

**Public Lecture by Dr. Thomas J. Kipps, M.D. Ph.D.
Professor and Head, UCSD Division of Hematology/Oncology
“Gene Therapy for Blood Cell Cancers”**

**October 16, 2002 at 6:00 p.m. in the Garren Auditorium, Basic Science Building
Sponsored by the Sam & Rose Stein Institute for Research on Aging, UCSD**

Chronic lymphocytic leukemia, or CLL as the disease is commonly known, is the most common adult leukemia in the United States. It is a slowly developing blood cancer in which too many defective white cells called lymphocytes are produced. Untreated, overproduction of the flawed lymphocytes eventually can crowd out other essential blood cells, resulting in a variety of ailments and a weakened immune system vulnerable to other diseases. For CLL, there is no cure, and traditional treatments such as chemotherapy or radiation do not appear to prolong survival. Clearly, there is a need for new forms of therapy.

Medical research has taught us much about the biology of CLL. This leukemia is derived from lymphocytes called “B lymphocytes”, or “B cells.” These lymphocytes ordinarily are the cells of the immune system that make antibodies. In addition, these cells can present antigens to “T cells,” the grand field marshals of the immune system. Through such interactions, the T cells can be stimulated to direct the body’s immune system to destroy invading bacteria, viruses, or even tumor cells. Despite the fact that the leukemia cells are derived from such B lymphocytes, the leukemia cells do not present their own leukemia-associated antigens to T cells. Because of this there is no immune response against the leukemia cells. Additional studies have revealed that leukemia cells are “stealth-like” because they lack expression of proteins that are required to stimulate T cells to respond productively to antigens, including leukemia-associated antigens. It appears that the leukemia cell has several defense mechanisms to evade immune detection, indicating that the leukemia cell has something to hide!

Fortunately, the “stealth” property of leukemia cells can be reversed. We found that hyper-activated T cells could reverse the immune suppressive features of CLL cells in the laboratory. This required that T cells express a protein, called “CD40-ligand” (otherwise called “CD154”), that can cross-link a protein called “CD40” on the leukemia cell surface. The “CD40-ligand” acts like a light-switch that can turn-on the leukemia cells’ ability to present antigens to T cells, including antigens that are peculiar to the leukemia cell itself. We speculated that leukemia cells that were engineered to make the CD40-ligand would be able to stimulate themselves into becoming better antigen presenting cells.

We examined various strategies for getting a gene encoding CD40-ligand into CLL cells. For this we examined the use of a crippled cold-virus that is not contagious and that cannot produce illness by itself. By inserting the gene that directs the cell to make CD40-ligand protein. The results of this are fairly dramatic. This infection converts a “stealth” like leukemia cell into a cell demanding attention by the immune system. Studies in the laboratory demonstrate that infected cells are far more effective in inducing anti-leukemia immune responses than non-modified leukemia cells, or even leukemia cells that had been cultured with activated T cells.

This formed the basis for an immune gene therapy for leukemia. Patients who enroll in the protocol undergo a procedure called leukapheresis. This is a process whereby the patient’s blood is withdrawn and the leukemia cells mechanically extracted. The rest of the blood is then immediately returned to the patient. The leukemia cells then are exposed to the genetically modified cold virus. The viruses invade the leukemia cells and then direct these cells to produce the CD40-ligand. Approximately one week after leukapheresis, the now-genetically modified leukemia cells are re-injected into the same patient. The modified leukemia cells express the CD40-ligand protein that acts as alarm bells, stimulating the patient’s immune system to attack the modified leukemia cells and all similar-looking leukemia cells.

In the Phase I study of eleven volunteers the optimal dose was identified and progression in the disease remains arrested in three of the volunteers. Phase II study is now under way here at UCSD and Harvard University to determine the effectiveness and will be completed within the next year. Additional volunteers are still being accepted. If anyone needs additional information about this study please contact Jan Bole at (858) 822-2405 or jbole@ucsd.edu.