be able to prolong, amplify, and shape a continuous immune response to cancer cells."

Weiner was asked by *Lancet* editors to write a review article discussing the newest research in this field. His co-authors are Madhav Dhodapkar, MD, of Yale University and Soldano Ferrone, MD, of the University of Pittsburgh.

Their analysis, based on reviewing the last eight years of research on monoclonal antibody treatment, suggests that a new era in use of these therapies is just around the corner. "Scientists have been able to use new tools to measure effectiveness of these therapies, and have found that antibodies are capable of stimulating the immune system in ways that had not been appreciated to date, and which we can now take advantage of," Weiner says.

Antibodies are immune system proteins that seek out and neutralize

molecules they recognize as foreign to a body, such as viruses and bacteria. Monoclonal antibodies are proteins crafted in a laboratory to recognize specific receptors, or antigens, on cancer cells; some antigens promote uncontrolled growth. These antibodies are designed to both attach to cancer receptors to inhibit their function and to alert and activate the immune system to the presence of these receptor proteins.

Monoclonal antibodies already offer effective treatment for a wide range of cancers, including breast cancer (Herceptin®, Avastin®), colorectal cancer (Erbitux®, Avastin), lung cancer (Avastin), and blood cancers (Rituxan®, Campath®), but they have appeared to primarily work by forcing tumor related receptors to shut down pro-growth signals, Weiner says.

"For years it has been presumed that the ability of antibodies to interfere with malignant cell-related signaling is the dominant mechanism of anticancer activity, but we have also known that the normal job of an antibody is to deliver an antigen to the body's immune system which then destroys the target," Weiner says.

Recent research by Weiner and others, however, now shows that antibodies can inhibit function not only as signaling manipulators but also as initiators of immune responses that leads to control of cancer, the authors say.

"We believe that Herceptin and Rituxan, as examples, work in part by immunizing people against cancer, but at this point, the magnitude of that response is variable and is frequently very small," Weiner says.

Scientists now believe that it will be possible to alter the antibodies so that they induce both kinds of human immunity - the innate immune response that is short-lasting and which directly kills tumor cells, and a long-lasting "memory" response that comes from the adaptive immune

response. "We have long thought that monoclonal antibodies are capable of stimulating the innate immune system, but we now have evidence that the therapy can prime an adaptive response as well. Such responses would make the treatment much more powerful, capable of keeping cancer under control," he says.

"For the first time we are using technology that can measure the immune response that is occurring in monoclonal antibody treatment, and which will help us build better antibodies that amplify and shape that immune response to become more powerful," Weiner says.

And in the future, it may be possible to build antibodies that are targeted to existing targets on a patient's tumor, as well as to targets that may appear as the cancer mutates. "This one-two punch would anticipate how the tumor changes over time and cut off the cancer's escape route," Weiner says. "These new directions are very exciting."

Source: Georgetown University Medical Center