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New target for cancer therapy identified, preclinical study shows

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Scientists from the Ludwig Institute for Cancer Research (LICR) in Brussels identified a new target for cancer therapy, an enzyme which prevents the immune system from recognizing and destroying certain types of tumors. Called tryptophan 2,3-dioxygenase or TDO, the enzyme works by depriving immune cells of tryptophan, an amino acid essential to their activity. TDO is produced by a significant number of human tumors. Scientists also show that blocking TDO activity with a novel TDO inhibitor promotes tumor rejection in mice. The study findings were published online today in the January 30 issue of the *Proceedings of the National Academy of Sciences* (*PNAS*).

Cancer immunotherapy — leveraging the body's own immune system to attack and destroy tumors — is emerging as a promising method for cancer treatment. Clinical testing of several immunotherapeutic approaches has shown variable success. Tumors often develop survival mechanisms to prevent the attack from the immune system. Researchers are now looking to evaluate the mechanisms that enable these tumors to escape detection by the immune system.

Previously, Brussels scientists from LICR and the de Duve Institute at the Université catholique de Louvain (UCL) studied one enzyme that proved to do just that. It is known as indoleamine 2,3 dioxygenase or IDO1 for short. IDO1 is expressed in many cancers, including prostate, colon, pancreas and cervical tumors. IDO1 blocks the immune system's ability to reject those tumors, by depriving immune cells of tryptophan. In the PNAS study released today, the same Belgian researchers have

shown that TDO is also expressed in various human tumors and degrades tryptophan in a similar manner. Tumors expressing TDO include bladder and liver cancers, as well as melanomas.

"Little is known about the TDO enzyme and its ability to trick the immune system and prevent it from destroying deadly tumors. Our research is the first to explore this relationship," said study lead investigator, Benoit J. Van den Eynde, M.D., Ph.D., Brussels Branch Director at LICR.

The group studied a series of 104 human tumor lines of different types to confirm the activity of TDO in tumor cells. They learned that 20 tumors expressed TDO only, 17 others expressed IDO1 only and 16 expressed both. The findings suggest that TDO and IDO1 enzymes represent complementary cancer immunotherapy targets, which if blocked could potentially impact 51% of all tumors.

Demonstrating TDO Expression and Its Role in Thwarting Immune Attack

Using a validated mouse tumor model, researchers established that TDO expression caused tumor cells to resist immune rejection. They first vaccinated the mice with an antigen that caused them to reject the tumor. Then they injected TDO-expressing tumor cells into the immunized mice. Researchers found that immunized mice no longer rejected the TDO-expressing tumors. This demonstrated that the presence of TDO prevented the immune system from attacking tumors.

In collaboration with scientists from the University of Namur (Belgium), the team then developed an active compound to inhibit TDO enzymatic activity. "Our study showed quite beautifully that the TDO inhibitor restored the ability of mice to reject tumors despite the presence of TDO

in tumor cells," said Dr. Van den Eynde.

Research recently published in the October 6, 2011 issue of *Nature* (Opitz, C.A. et al.) validates today's study results by showing that TDO expression in human glioblastomas promotes tumor progression.

Toward Clinical Development of a TDO-inhibitor

The research team is moving forward to validate TDO inhibition in other preclinical models. Working closely with LICR colleagues in San Diego, the team will also conduct high-throughput screening to find a more stable TDO-inhibitor compound that can be advanced in clinical testing.

LICR plans, conducts, administers, and sponsors its own clinical trials as part of its technology development process. This process allows basic investigations to continue into early stage clinical evaluation of a new therapy, and makes the clinic an essential arm of the research enterprise.

"We will continue to search for inhibitors of TDO, an important new clinical target," confirmed Jonathan Skipper, Ph.D., Executive Director, Technology Development at LICR. "LICR intends to license its discovery to a new commercial enterprise in the near future."

Provided by Ludwig Institute for Cancer Research