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GemPharmatech Co.,Ltd

B6-F8-KO

Strain Name：B6/JGpt-*F8* ^{em430Cd5d452}/Gpt

For short：B6-F8-KO

Strain Type：Knock-out

Strain Number：T004727

Background：C57BL/6JGpt

Description

Hemophilia is a group of coagulopathy caused by genetic defects in some coagulation factor genes. It is mainly include two types: hemophilia A and hemophilia B, and the incidence of hemophilia A is higher, accounting for about 80-85% of patients with hemophilia[1-2]. The main symptoms of patients with hemophilia are spontaneous or non-spontaneous bleeding, including unstoppable bleeding during trauma or surgery, permanent joint damage caused by repeated bleeding in the joint cavity [3].

Hemophilia A (HA) is a bleeding disorder caused by the loss of clotting factor VIII (FVIII). FVIII is mainly produced by the liver and secreted into the blood, participates in the endogenous coagulation pathway, and activates downstream coagulation factors and prothrombin, eventually forming a hemostatic plug to exert hemostatic function. The coding gene *F8* is located on the X chromosome, and can generate multiple mutations such as point, missenses, translocations, and insertions mutations. These mutations can cause insufficient synthesis of FVIII or dysfunction, leading to hemophilia [4-5].

GemPharmatech use the gene editing technology to knock out some exons of the *F8* gene in C57BL/6JGpt mice to cause frameshift mutations and FVIII protein deletion, developed B6-F8-KO mouse model independently, a mouse model with hemophilia A. This model can simulate the main symptoms and pathogenesis of patients with hemophilia. It can be used not only for the screening of therapeutic drugs for hemophilia A, but also for the effectiveness and safety evaluation of related gene therapy methods.

Strategy

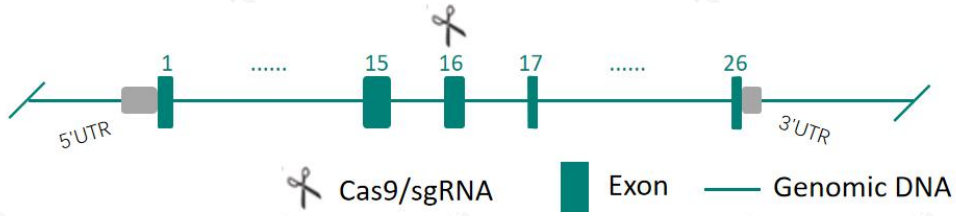

Fig.1 Schematic diagram of *F8* knock out strategy in C57BL/6JGpt mice.

Application

1. Screening for the treatment of hemophilia A
2. Evaluation of efficacy and safety of hemophilia A gene therapy
3. Study on the pathogenesis of hemophilia

Data support

1. *F8* mRNA expression detection

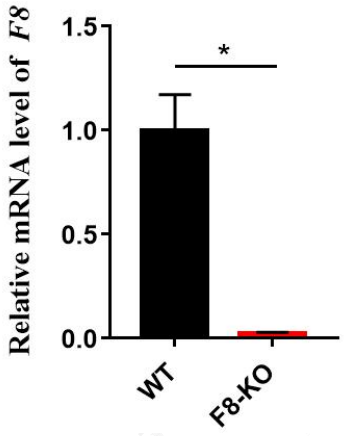

Fig.2 Detection of *F8* mRNA expression in WT and B6-F8-KO mice. B6-F8-KO mice *F8* gene successfully knocked out in mouse liver.

2. FVIII activity

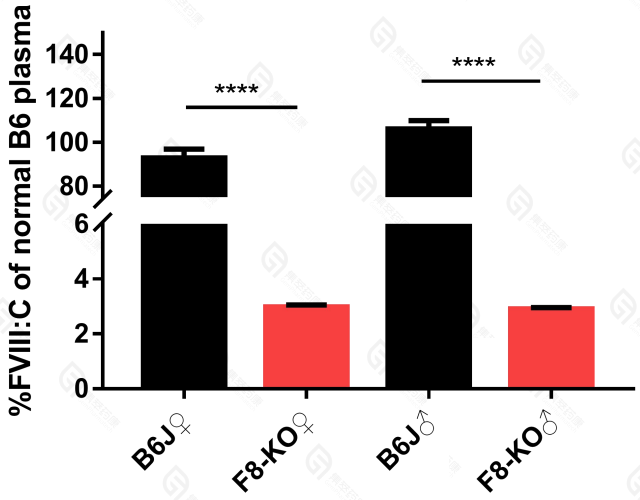

Fig.3 Detection of FVIII activity in F8-KO mice. The F8 activity of B6-F8-KO mice was 3% of that of C57BL/6J mice, which was a model of moderate hemophilia. (Data were presented as Mean ± SEM, ****, P≤0.0001)

3. Activated partial thromboplastin time test

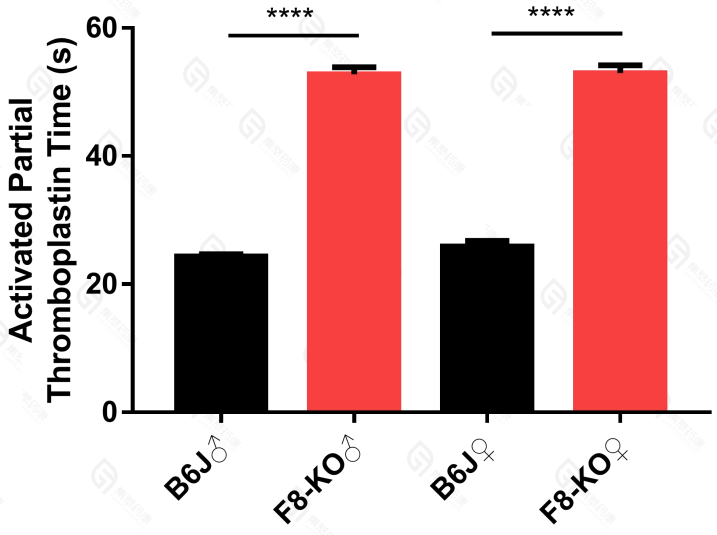

Figure 4. Detection of APTT in WT and F8-KO mice. The APTT in F8-KO mice was significantly longer than that in control mice. (Data were presented as Mean ± SEM, ****, P≤0.0001)

4. Bleeding volume and clotting time test

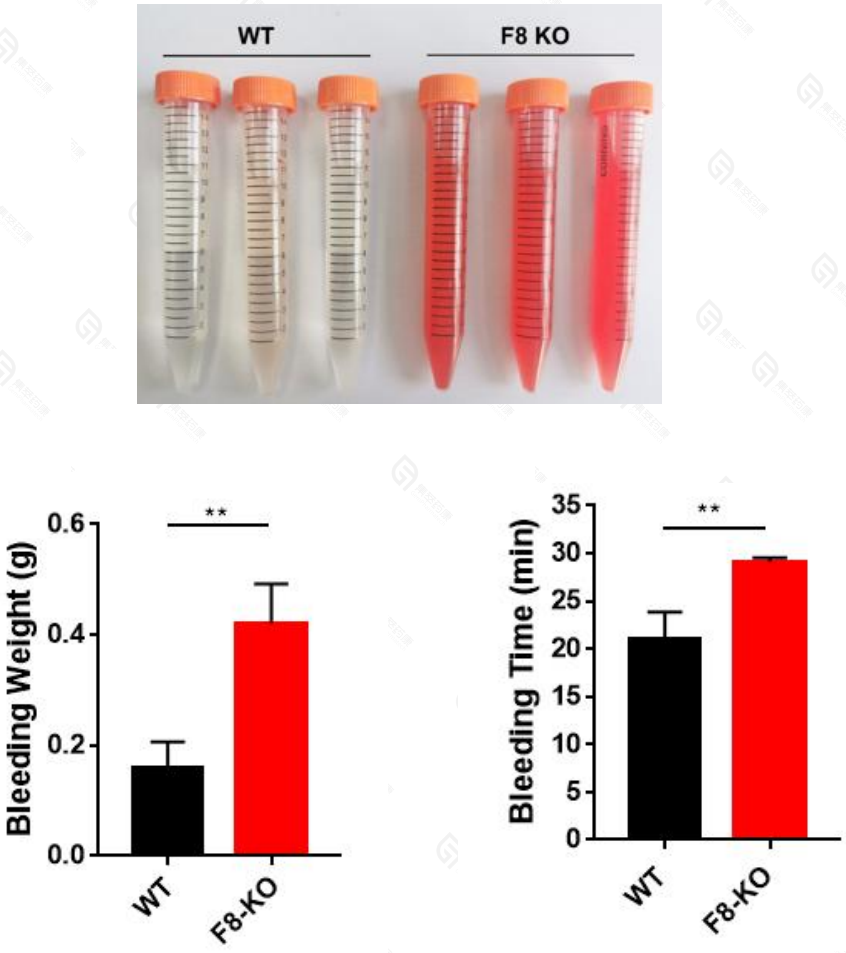

Fig.5 Detection of bleeding volume and coagulation time in B6-F8-KO mice. B6-F8-KO mice had significantly increased bleeding volume and coagulation duration after tail vein amputation compared with wild-type mice.

References

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2. Merlin S, Cannizzo ES, et al. "A Novel Platform for Immune Tolerance Induction in Hemophilia A Mice." Mol Ther, 2017 Aug, 25(8):1815-1830.

3. Giancarlo Castaman, et al. "Hemophilia A And B: Molecular And Clinical Similarities And Differences." Haematologica September 2019 104: 1702-1709.

4. G Kemball-Cook, et al. "The factor VIII Structure and Mutation Resource Site: HAMSTeRS version 4." Nucleic Acids Res. 1998 Jan 1; 26(1): 216–219.

5. El-Maarri O, et al. "Analysis of mRNA in hemophilia A patients with undetectable mutations reveals normal splicing in the factor VIII gene." J Thromb Haemost. 2005 Feb;3(2):332-339.