# UCSD Researchers Identify Potential New Drug Target for Chronic Leukemia

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Researchers at the University of California, San Diego (UCSD) and the Moores UCSD Cancer Center have discovered what could be a novel drug target for an often difficult-to-treat form of leukemia. The investigators have identified a unique "signature" or pattern of a specific family of enzymes in patients with chronic lymphocytic leukemia (CLL), the most common form of adult leukemia.

Paul Insel, M.D., professor of pharmacology and medicine at the UC San Diego School of Medicine and his co-workers compared white blood cells in patients with CLL to those of healthy adults. They found that one form of the group of enzymes, collectively known as cyclic nucleotide phosphodiesterases, was 10 times higher in CLL patients than in normal individuals. The specific type of enzyme, phosphodiesterase 7B (PDE7B), controls the levels of cyclic AMP (cAMP), a molecule that can promote programmed cell death, a process that is defective in CLL. The team reports its findings this week in the *Proceedings of the National Academy of Sciences*.

Whereas most cancers have out-of-control cell growth, CLL is characterized by an overabundance of white blood cells that do not die when they should, Insel explained.

The scientists subsequently tested the effects of drugs that blocked PDE7B in CLL cells, and found that this raised cAMP levels and caused CLL cells to undergo cell death. He explained that since PDE7B degrades cAMP, blocking PDE7B in essence takes the clamp off of programmed cell death, enabling CLL cells to die.

"PDE7B is thus a new drug target for CLL," he said. "We have preliminary data from patient samples studied in the laboratory showing that we can increase the killing of CLL cells even more if we block PDE7B and also add other drugs used to treat CLL."

He noted that a test for PDE7B might also potentially be used as a way to detect CLL, though this has yet to be proven. CLL, which usually strikes adults over age 35, has two major forms. One form progresses slowly, with few symptoms for years, and can be difficult to detect. The other form is more aggressive and dangerous. No one knows what makes one form different from the

other. Current therapies have limited effectiveness, especially once the disease is in its aggressive phase.

The researchers are planning to screen potential drugs to treat CLL based on the PDE7B-cAMP connection. They are also exploring other potential treatment strategies to increase cAMP or disrupt its breakdown.

"We think that CLL cells may have found ways to help keep themselves alive by preventing cAMP from increasing," Insel said. "This paper provides a validation of the importance of the cAMP pathway as a target for drugs that might be used to treat CLL."

The American Cancer Society estimates that, in 2008, there will be about 15,110 new cases of CLL in the United States. About 4,390 people in this country will die of CLL during 2008.

Other contributors to the work include Thomas Kipps, M.D., Ph.D., Lingzhi Zhang, Ph.D., Fiona Murray, Ph.D., Anja Zahno, Joan Kanter, Daisy Chou, Ryan Suda, Michael Fenlon, Laura Rassenti, Ph.D. and Howard Cottam, Ph.D.

The Moores UCSD Cancer Center is one of the nation's 41 National Cancer Institute-designated Comprehensive Cancer Centers, combining research, clinical care and community outreach to advance the prevention, treatment and cure of cancer.

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