B6-hPCSK9-UTR

Strain Name: B6/JGpt-*Pcsk9*$^{em1Cin(hPCSK9\text{-}UTR)}$/Gpt
Strain Number: T053388
Strain Type: Knock-in
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-UTR mice which humanize the entire coding region and 3' UTR of the mouse PCSK9 gene. This strain is suitable for the in vivo screening and evaluation of RNAi therapy that target hPCSK9, especially target the 3' UTR of hPCSK9 mRNA.

Application

1. Cardiovascular disease research;
2. Screen and evaluate RNAi therapy that target hPCSK9.

Data support

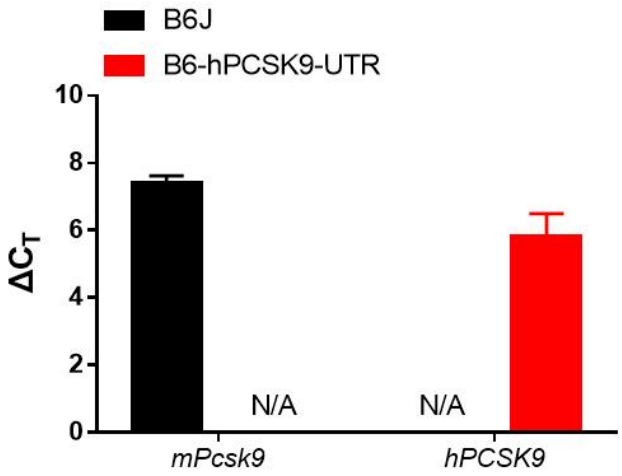

Fig 1. Detection of hPCSK9 mRNA expression in B6-hPCSK9-UTR mice

Only human PCSK9 mRNA but not murine PCSK9 mRNA was expressed in the liver of B6-hPCSK9-UTR mice (5 weeks old). Data were presented as Mean±SD，n=2。

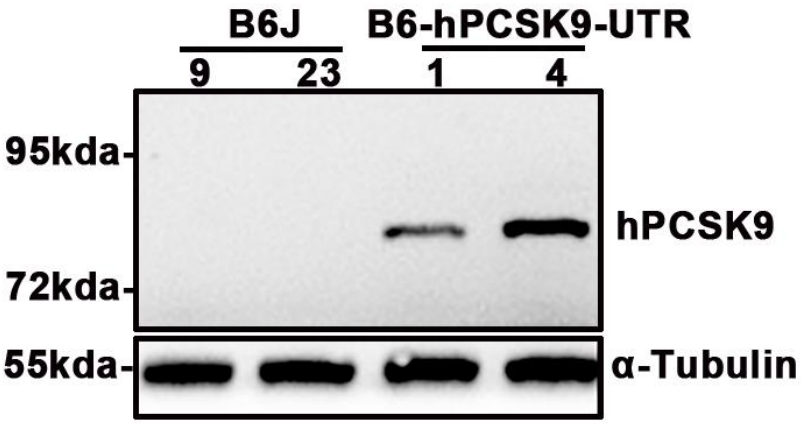

Fig 2. Detection of hPCSK9 protein expression in the liver of B6-hPCSK9-UTR mice

hPCSK9 protein was detected in the liver of B6-hPCSK9-UTR mice but not in the liver of C57BL/6J mice (5 weeks old).

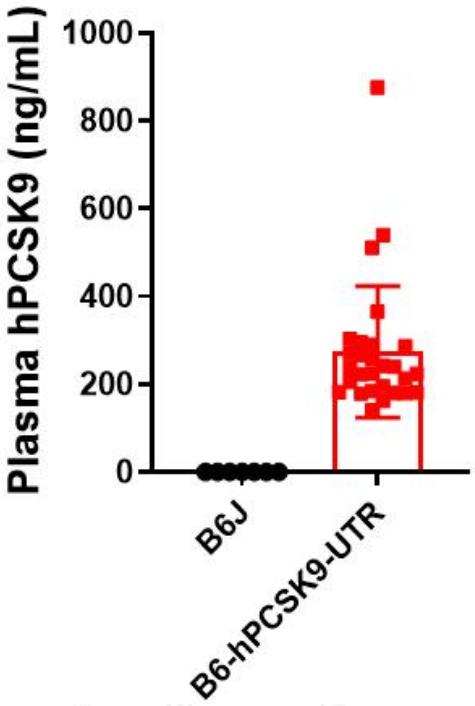

Fig 3. Detection of hPCSK9 protein expression in plasma of B6-hPCSK9-UTR mice

hPCSK9 protein was detected in the plasma of B6-hPCSK9-UTR mice but not in the plasma of C57BL/6J mice (5 weeks old).

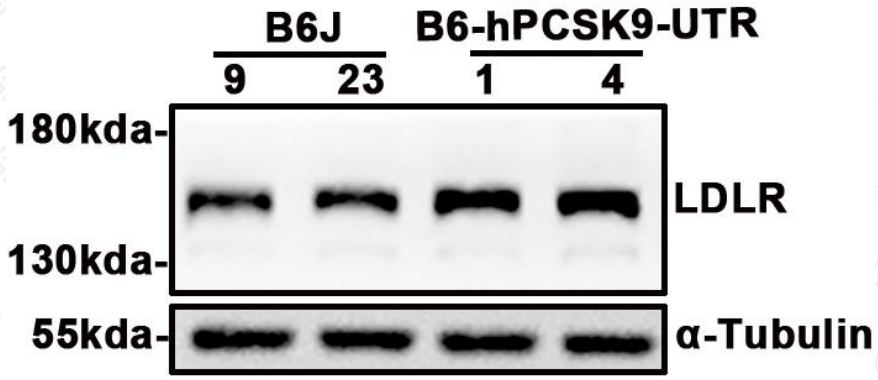

Fig 4. Detection of LDLR protein expression in B6-hPCSK9-UTR mice

The expression level of liver LDLR was higher in B6-hPCSK9-UTR mice than that in C57BL/6J mice (5 weeks old).

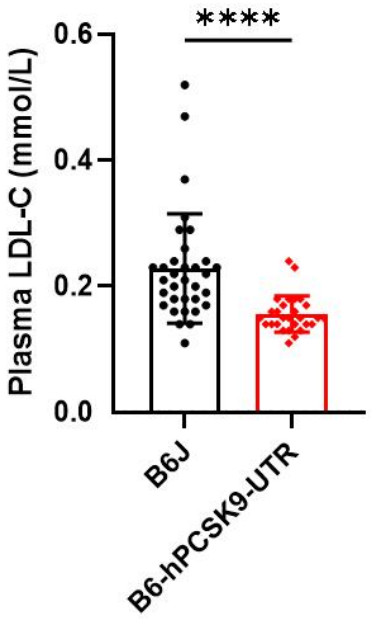

Fig 5.Detection of LDL-C levels in B6-hPCSK9-UTR mice

The plasma LDL-C level was slightly decreased in in B6-hPCSK9-UTR mice than that in C57BL/6J mice (8 weeks old). Data were presented as Mean±SD，n=28~33. ****, p<0.0001 by unpaired t test.

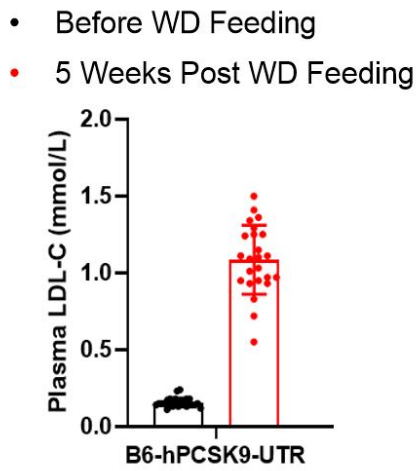

Fig 6. Detection of LDL-C levels in Western diet-fed B6-hPCSK9-UTR mice

Plasma LDL-C level in B6-hPCSK9-UTR mice significantly increased after 5 weeks of Western diet feeding

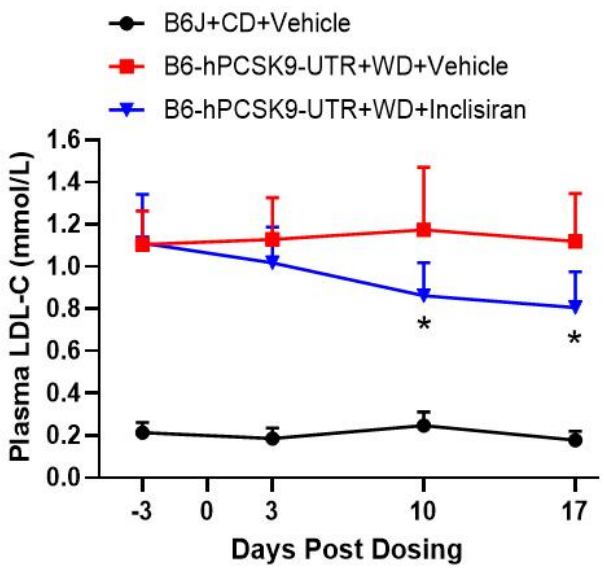

Fig 7. Detection of LDL-C levels in B6-hPCSK9-UTR mice post dosing

A single subcutaneous injection of Inclisiran (6mpk) could significantly reduce the plasma LDL-C level of western diet-fed B6-hPCSK9-UTR mice. Data were presented as Mean±SD, n=5~6. *, p<0.05 Vs B6-hPCSK9-UTR+WD by one way ANOVA with Dunnett's post-hoc test.

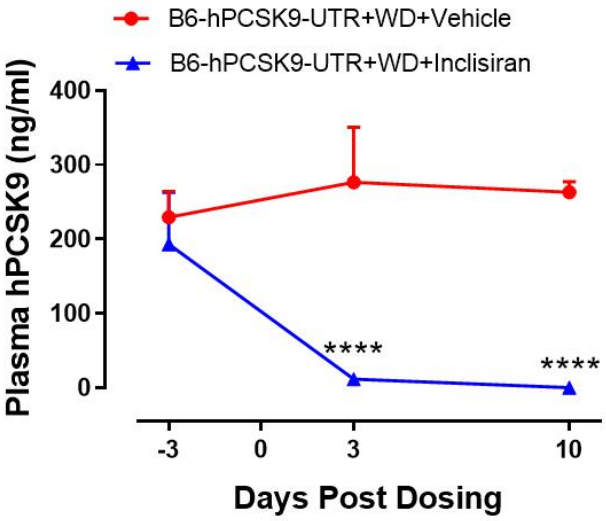

Fig 8. Detection of hPCSK9 protein expression in B6-hPCSK9-UTR mice post dosing

A single subcutaneous injection of Inclisiran (6mpk) could significantly reduce the plasma hPCSK9 level of western diet-fed B6-hPCSK9-UTR mice. Data were presented as Mean±SD, n=5~6. ****, p<0.0001 Vs B6-hPCSK9-UTR+WD by one way ANOVA with Dunnett's post-hoc test.

References

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