江苏集萃药康生物科技有限公司
GemPharmatech Co.,Ltd

B6-hPCSK9

Strain Name：B6/JGpt-*Pcsk9*$^{em1Cin(hPCSK9)}$/Gpt

For short：B6-hPCSK9

Strain Type：KI

Strain Number：T015765

Background：C57BL/6JGpt

Description

Plasma LDL-C are cleared from the plasma mainly through the LDLR pathway. After LDL binds to LDLR, LDL and LDLR are internalized into clathrincoated pits and degraded in the lysosome. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a known secretory factor that negatively regulates the expression level of LDLR on the cell membrane. PCSK9 mainly expressed in the liver tissues. Secreted PCSK9 binds to the LDLR and then increases lysosomal degradation. Studies on the human PCSK9 gene have shown that PCSK9 gain-of-function mutations are related to familial hyperlipidemia, and PCSK9 loss-of-function mutations have 15 to 28% lower LDL-C levels than ordinary people. Similarly, overexpression and knockout of PCSK9 in mice could down-regulate and up-regulate the expression level of LDLR, respectively, resulting in hyperlipidemia and hypolipidemia in these two mice line. Therefore, PCSK9 is an important regulator in the cholesterol metabolism pathway. Inhibiting PCSK9 expression level or activity could significantly reduce the level of "bad" cholesterol LDL-C. Thus, PCSK9 is an efficient target for the development of anti-hyperlipidemia drugs.

Gempharmatech has develop the B6-hPCSK9 mice which humanize the entire coding region of the mouse PCSK9 gene. The liver LDLR expression level and plasma LDL-C level of this strain are similar to those of wild-type mice. B6-hPCSK9 mice could develop hyperlipidemia through feeding with high-cholesterol diet. Thus, B6-hPCSK9 mice is an ideal animal model for evaluating the efficacy of anti-hyperlipidemia drugs targeted PCSK9.

Strategy

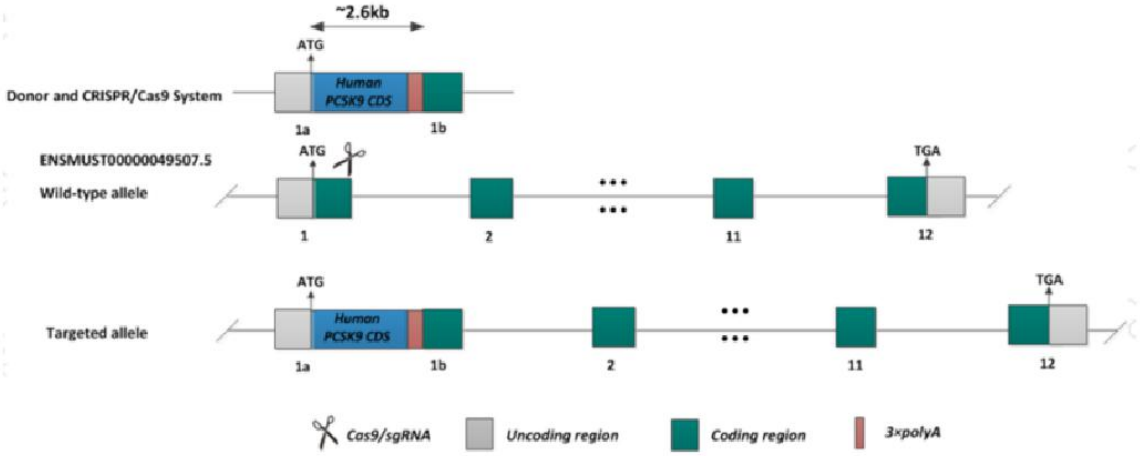

Fig.1 Schematic diagram of B6-hPCSK9 mice.

Application

1. Cardiovascular disease research;

2. Screen and evaluate humanized PCSK9 antibody;

3. Evaluation of the combined effect of PCSK9 antibody and lipid-lowering drugs, such as statin.

Data support

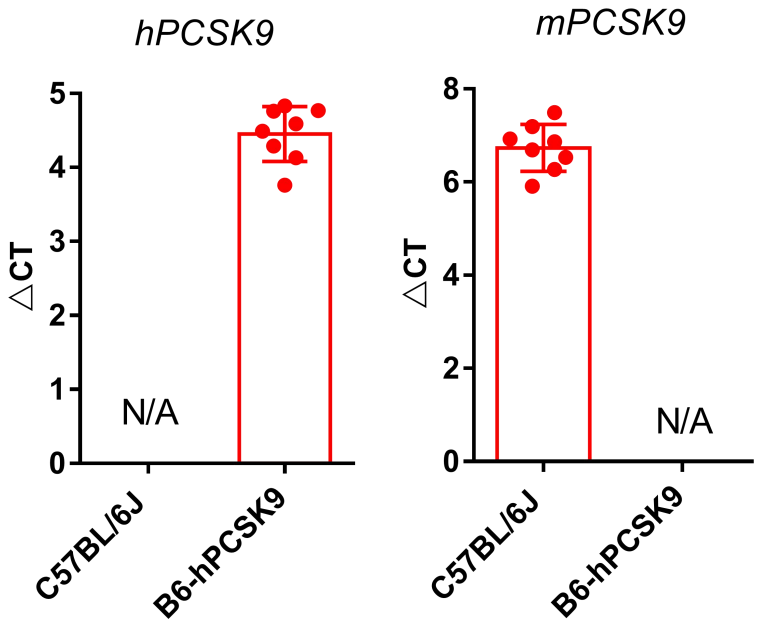

Fig 1. Only human PCSK9 mRNA but not murine PCSK9 mRNA was expressed in the liver of B6-hPCSK9 mice (5 weeks old). Data were presented as Mean±SD，n=8。

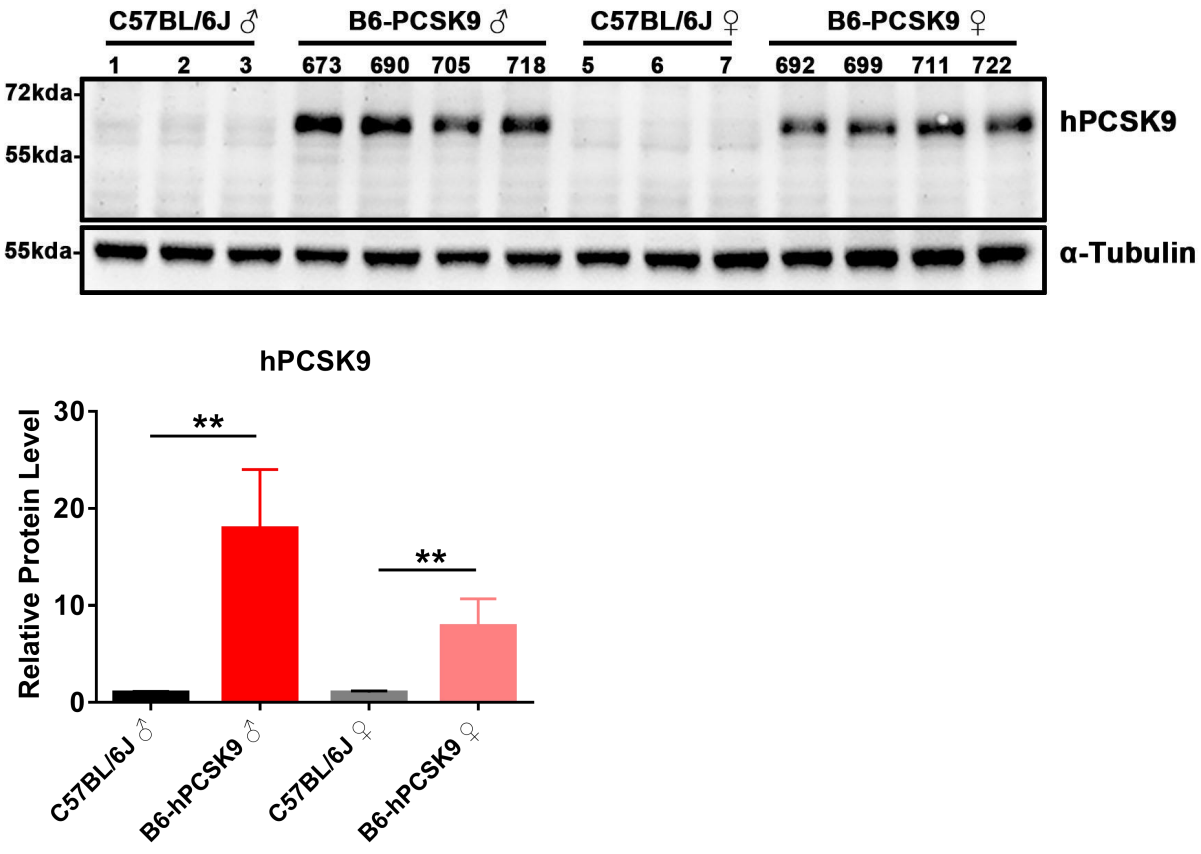

Fig 2. hPCSK9 protein was detected in the liver of B6-hPCSK9 mice but not in the liver of C57BL/6J mice (5 weeks old). Data were presented as Mean±SD，n=3~4. **，p<0.01 by unpaired t test.

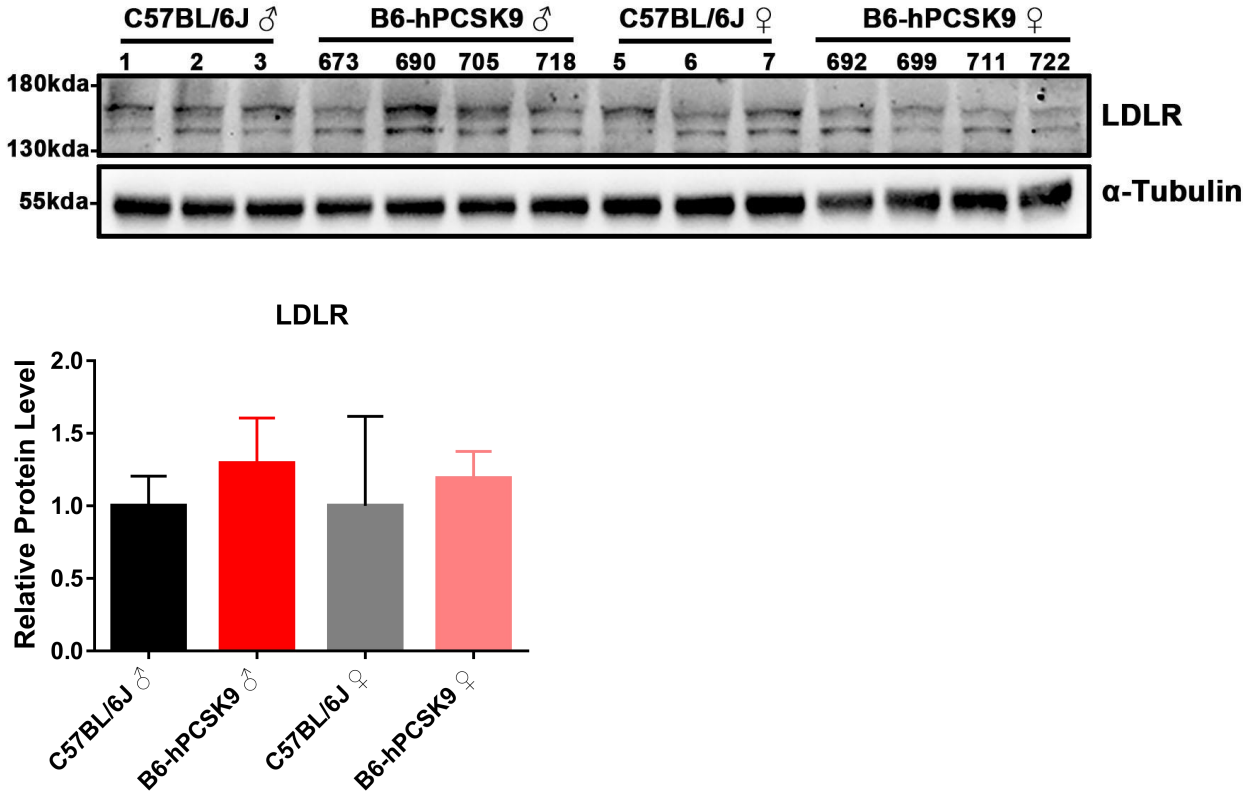

Fig 3. There were no significant difference of liver LDLR expression between C57BL/6J and B6-hPCSK9 mice (5 weeks old). Data were presented as Mean±SD，n=3~4.

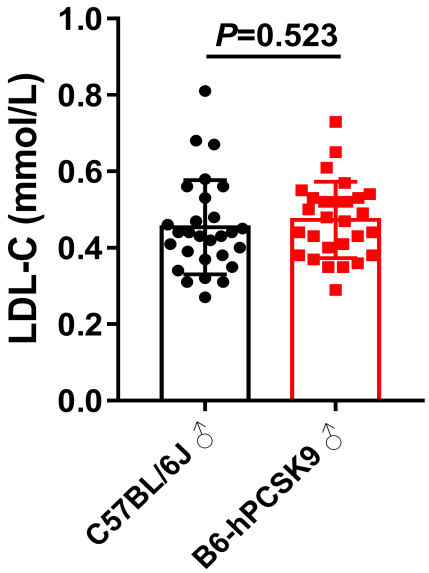

Fig 4 There were no significant difference of plasma LDL-C level between C57BL/6J and B6-hPCSK9 mice (8 weeks old). Data were presented as Mean±SD，n=20. P=0.523 by unpaired t test。

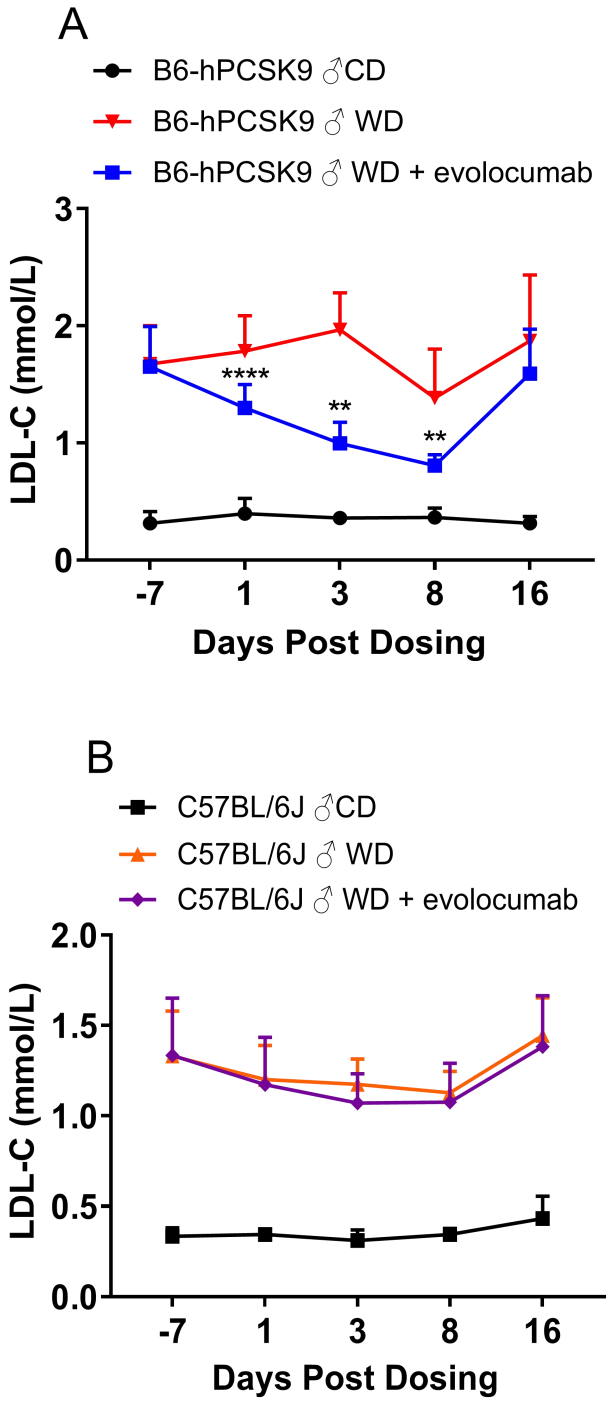

Fig 5. A single tail vein injection of evolocumab (20mpk) could significantly reduce the plasma LDL-C level of western diet-fed B6-hPCSK9 mice, but no similar effect was observed in western diet-fed C57BL/6J mice. Data were presented as Mean±SD, n=5~8。**, $p<0.01$; ***, $p<0.001$ Vs B6-hPCSK9+WD by unpaired t test。

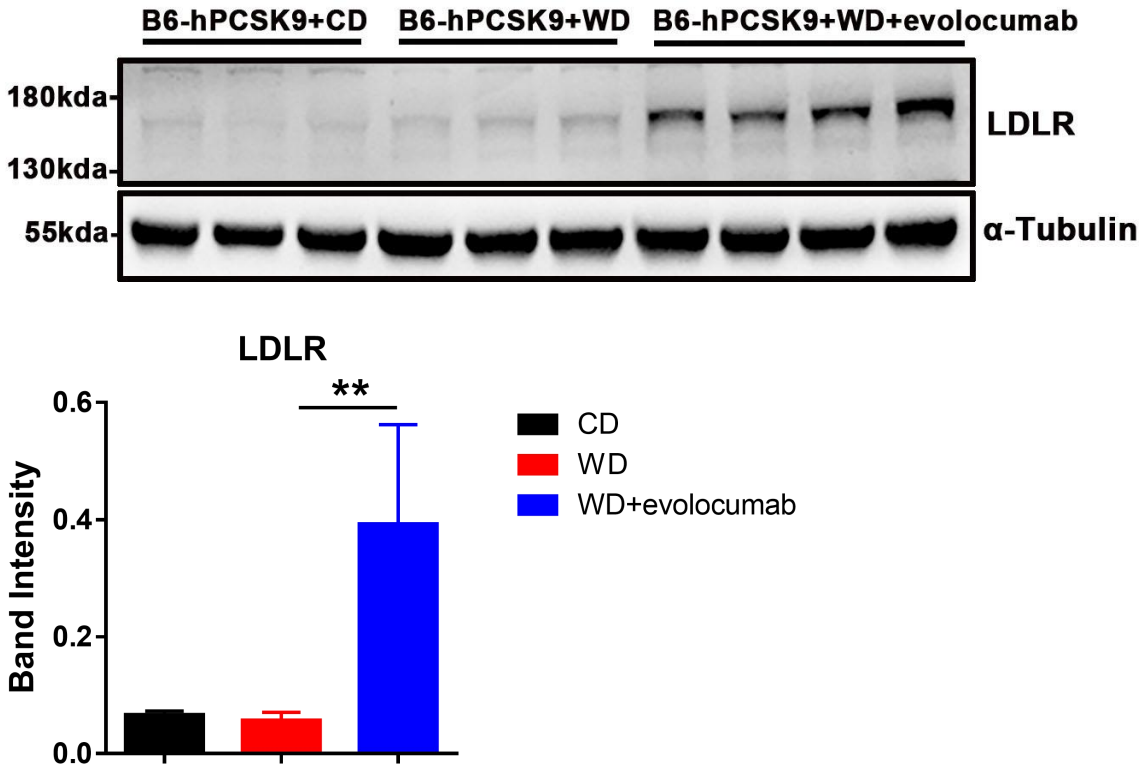

Fig 6. 3 days after a single tail vein injection of evolocumab (20mpk), the expression level of liver LDLR in western diet-fed B6-hPCSK9 mice was significantly increased. Data were presented as Mean ±SD, n=3~4。 **, p<0.05 Vs B6-hPCSK9+WD by one way ANOVA with Fisher`s LSD test。

References

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