

Bioengineered protein shows preliminary promise as new therapy for hemophilia

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A genetically engineered clotting factor that controlled hemophilia in an animal study offers a novel potential treatment for human hemophilia and a broad range of other bleeding problems.

The researchers took the naturally occurring coagulation factor Xa (FXa), a protein active in blood clotting, and engineered it into a novel variant that safely controlled bleeding in mouse models of hemophilia. "Our designed variant alters the shape of FXa to make it safer and efficacious compared to the wild-type factor, but much longer-lasting in [blood circulation](#)," said study leader Rodney A. Camire, Ph.D., a [hematology](#) researcher at The Children's Hospital of Philadelphia.

"The shape of the variant FXa changes when it interacts with another clotting factor made available following an injury," added Camire. "This increases the functioning of the protein which helps stop bleeding." Camire is an associate professor of Pediatrics in the Perelman School of Medicine at the University of Pennsylvania.

The study appears online today in [Nature Biotechnology](#), and will be published in the journal's November 2011 print issue.

In hemophilia, an inherited single-gene mutation impairs a patient's ability to produce a blood-clotting protein, leading to spontaneous, sometimes life-threatening bleeding episodes. The two major forms of the disease, which occurs almost solely in males, are hemophilia A and hemophilia B, characterized by which specific clotting factor is

deficient. Patients are treated with frequent infusions of clotting proteins, which are expensive and sometimes stimulate the body to produce antibodies that negate the benefits of treatment.

Roughly 20 to 30 percent of patients with hemophilia A and 5 percent of hemophilia B patients develop these inhibiting antibodies. For those patients, the conventional treatment, called "bypass therapy," is to use drugs such as factor VIIA and activated prothrombin complex concentrates (aPCCs) to restore blood clotting capability. But these agents are costly (as much as \$30,000 per treatment) and not always effective. Camire added that, in the current [animal study](#), they were able to show the variant protein is more effective at a lower dose than FVIIa.

The range of options for hemophilia patients could improve if the study results in animals were to be duplicated in humans. "The variant we have developed puts FXa back on the table as a possible therapeutic agent," said Camire. Naturally occurring (wild-type) FXa, due to its particular shape, is not useful as a therapy because normal biological processes shut down its functioning very quickly.

By custom-designing a different shape for the FXa protein, Camire's study team gives it a longer period of activity, while limiting its ability to engage in unwanted biochemical reactions, such as triggering excessive clotting. "This potentially could lead to a new class of bypass therapy for hemophilia, but acting further downstream in the clot-forming pathway than existing treatments," said Camire, who has investigated the biochemistry of blood-clotting proteins for more than a decade.

When infused into mice with hemophilia, the FXa variant reduced blood loss after injury, as it safely restored [blood clotting](#) ability. Further studies are necessary in large animal models to determine whether this approach can become a clinical treatment for [hemophilia](#) patients who have developed inhibitors, or even more broadly as a drug for

uncontrolled bleeding in other clinical situations.

More information: "A zymogen-like factor Xa variant corrects the coagulation defect in hemophilia," Nature Biotechnology, published online Oct. 23, 2011, to appear in Nov. 2011 print edition. [doi: 10.1038/nbt.1995](https://doi.org/10.1038/nbt.1995)

Provided by Children's Hospital of Philadelphia

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