

Researchers demonstrate safety of gene therapy using adult stem cells

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A new study by UC Davis researchers provides evidence that methods using human bone marrow-derived stem cells to deliver gene therapy to cure diseases of the blood, bone marrow and certain types of cancer do not cause the development of tumors or leukemia. The study was published online in the May 6, 2008 issue of *Molecular Therapy*.

"The results of our decade-long study of adult human stem cell transplantation shows that there is little risk of adverse events caused by gene transfer, and that adult human stem cells do not pose a cancer risk when implanted into different organs," said Jan Nolte, senior author of the study and director of the UC Davis Stem Cell Program.

Nolte and her colleagues tested the safety of gene transfer into bone marrow stem cells from human donors in more than 600 mice. None of the transplanted mice developed leukemia or solid tumors caused by the gene therapy treatment, during the evaluation period of up to 18 months.

"These data are critical for advancing stem cell research leading toward therapies," Nolte said. "We've shown that adult stem cells follow natural cues to reach target locations, they function normally when they get there and do not exhibit the unchecked cell growth that is the hallmark of cancer."

Gene therapy trials using human bone marrow cells began in the early 1990s and have since included roughly 1,000 patients worldwide. In 2000, a leukemia-like condition emerged in three participants in a clinical trial in France, halting the trial and calling into question the safety of the method. Researchers suspected that the gene transferred in this trial gave the transplanted cells an enhanced growth capacity that led to the cancers.

"After those studies in France, the gene therapy

community felt that further biosafety testing was warranted," explained Gerhard Bauer, lead author of the study and an assistant professor of hematology and oncology. "Due to the significantly large number of study animals, our investigation further illuminates the safety of gene therapy using hematopoietic stem cells. It allows us to rest easier with the knowledge that if we insert corrective genes into human bone marrow stem cells and administer those cells to human patients, we are providing a relatively safe therapy."

Today, gene therapy using the adult blood-forming cells found in bone marrow (known as hematopoietic stem cells) is normally done in an autologous transplant setting. The therapy involves taking hematopoietic stem cells from a person who needs treatment, genetically modifying the cells — perhaps by adding a missing gene — and then re-inserting the cells back into the same person. This treatment eliminates the complications of graft-versus-host disease or host rejection that can occur in allogeneic transplants (therapy where the cell donor is different from the recipient).

In the current study, 630 immunodeficient mice received mesenchymal stem cells from one human bone marrow donor and hematopoietic stem cells from another. Mesenchymal stem cells are a type of cell found in bone marrow that support the function of hematopoietic stem cells, and can give rise to bone, cartilage, fat, and muscle. Genes were inserted into the hematopoietic stem cells using one of two viral vectors — either a retrovirus or a lentivirus — before they were transplanted into the mice, along with genetically modified mesenchymal stem cells.

Of the mice used in the long-term study, four developed human leukemia. None of those mice, however, were found to have vector DNA present in the malignant cells.

"This is evidence of a natural tendency for human

bone marrow stem cells to develop leukemia in long-term studies, not that the leukemia was caused by the genetic modification," Bauer explained. "It's a good statistical control for our method."

Bauer noted that while the current study results are important for use with adult stem cells, they are not applicable to human embryonic stem cells, which have completely different properties.

"Our experiments did not involve human embryonic stem cells, so we have a lot of stringent work to do to ensure that those types of stem cells can be used safely for human clinical trials," said Bauer. "It certainly is possible, and we are working hard to establish safe and effective human embryonic stem cell-based cures for patients as well."

Nolta and Bauer have worked on eighteen cell and gene therapy clinical therapy trials during their 12 years as colleagues, including stem cell gene therapy trials for adenosine deaminase deficiency, also known as the "Bubble Boy Disease," and stem cell gene therapy for HIV, with colleagues from Children's Hospital Los Angeles, who are also co-authors on the current report.

Bauer is the director of UC Davis' Good Manufacturing Practice (GMP) laboratory in Sacramento. Upon its completion, UC Davis will be one of the few universities with a large GMP facility where scientists will work in an ultra-clean environment to derive cellular products that, after certification and extensive testing, will be used to treat patients. The California Institute for Regenerative Medicine (CIRM) has recommended funding for this new facility to help bring a wide range of stem cell therapy cures to patients throughout California.

According to Nolta, the results of the current study will allow UC Davis to move forward with increased certainty as it prepares for clinical trials.

"We are ready to further develop and test this safe approach to creating effective therapies, and are also using the same model to test the safety of embryonic stem cell-based therapies to fulfill the promise of regenerative medicine." she said.

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