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******Bone marrow "cleansed" of cancer cells in leukemic mice

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DALLAS--Using an assassin's drug attached to a cancer-seeking antibody, researchers at The University of Texas Health Science Center at Dallas have successfully eradicated cancer cells from the bone marrow of leukemic mice.

Findings from the animal studies at the health science center were released this week in the "Nature" magazine article "Selective Killing of Leukemia Cells by Antibody-Toxin Conjugates: Implications for Autologous Bone Marrow Transplantation."

Authored by Drs. Jonathan Uhr, professor and chairman of Microbiology; Ellen Vitetta, professor of Microbiology; and Keith Krolick, instructor in Microbiology, the paper documents that at least 99.9 percent of tumor cells from diseased mice marrow are eradicated.

The findings, should they also be applicable to human treatment, suggest that permanent remission may be achieved in patients with certain kinds of cancer.

Uhr explained that the concept of bone marrow treatment is actually a rescue technique used to save a patient's life following treatments with high doses of radiation and chemotherapy (cancer killing drugs).

"The combined treatment is drastic. Patients with certain advanced cancers are given supralethal doses of radiation and drugs to wipe out all of their rapidly reproducing cells. The treatment kills both normal and cancerous cells. To replace the normal ones, the patient is then given a bone marrow transplant."

It is in this marrow, Uhr says, that all of the cells necessary to repopulate the patient's blood cells are made.

Because of tissue incompatibility problems, the trend has been to give patients back their own marrow instead of marrow from an unmatched donor. But there is also a danger of reintroducing some of the cancerous cells using this technique.

"When it is suspected that a cancer patient in remission (seemingly free of the disease) might relapse, bone marrow is taken from them while they are still well. This marrow is then frozen and stored.

"If the cancer recurs, the treatment is to give them the supralethal doses and reintroduce their saved marrow."

If successful, Uhr says the treatment can achieve long remissions for these patients. "But if there are cancer cells in the marrow--despite the fact that it was taken during the remission--then the cancer could recur."

"What we did," Vitetta explained, "was to discover an antibody in a mouse model that would react with tumor cells but not the delicate stem cells of the marrow that can repopulate the blood, lymph nodes and spleen.

"To this antibody we attached a modified form of the toxin, ricin."

Vitetta says the antibody-ricin molecule complex will selectively kill the tumor cells in a test tube, leaving the normal cells alone.

(more)

"It's a kind of guided missle approach," she explained. "There are a number of research groups currently developing this approach and all of us are beneficiaries of two decades of basic studies on how plant and animal toxins kill cells."

An extract of the castor bean, ricin in its purest form is quite deadly. Because as little as 100 micrograms (barely visible) is needed to kill a human, it has gained notoriety as an assassins drug.

The powerful chemical received world-wide media attention in 1978 when an unidentified agent murdered a self-exiled Bulgarian named Georgi Markoff, by shooting a tiny bullet of the substance into his leg through the tip of an umbrella.

Vitetta explained that the ricin is rendered harmless to the stem cells by removing its normal binding ability.

"Ricin has two peptide chains, A and B. A is the toxic element and inhibits protein synthesis. B acts as a binder. We've eliminated B from the ricin molecule and replaced it with our specific antibody."

The researchers' mouse model, called BCL_1, mimmicks almost exactly the human cancer chronic lymphocytic leukemia (CLL) making it an excellent study guide for their work. Another important feature of the model is that the researchers can actually measure the number of tumor cells needed to give the animal the disease. They have documented that as few as one tumor cell can give a normal mouse the disease.

"Because it only takes one cell, we are able to measure our results very accurately. We believe that if we leave one cell behind when we cleanse the marrow, the mouse will get the disease.

"The fact is, over 80% of the mice did not get the tumor and the few that did appeared to get it from about one to 10 tumor cells that apparently escaped killing."

Other "cleansing" techniques using specific antibodies are currently in use and the researchers have compared in their paper the most common one, "antibody and complement," to their antibody-A chain conjugate.

Vitetta explained that the antibody and complement approach is being used successfully in human and animal trials. Complement, a protein in normal blood also kills cancer cells by binding to them after the cancer cells have interacted with anti-tumor antibodies.

"The problem though, is that it is sometimes hard to kill every last cancer cell using this treatment. Also, the complement is very expensive, large amounts are needed and the results are not always reproducible.

"The antibody-A chain conjugate is highly efficient in contrast to the complement."

Although the researchers are very encouraged by the results using this technique, they are reluctant to say whether or not the animal studies could indicate a potential cure for humans.

"You can never say 'cure' even with the mice. We will have to watch them for their lifetime to be sure there is no relapse.

"We can't say that there isn't a chance that one cell might still be lurking around. What may be happening is that the mice receiving the marrow may have been given an immune response that keeps any remaining tumor cells from dividing. When the animal ages and the immune response breaks down, any remaining tumor cells could take off and give the animal cancer."

Still, the researchers admit that they are hopeful the new technique will be successful with humans.

"Studies with humans are just beginning. These studies are slightly different but use the same principles--to delete a cancerous cell population from the marrow and give it back to the patient.

"It is obviously a very exciting concept," Vitetta says.

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