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UC Davis researchers exploring gene therapy to fight AIDS

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The apparent success of a case in which German doctors cured a man of AIDS using a bone marrow transplant comes as no surprise to Gerhard Bauer, a UC Davis stem cell researcher. Bauer has been working for more than 10 years on a similar cure for AIDS based on replacing the devastated immune system of an HIV-infected patient with stem cells that have been engineered to resist human immunodeficiency syndrome.

Bauer plans to present the preliminary results of his latest research at the 50th annual meeting of the American Society for Hematology in San Francisco on Sunday, December 6, 2008, from 6 to 8 p.m. at the Moscone Center. He and his UC Davis research team will present a poster detailing the development of a mouse model that allows pre-clinical testing of their new gene-therapy protocol, which they hope will pave the way for human clinical trials within five years.

"The case in Germany was a natural gene-therapy experiment," explained Bauer, an assistant professor of hematology and oncology and director of a good manufacturing practice (GMP) laboratory now under construction in the new UC Davis Institute for Regenerative Cures in Sacramento. "We are working on a similar approach to genetically engineer a patient's own stem cells in a way that mimics this natural immunity. The German case offers further proof that genetic engineering provides a pathway to success, and gene therapy offers real hope as a cure for AIDS."

Last month, German doctors reported that they had cured a 42-year-old

of acquired immune deficiency syndrome, or AIDS. The patient, an American living in Berlin, also had leukemia, which is best treated by a bone marrow transplant. Thinking they might be able to cure the man of both diseases, the physicians gave him a bone marrow transplant from a person with natural immunity to HIV. The patient has now lived for 20 months since the transplant without any detectable traces of HIV.

To establish similar immunity in HIV patients, the UC Davis team manipulated human skin cells to give these cells many of the same properties as stem cells. These transformed cells, called induced pluripotent stem (IPS) cells, are capable of differentiating into, among other cell types, hematopoietic stem cells, which are normally found in bone marrow and are responsible for producing the various types of immune cells.

"If we can replace normal immune cells with HIV-resistant ones, we can cure AIDS," Bauer said.

Bauer and stem cell program research associate Joseph Anderson have developed several anti-HIV genes that they plan to insert into IPS cells using standard gene-therapy techniques and viral vectors (viruses that efficiently insert the genes they carry into host cells). These engineered IPS cells could then be differentiated into bone marrow stem cells and introduced into the patient using a procedure similar to a bone marrow transplant.

"The hope is that one day we will use a patient's own skin cells to develop the engineered IPS cells to avoid possible rejection," said Bauer, who worked on clinical HIV gene therapy trials at Childrens Hospital Los Angeles before coming to UC Davis. "As in the German case, the end result would be an immune system that produces HIV-resistant immune cells."

In theory, the experimental treatment would result in an immune system that remains functional, even in the face of an HIV infection, but would halt or slow the progression toward AIDS.

"The anti-HIV genes take advantage of how HIV works," added Anderson, who is now writing a paper about the investigation. "The virus targets cells that are descendants of hemopoeitic stem cells."

During the first stages of infection, HIV targets macrophage cells, gaining entrance into the cell by binding to a receptor called CCR5 on the cell's surface. Later in the infection it targets CD4+ T cells, binding to the CXCR4 receptor on the surface of these cells and bringing on full-blown AIDS.

What researchers discovered is that there is a natural mutation in less than 1 percent of Caucasians that results in a lack of CCR5 receptors on any of their cells.

"We also found that these people are naturally resistant to HIV," said Bauer. "So, more than 10 years ago, we began our work creating a gene that would knock down expression of CCR5 and other key receptors and interfere with other routes of HIV infection."

For IPS-based anti-HIV gene therapy to become reality, UC Davis researchers must first conduct safety and efficacy trials. Researchers have created a mouse model that replicates a normally functioning human immune system.

"We can now move forward and test the safety of the viral vectors, as well as the ability of anti-HIV genes to inhibit HIV infection," noted Anderson. "The humanized mouse model is an important step toward bringing this possible cure to patients."

Bauer and Anderson are hoping to demonstrate in their mouse model that HIV-infection cannot occur following their gene therapy treatment, providing the needed confidence in safety before embarking on clinical trials. This work and studies on the clinical use of IPS cells, Bauer predicts, will lead to a cure for AIDS.

"A real cure will come when we can replace all the hematopoietic stem cells with HIV resistant stem cells. What is so exciting is that we're clearly on the path of doing just that," said Bauer.

Source: University of California - Davis - Health System

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