Study using stem cell therapy shows promise in fight against HIV

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UC Davis Health System researchers are a step closer to launching human clinical trials involving the use of an innovative stem cell therapy to fight the virus that causes AIDS.

In a paper published in the May issue of the Journal of Virology, the UC Davis HIV team demonstrated both the safety and efficacy of transplanting anti-HIV stem cells into mice that represent models of infected patients. The technique, which involves replacing the immune system with stem cells engineered with a triple combination of HIV-resistant genes, proved capable of replicating a normally functioning human immune system by protecting and expanding HIV-resistant immune cells. The cells thrived and self-renewed even when challenged with an HIV viral load.

"We envision this as a potential functional cure for patients infected with HIV, giving them the ability to maintain a normal immune system through genetic resistance," said lead author Joseph Anderson, an assistant adjunct professor of internal medicine and a stem cell researcher at the UC Davis Institute for Regenerative Cures. "Ideally, it would be a one-time treatment through which stem cells express HIV-resistant genes, which in turn generate an entire HIV-resistant immune system."

To establish immunity in mice whose immune systems paralleled those of patients with HIV, Anderson and his team genetically modified human blood stem cells, which are responsible for producing the various types of immune cells in the body.

Building on work that members of the team have pursued over the last decade, they developed several anti-HIV genes that were inserted into blood stem cells using standard gene-therapy techniques and viral vectors (viruses that efficiently insert the genes they carry into host cells). The resulting combination vector contained:

a human/rhesus macaque TRIM5 isoform, which disrupts HIV from uncoating in the cytoplasm a CCR5 short hairpin RNA (shRNA), which prevents certain strains of HIV from attaching to target cells a TAR decoy, which stops HIV genes from being expressed inside of the cell by soaking up a critical protein needed for HIV gene expression These engineered blood stem cells, which could be differentiated into normal and functional human immune cells, were introduced into the mice. The goal was to validate whether this experimental treatment would result in an immune system that remained functional, even in the face of an HIV infection, and would halt or slow the progression toward AIDS.

The results were successful on all counts.

"After we challenged transplanted mice with live HIV, we demonstrated that the cells with HIV-resistant genes were protected from infection and survived in the face of a viral challenge, maintaining normal human CD4 levels," said Anderson. CD4+ T-cells are a type of specialized immune cell that HIV attacks and uses to make more copies of HIV.

"We actually saw an expansion of resistant cells after the viral challenge, because other cells which were not resistant were being killed off, and only the resistant cells remained, which took over the immune system and maintained normal CD4 levels," added Anderson.

The data provided from the study confirm the safety and efficacy of this combination anti-HIV lentiviral vector in a hematopoietic stem cell gene therapy setting for HIV and validated its potential application in future human clinical trials. The team has submitted a grant application for human clinical trials and is currently seeking regulatory approval, which is necessary to move on to clinical trials.

"This research represents an important step in our fight against HIV/AIDS," said Richard Pollard, chief

of infectious diseases at UC Davis and one of the study's co-authors. "Clinical trials could give us the critical information we need to determine whether our approach truly represents a functional cure for a terrible disease that has affected millions and millions of people."

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