New gene therapy targets hemophilia

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Researchers at the UNC School of Medicine and the Medical College of Wisconsin found that a new kind of gene therapy led to a dramatic decline in bleeding events in dogs with naturally occurring hemophilia A, a serious and costly bleeding condition that affects about 50,000 people in the United States and millions more around the world.

Before the gene treatment, the animals experienced about five serious bleeding events a year. After receiving the novel gene therapy, though,

they experienced substantially fewer bleeding events over three years, as reported in the journal *Nature Communications*.

"The promise and the hope for gene therapy is that people with hemophilia would be given a single therapeutic injection and then would express the protein they are missing for an extended period of time, ideally for years or even their entire lifetimes," said Tim Nichols, director of the Francis Owen Blood Research Laboratory at UNC and co-author of the paper. The hope is that after successful gene therapy, people with hemophilia would experience far fewer bleeding events because their blood would clot better.

People with hemophilia A lack the coagulation factor VIII in their blood plasma – the liquid in which red, white, and platelet cells are suspended.

"Bleeding events in hemophilia are severe, and without prompt factor VIII replacement, the disease can be crippling or fatal," said Nichols, a professor of medicine and pathology. "The random and spontaneous nature of the bleeding is a major challenge for people with hemophilia and their families."

In underdeveloped countries, people with hemophilia and many undiagnosed people typically die from bleeding in their late teens or early 20s. In developed countries, patients usually live fairly normal lives, as long as they receive preventive injections of recombinant protein therapy a few times a week. The disease requires life-long management that is not without health risks. The annual cost of medications alone is about $200,000 a year.

However, about 35 percent of people with hemophilia A develop an antibody response that blocks the factor VIII therapy. They require continuous infusions of various protein factors and they face a higher mortality rate. Also, the cost of treatment can easily rise to $2 million or

more a year per patient.

Nichols and David Wilcox from the Medical College of Wisconsin figured out a potential way around the antibody response in dogs with naturally occurring hemophilia A.

Using a plasmapheresis machine and a blood-enrichment technique, the research team isolated specific platelet precursor cells from three dogs that have hemophilia A. The team then engineered those platelet precursor cells to incorporate a gene therapy vector that expresses factor VIII. The researchers put those engineered platelet precursors back into the dogs. As the cells proliferated and produced new platelets, more and more were found to express factor VIII.

Then, nature took over. Platelets naturally discharge their contents at sites of vascular injury and bleeding. In this experiment, the contents included factor VIII.

In the 2 1/2 years since the dogs received the gene therapy, researchers found that factor VIII was still being expressed in platelets that were coursing throughout the vascular systems of all three dogs. All three experienced much less bleeding. In the dog that expressed the most factor VIII in platelets, the bleeding was limited to just one serious event each year over the course of three years. And such bleeding events were easily treatable with current standard therapies.

"This has been very successful," Nichols said. "And now we want to explore the possibility of moving it into human clinical trials for people with hemophilia A, similar to what Paul Monahan and Jude Samulski at UNC are currently doing for people with hemophilia B, which is a deficiency of factor IX."

If approved, the platelet-targeted therapy would likely be restricted to

patients who develop the antibody that stifles factor VIII therapy through normal injections. But as the gene therapy is refined, it could become a viable option for people with blood disorders who don't have inhibitory antibodies.

More information: Platelet-targeted gene therapy with human factor VIII establishes haemostasis in dogs with haemophilia A. Lily M. Du, Paquita Nurden, Alan T. Nurden, Timothy C. Nichols, Dwight A. Bellinger, Eric S. Jensen, Sandra L. Haberichter, Elizabeth Merricks, Robin A. Raymer, Juan Fang, Sevasti B. Koukouritaki, Paula M. Jacobi, Troy B. Hawkins, Kenneth Cornetta, Qizhen Shi & David A. Wilcox. *Nature Communications* 4, Article number: 2773 DOI: 10.1038/ncomms3773

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