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Researchers target 'cell sleep' to lower chances of cancer recurrence

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An international research team led by University of Pittsburgh Cancer Institute (UPCI) scientists discovered that by preventing cancer cells from entering a state of cellular sleep, cancer drugs are more effective, and there is a lower chance of cancer recurrence. The findings, which will be published in the August 15 issue of the journal *Cancer Research* and are available online, are the first to show that it is possible to therapeutically target cancer cells to keep them from entering a cellular state called quiescence, or "cell sleep." Quiescence can be a dangerous source of tumor recurrence because cancer drugs don't typically destroy quiescent cells.

"Successful cancer therapy often is hampered by tumor cell quiescence because these cells remain viable and are a reservoir for tumor progression," said Anette Duensing, M.D., assistant professor of pathology at UPCI. "By inhibiting a key regulator of quiescence, we are able to kill a larger fraction of cancer cells."

Dr. Duensing and her colleagues made the discovery while studying gastrointestinal stromal tumors (GISTs), which are uncommon tumors that begin in the walls of the gastrointestinal tract. According to the American Cancer Society, about 5,000 cases of GISTs occur each year in the United States with an estimated five-year survival rate of 45 percent in patients with advanced disease.

GISTs are caused by a single gene mutation, which means they can be successfully treated with the targeted therapy drug imatinib, known by

the trade name Gleevec. Unlike traditional chemotherapy, which kills all rapidly dividing cells, targeted therapy stops cancer by interfering with specific molecules needed for tumor growth.

Unfortunately, GISTs rapidly develop resistance to the treatment and complete cancer remission using Gleevec is rare. A key regulator of the cancer cell sleep process is a protein complex called DREAM, which is named for the multiple proteins involved. Gleevec induces cell sleep using the DREAM complex, which means that the drug intrinsically limits its own effectiveness.

"When we disrupted the DREAM complex in the lab, we significantly increased cancer cell death using Gleevec," said Dr. Duensing. "This underscores the importance of the DREAM complex as a novel drug target worthy of preclinical and clinical investigations."

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