Supplemental Figures:

Supplemental Figure 1 Hematoxylin and eosin stained morphology timeline of CCl_4 induced liver injury. (A) H&E of the uninjured adult mouse liver. (B) 6 hours following CCl_4 administration, hepatocytes closest to the central vein (inside dashed lines) begin to show signs of steatosis (*). (C) By 12 hours, the affected area broadens and more hepatocytes show signs of steatosis (*). (D) 1 day after CCl_4 administration, apoptotic cells (arrowheads) are observed within the affected pericentral region. (E) Massive centrilobular necrosis becomes obvious by day 2 after CCl_4 administration (inside dashed lines). (F) The repair phase begins around 3 days following CCl_4 administration. Inflammatory infiltration is readily visible, as macrophages and neutrophils invade the necrotic debris. (G) By day 4, the injured area shrinks in size due to the proliferation of hepatocytes and the clearing out of the necrotic debris. (H) By 1 week after CCl_4, the liver lobule looks most normal. Remnant inflammatory infiltration can be observed at some central veins. (I) The normal histology of the liver lobule is restored by 2 weeks after CCl_4. CV = central vein, PV = portal vein. All images taken with a 10x objective.

Supplemental Figure 2 Axin2 mRNA *in situ* hybridization timeline of CCl_4 induced liver injury. (A) Axin2 expression (red dots) is limited to pericentral hepatocytes in the uninjured liver. (B) Loss of Axin2 expression in the pericentral region is evident by 6 hours after CCl_4. (C & D) Robust Axin2 expression is observed in mid-lobular hepatocytes adjacent to the injury border by day 3. (E & F) Normal Axin2 expression pattern in pericentral hepatocytes is re-established upon injury recovery. CV = central vein, PV = portal vein. Dashed lines denote injury border. 100μm scale bars.

Supplemental Figure 3 Label dilution studies in injured Axin2-rtTA; Tet-O-H2BGFP reporter mice. (A) Schematic of CCl_4 injury and doxycycline (Dox) "pulse-chase" scheduling. (B) Peri-injury Axin2+ hepatocytes (green) are labeled after 48 hours of 1 mg/mL doxycycline chase following CCl_4 (day 3). (C) After an 11 day "chase" period, newly re-populated pericentral region contains predominantly H2BGFP-labeled hepatocytes. At this timpeoint, it is evident that H2BGFP signal intensity is significantly lower than that observed at day 3, however GFP signal for the image shown was enhanced in order for dim H2BGFP signal to be visualized. 100um scale bars shown. CV = central vein, PV = portal vein. Dashed lines represent injury border. (D) There was an overall increase in the amount of labeled cells, as measured by GFP+ nuclear area, over the injury repair course, though this increase did not reach statistical significance (n=4 animals analyzed per timepoint, error bars represent S.E.M.). (E) Quantification of GFP intensity by flow cytometry. GFP mean fluorescence intensity (MFI) was normalized to that of the GFP+ population observed in day 3 samples. Each symbol represents the MFI for one animal, n=3 animals for day 3, n=2 for days 7, and n=2 for day 14. ***p-val<0.001 by multiple comparisons using one-way ANOVA.

Supplemental Figure 4 mRNA *in situ* hybridization for Wnt2, Wnt9b, Wnt4, and Wnt5a. (A) Wnt2 is expressed in the injured tissue as well as in the uninjured and recovered liver. (B) Wnt9b expression broadens during repair. (C) Wnt4 is expressed in the injured area

when inflammatory infiltration is at its peak (day 4 after CCl_4). (D) Wnt5a is also expressed in the injured area only when inflammatory infiltration is at its peak (day 4 after CCl_4). Diffuse pink staining found in the day 3 column is non-specific stain trapping by damaged tissue. Positive signal are the red puncta. 100μm scale bars. Arrows indicate examples of positive *in situ* signal.

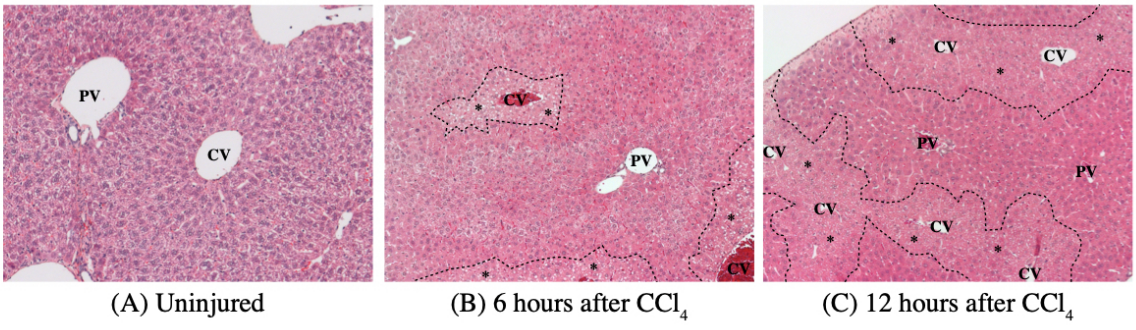
Supplemental Figure 5 (A) Single cell RNA-seq derived gene expression profile of non-parenchymal cells in the day 3 CCl_4-injured liver; each row represents an individual gene, each column represents an individual cell. Yellow denotes more expression, magenta denotes less expression. Cells are grouped by cell type as shown in the (C) legend. (B) tSNE plot showing contribution from individual animals, color coded according to leged in upper right corner of the plot. (D) Violin plots of log-normalized expression (natural logarithm of 1+counts per 10,000) of cell type specific markers used to identify seven distinct non-parenchymal cell clusters after injury. (E) Frequency of specific cell types sampled in scRNA-seq analysis. (F) Violin plots of log-normalized expression of Wnt5a show that very few Wnt5a expressing cells were captured in our scRNA-seq experiments.

Supplemental Figure 6 Double mRNA *in situ* hybridization for Wnt 2, 4, 5a, 9b and Pecam1 (endothelial cells), Adgre1 (Kupffer cells/macrophages), or Reelin (stellate cells) in the day 3 injured liver. (A) Wnt2 is expressed by Pecam1+ cells but not by Adgre1 or Reln positive cells. (B) Wnt9b is expressed by Pecam1+ cells but not by Reln positive cells. There is 1 cell that expresses both Wnt9b and Adgre1 in the image shown. (C) Wnt4 is expressed by Reln+ cells, but not by Adgre1 or Pecam1 positive cells. (D) Wnt5a is expressed by Reln+ cells, but not by Pecam1 positive cells. There is 1 cell that is double positive for Wnt5a and Adgre1 in the image shown. Blue puncta represents positive Wnt signal, red puncta represents positive cell-type specific marker signal. Diffuse pink staining found in the pericentral necrotic tissue is due to color trapping by damaged tissue. 100μm scale bars. Arrowheads indicate examples of double-positive *in situ* signal.

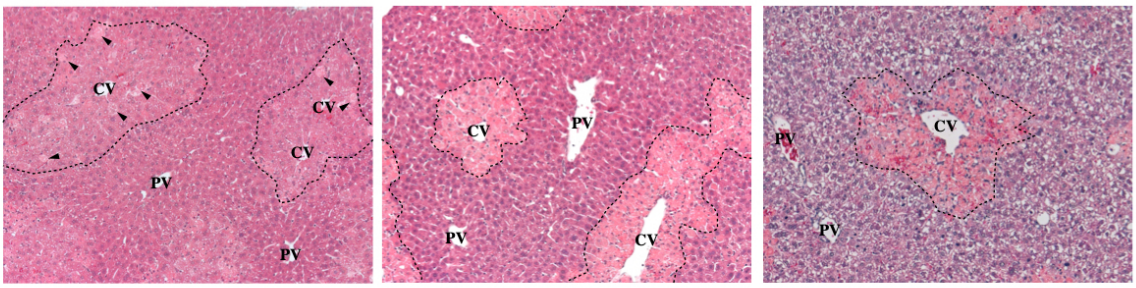
Supplemental Figure 7 Hepatocyte number following injury and upon injury repair. (A) Diagram of ImageJ automated thresholding and particle analysis workflow that was used to generate hepatocyte count data. (B) The number of hepatocytes significantly increased between 3 days (n=3) and 14 days (n=4) following CCl_4 injury. Error bars show S.E.M. ****$p<0.0001$ by two-tailed t-test.

Supplemental Figure 8 Initial injury response to CCl_4 in control and Bcat-cKO mice. (A) Control and Bcat-cKO mice exhibited similar extent of parenchymal injury following 1mL/kg CCl_4 administration on injury day 2. Error bars show S.E.M., n.s. = not statistically significant ($p=0.9$) by two-tailed t-test for n=3 control and n=3 Bcat-cKO animals.

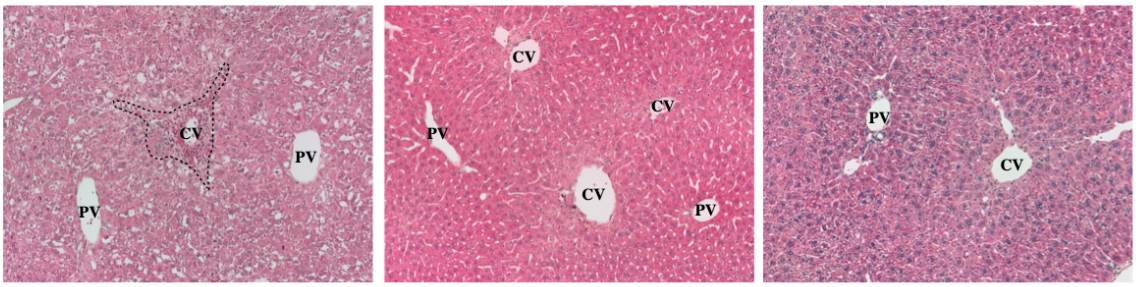
Supplemental Figure 1: H&E morphology timeline of CCl_4 induced liver injury



(A) Uninjured (B) 6 hours after CCl_4 (C) 12 hours after CCl_4

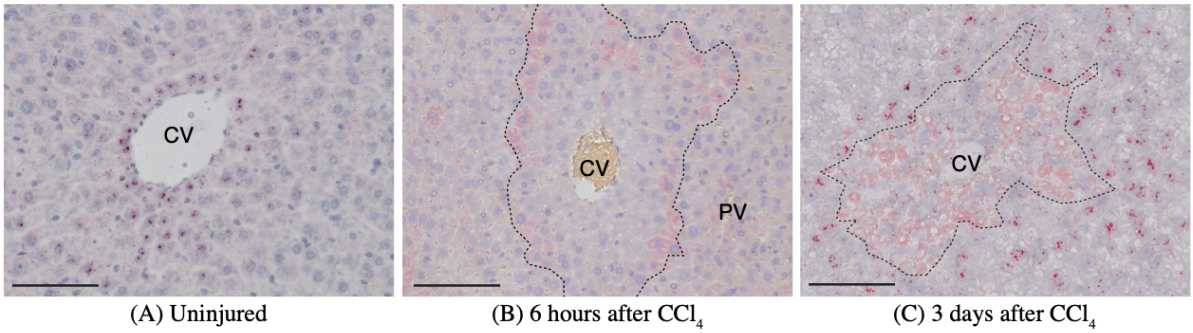


(D) 1 day after CCl_4 (E) 2 days after CCl_4 (F) 3 days after CCl_4

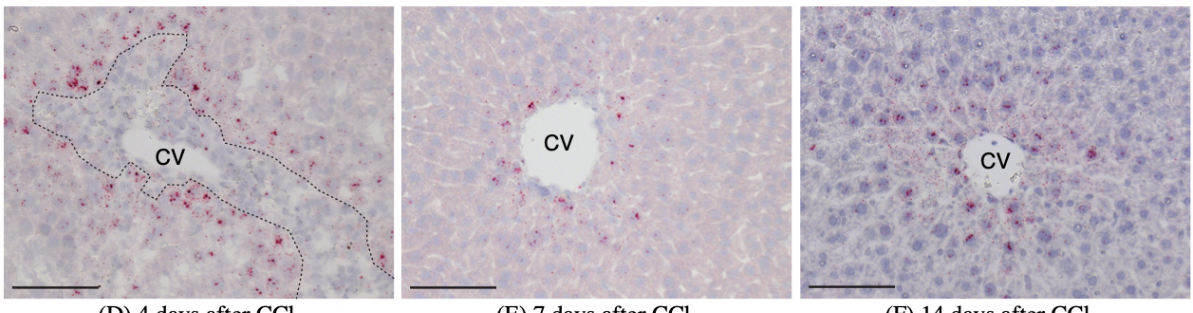


(G) 4 days after CCl_4 (H) 7 days after CCl_4 (I) 14 days after CCl_4

Supplemental Figure 2: Axin2 mRNA*in situ*hybridization timeline of CCl_4 induced liver injury

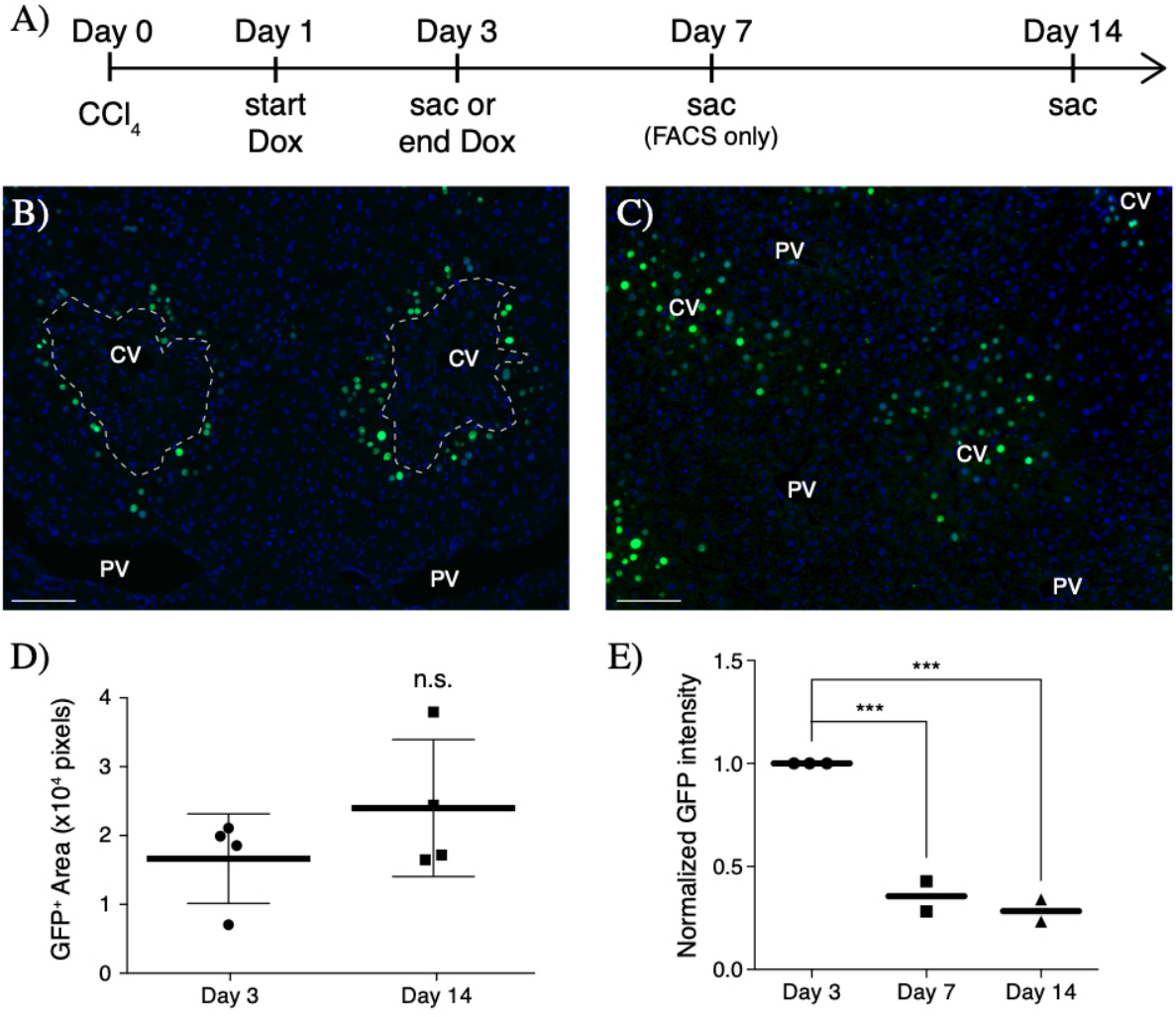


(A) Uninjured (B) 6 hours after CCl_4 (C) 3 days after CCl_4

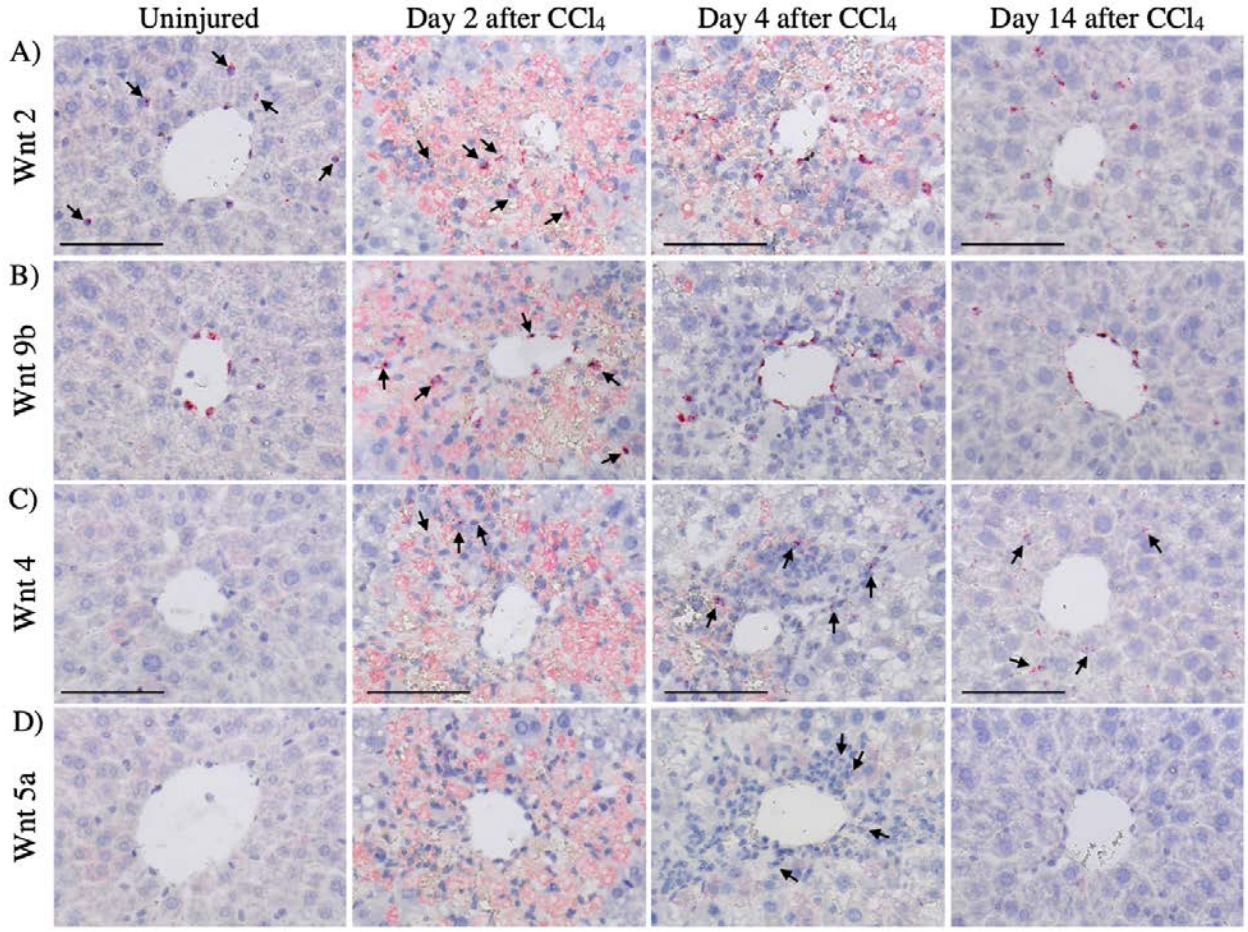


(D) 4 days after CCl_4 (E) 7 days after CCl_4 (F) 14 days after CCl_4

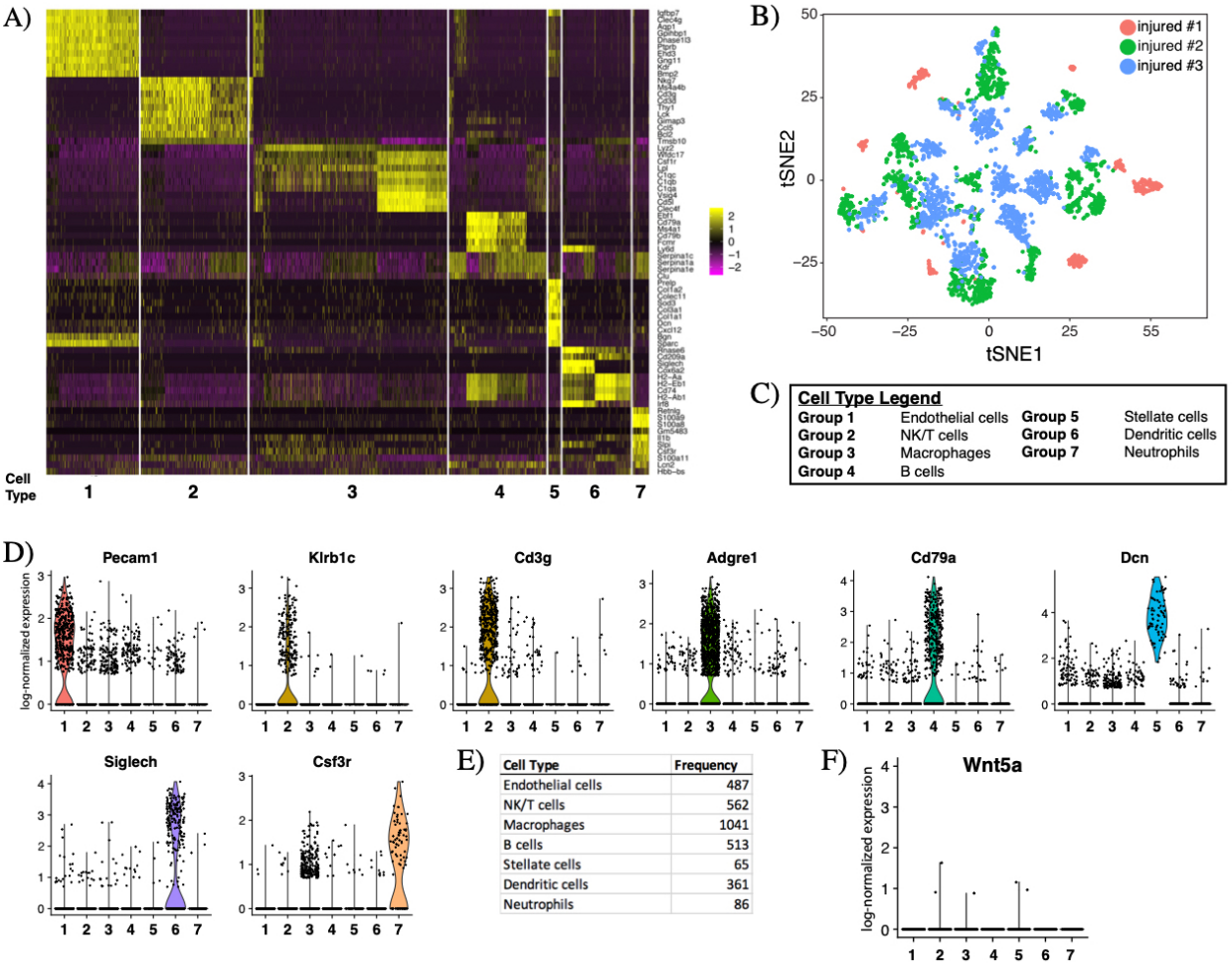
Supplementary Figure 3:



Supplementary Figure 4

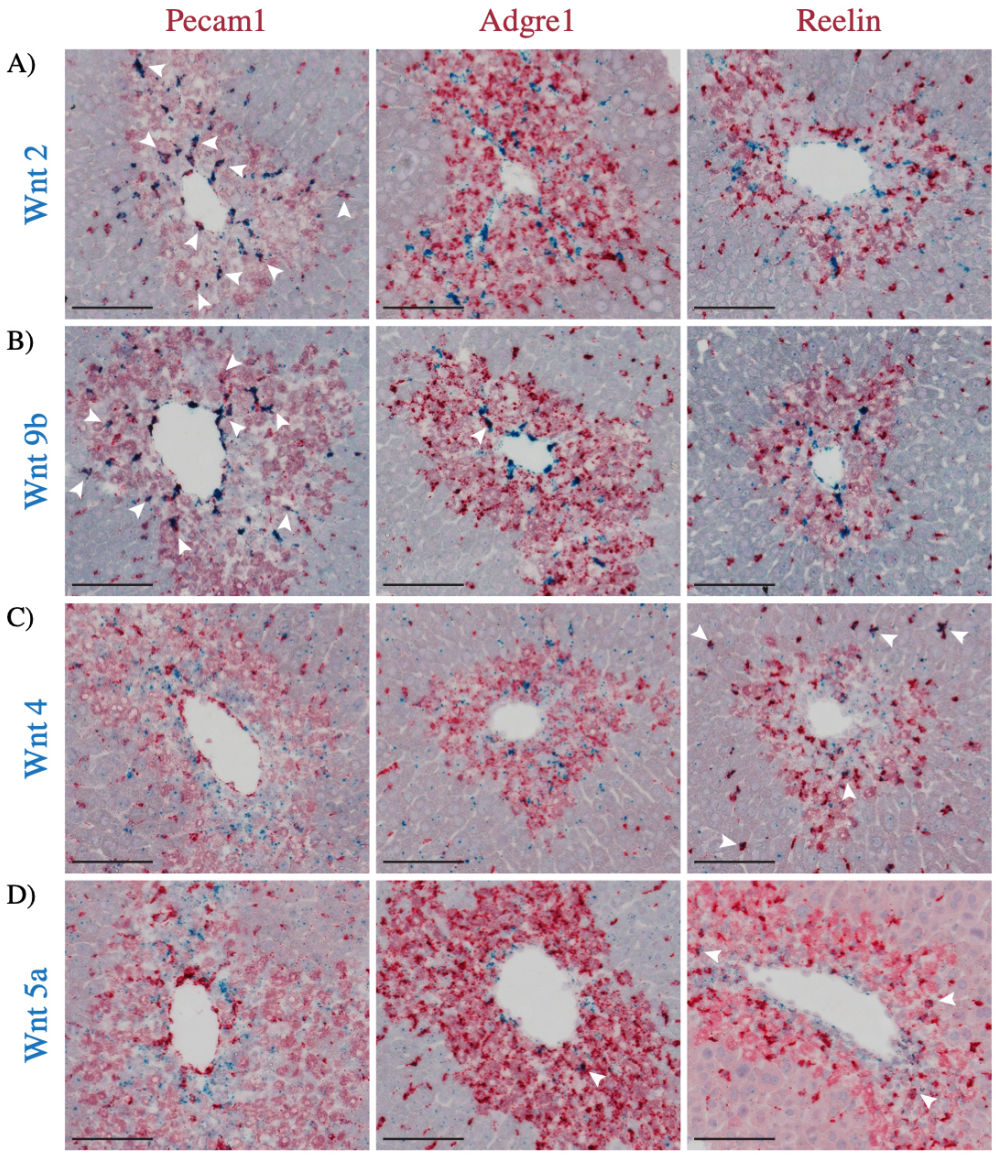


Supplementary Figure 5



Cell Type	Frequency
Endothelial cells	487
NK/T cells	562
Macrophages	1041
B cells	513
Stellate cells	65
Dendritic cells	361
Neutrophils	86

Supplemental Figure 6 -- double in situs



Supplementary Figures 7 and 8