TRIMming HIV

By Lauren Martz, Staff Writer

Evolution has rendered New World owl monkeys (*Aotus* genus) highly resistant to retroviral infections by means of a protein, AoT5Cyp, which is a fusion of two genes, *TRIM5* and *CypA*. Swiss researchers have now engineered a humanized version of AoT5Cyp in the hope that it will prevent HIV replication in humans while minimizing the risk of adverse immune responses.¹

The study was led by Jeremy Luban, professor in the Department of Microbiology and Molecular Medicine at the **University of Geneva**.

Tripartite motif-containing 5 (TRIM5) has all the characteristics of a potential gene therapy candidate for HIV: it immediately inhibits HIV after the virus enters the cell—before the virus can go through reverse transcription, mutation and development of resistance to treatment.² However, although primate orthologs of *TRIM5* have shown potent anti-HIV-1 activity in human cells, the human variant has shown very little effect.³ This is perhaps due to the absence of the cyclophilin A (CypA) portion, which is a retrovirus capsid-binding protein.⁴

The primate fusion protein AoT5Cyp acts on HIV-1 within minutes of viral entry into the cell and potently inhibits HIV-1 infection in human cells, according to findings reported by Luban's group in 2004.⁵ The catch was that the risk of immunogenicity from the foreign molecule prevented its use in humans.

To work around this, Luban and his team used the human version, hT5Cyp, to transduce human CD4⁺ T cells and macrophages and showed that the cells were protected from infection when cultured with HIV-1, HIV-2 or simian immunodeficiency virus (SIV).

hT5Cyp also showed better inhibition of viral replication than TRIM5 protein from rhesus macaques. hT5Cyp also improved cell survival without affecting cell function or eliciting viral resistance.

In mice that lack B, T and NK cells and that don't reject xenografts, lentiviral gene therapy with hT5Cyp in human CD4⁺ T cells followed by HIV-1 challenge resulted in less viremia and infection in the lymphoid organs than lentiviral gene therapy with a control protein. The group published its findings in *The Journal of Clinical Investigation*.

Thomas Davis, CMO and SVP of clinical development at **Celldex Therapeutics Inc.**, said hT5Cyp potentially could be given as a protein therapeutic. The catch, he said, is that "it would require repeated administration. The gene-therapy approach would therefore be preferable in that continuous *in vivo* production could eliminate the need for chronic therapy."

Celldex's CDX-2401 is a prophylactic vaccine consisting of an HIV antigen and a mAb specific for the dendritic cell receptor DEC-205. Davis said the vaccine, which is in preclinical testing, should generate prolonged innate immunity against the virus.

Junction malfunction?

Although the use of human components in hT5Cyp mitigates immunogenicity concerns, it does have a spot that Luban said potentially could be recognized by the immune system as a foreign peptide—the junction between the human TRIM5 and CypA proteins.

At this point, Luban said, his group thinks the fusion protein "would be relatively safe. All 10 species of owl monkeys have the same kind of gene and they seem to be happy."

On the other hand, Alexander Tsygankov, associate professor of microbiology and immunity at the **Temple University School of Medicine**, was circumspect.

"The proposed therapeutic protein has a novel, potentially immunogenic epitope: the fusion site between TRIM5 and cyclophilin. This epitope may cause an immune response," he told *SciBX*. "The authors think it will not, but it is impossible to know for sure."

Tsygankov added that "genes interfering with HIV-1 infection may also interfere with normal cellular functions, and this would be unacceptable."

In reply, Luban countered that his group saw "no disruption of normal cell function in our experiments."

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—Philip Gregory,
Sangamo BioSciences Inc.

Getting HIV's vector

Luban told *SciBX* that the next steps will be to develop hT5Cyp into a gene therapy that targets hematopoietic stem cells.

Philip Gregory, CSO and VP of research at **Sangamo BioSciences Inc.**, agreed that this is a logical next step. "The next cell type to test would be hematopoietic progenitor cells, as transplant would provide lineages for all of the cells that can combat the HIV infection," he said.

Sangamo's SB-728-T is in Phase I testing to treat HIV. It is composed of autologous CD4⁺ T cells genetically modified at the *CC chemokine receptor 5 (CCR5)* gene by *CCR5*-specific zinc finger DNA-binding protein nucleases (ZFNs).

Tsygankov also agreed about the next step, but with a caveat. "It appears that hematopoietic progenitors are potentially more promising targets than T cells because they give rise to all types of immune cells," he said. "But hematopoietic progenitors are more resistant to lentiviral transduction than T cells."

Luban noted that the process "would involve an autologous transplant of hematopoietic stem cells that had been transduced with vectors to deliver the gene. Ultimately, I think the main limitation here is the development of safe and effective vectors for gene delivery to hematopoietic stem cells."

Luban told *SciBX* that **Columbia University**, where he formerly

was a professor, filed a patent on the original discovery of the owl monkey protein AoT5Cyp and has filed for a second patent covering the human fusion gene. He said that the university is interested in licensing the IP.

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