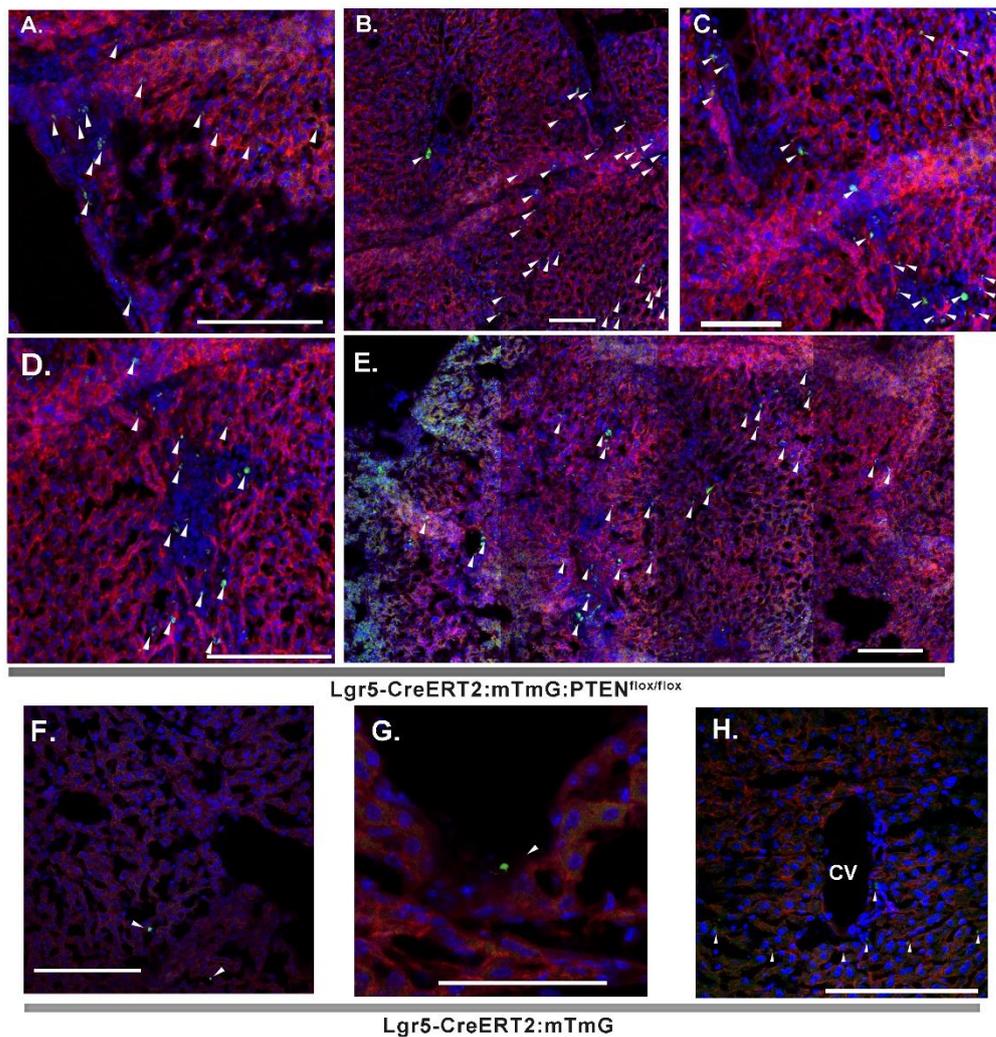
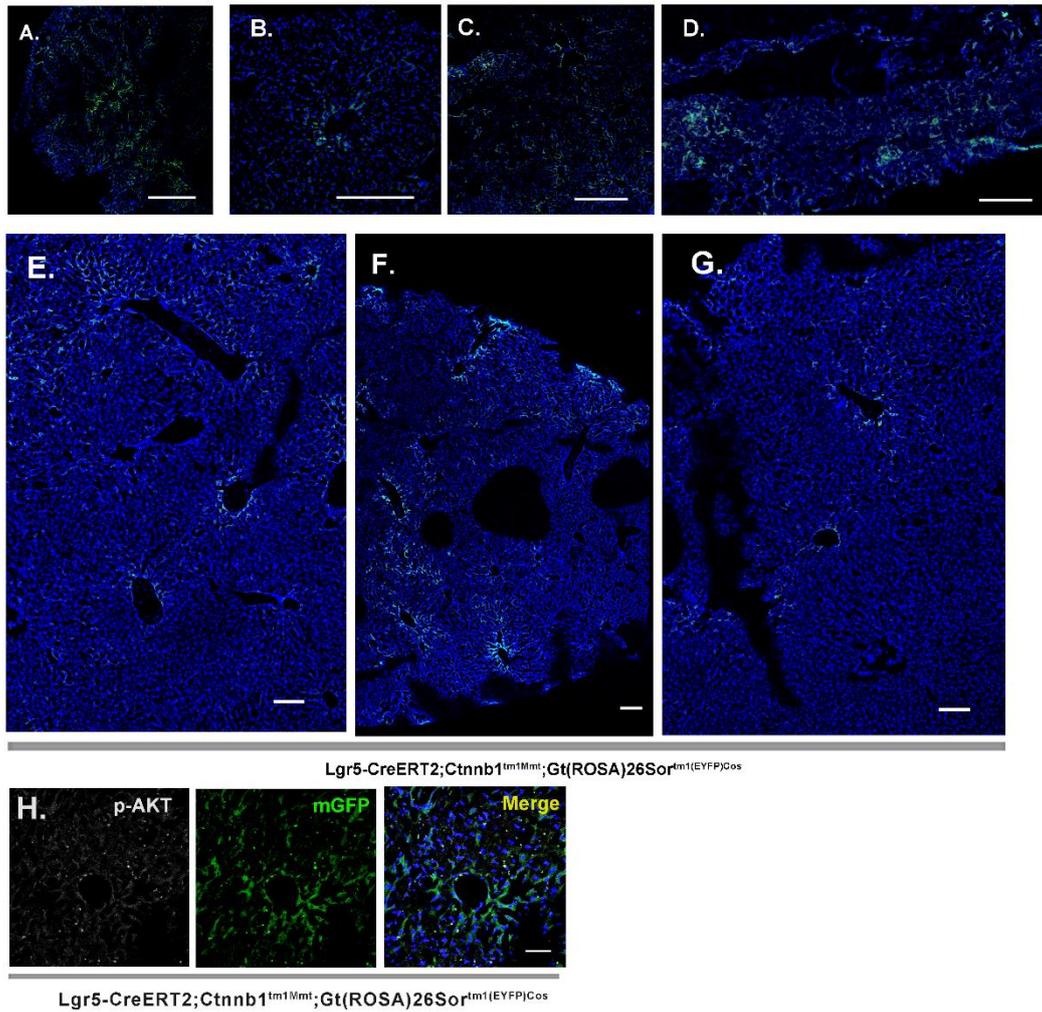


**Supplementary Figure 1.** Schematic diagram of the mouse hybridization in this experiment:  $Lgr5CreER$ ;  $mTmG$  mice were crossed with  $PTEN^{flox/flox}$  mice to obtain  $Lgr5CreER$ ;  $mTmG$ ;  $PTEN^{flox/flox}$  mice.  $Lgr5CreER$ ;  $mTmG$  mice were mated with  $Ctnnb1^{flox/flox}$  mice to obtain  $Lgr5CreER$ ;  $mTmG$ ;  $Ctnnb1^{flox/flox}$  mice. Then  $Lgr5CreER$ ;  $mTmG$ ;  $PTEN^{flox/flox}$  mice were crossed with  $Lgr5CreER$ ;  $mTmG$ ;  $Ctnnb1^{flox/flox}$  mice to obtain  $Lgr5CreER$ ;  $mTmG$ ;  $PTEN^{flox/flox}$ ;  $Ctnnb1^{flox/flox}$  mice. In order to overexpress an activated form of  $\beta$ -catenin in  $Lgr5$ -expressing cells, we crossed  $Lgr5CreER$  mice

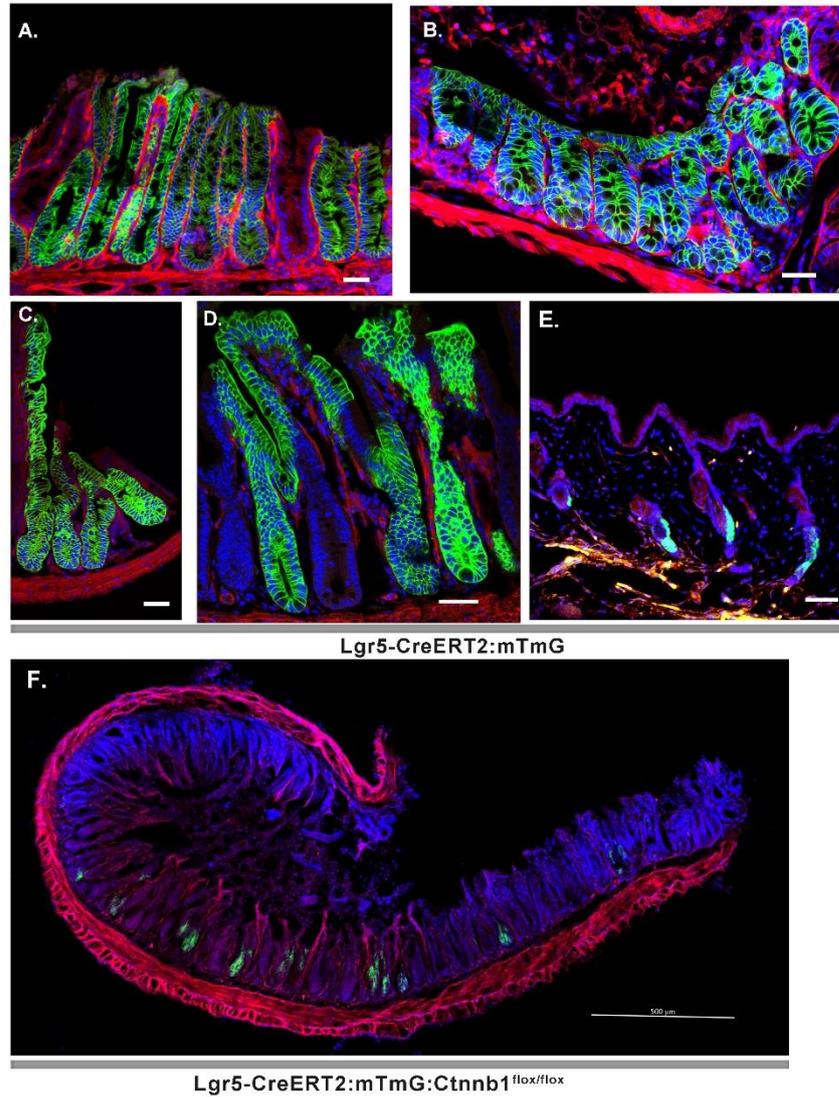
with  $Ctnnb1^{tm1Mmt}$ ;  $Gt(ROSA)26Sor^{tm1(EYFP)Cos}$  mice to obtain Lgr5CreER;  
 $Ctnnb1^{tm1Mmt}$ ;  $Gt(ROSA)26Sor^{tm1(EYFP)Cos}$  mice.



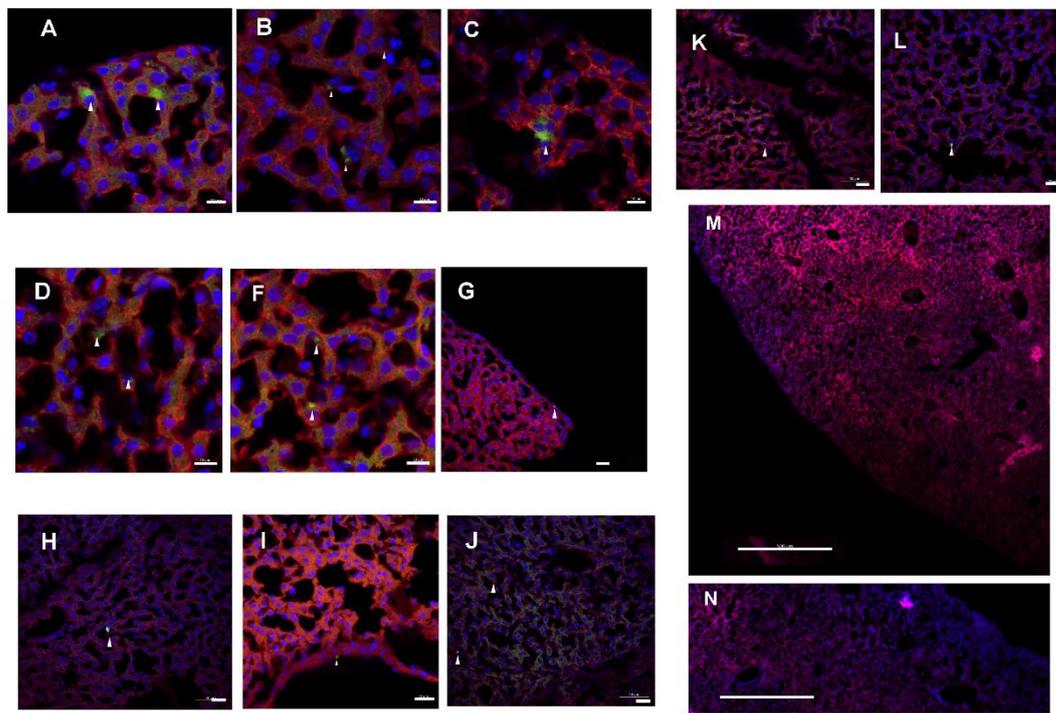
**Supplementary Figure 2. Involvement of PTEN-mediated AKT signaling in Lgr5+ hepatocyte expansion.** (A-E) Analysis of Lgr5+ hepatocyte fate in Lgr5CreER; mTmG; PTEN<sup>flox/flox</sup> reporter mice. Importantly, the number of mGFP+ cells increased compared to control Lgr5CreER; mTmG mice. (F-H) Lgr5+ hepatocytes and their progeny are distributed sporadically in Lgr5CreER; mTmG mice, accounting for only a small part of the total liver. Scale bar: 50  $\mu$ m.



**Supplementary Figure 3. Ectopic activation of  $\beta$ -catenin leads to expansion of Lgr5<sup>+</sup> hepatocytes.** (A-G) The increased distribution of Lgr5<sup>+</sup> hepatocytes triggered by the activation of  $\beta$ -catenin. Scale bar: 50  $\mu$ m.



**Supplementary Figure 4. Tracing of stem cells in the colon, small intestine, and hair follicle.** Analysis of Lgr5-expressing stem cells and their progeny (green) in the (A-B) colon, (C-D) small intestine and (E) hair follicles. (F)  $\beta$ -catenin deletion in Lgr5+ stem cells significantly inhibited their differentiation in Lgr5CreER; mTmG; Ctnnb1<sup>flox/flox</sup> mice. Scale bar: 20  $\mu$ m (A-E), 500  $\mu$ m (F).



Lgr5-CreERT2:mTmG:PTEN<sup>flx/flx</sup>;Ctnnb1<sup>flx/flx</sup>

**Supplementary Figure 5. The simultaneous inhibition of PTEN and  $\beta$ -catenin resulted in only sporadic Lgr5<sup>+</sup> hepatocytes in the liver.** Images of Lgr5-lineage cells in the liver upon PTEN and  $\beta$ -catenin deletion. Note that almost no mGFP-labeled cells were observed in the liver. Scale bar: 20  $\mu$ m (A-L), 500  $\mu$ m (M-N).