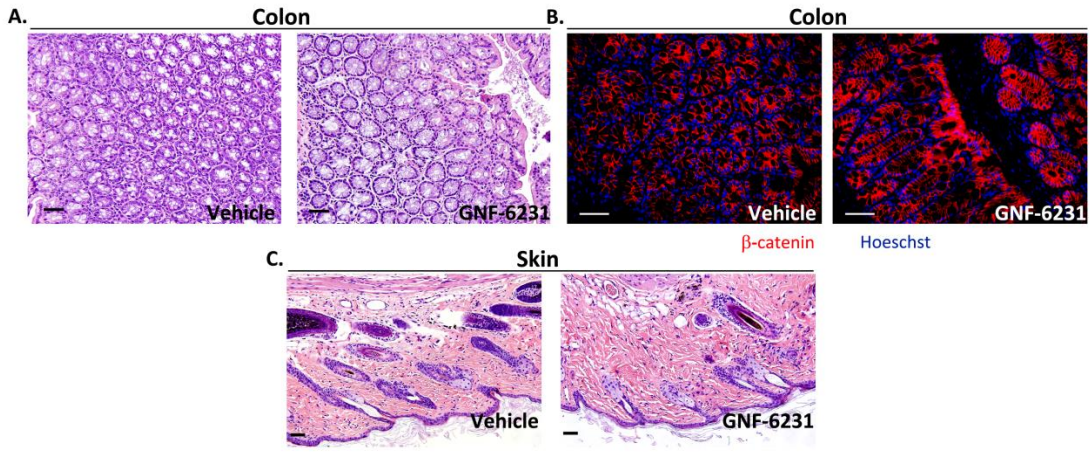
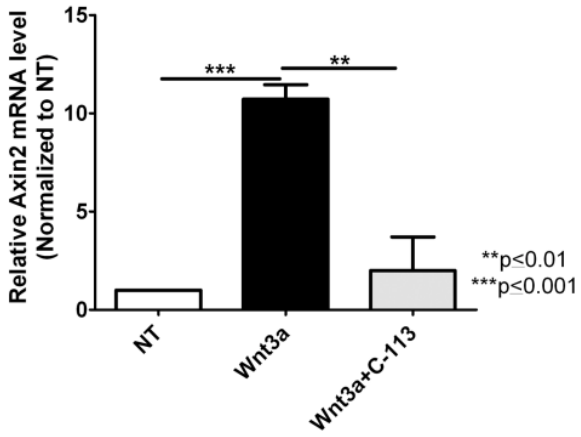
Supplementary Figure 1.



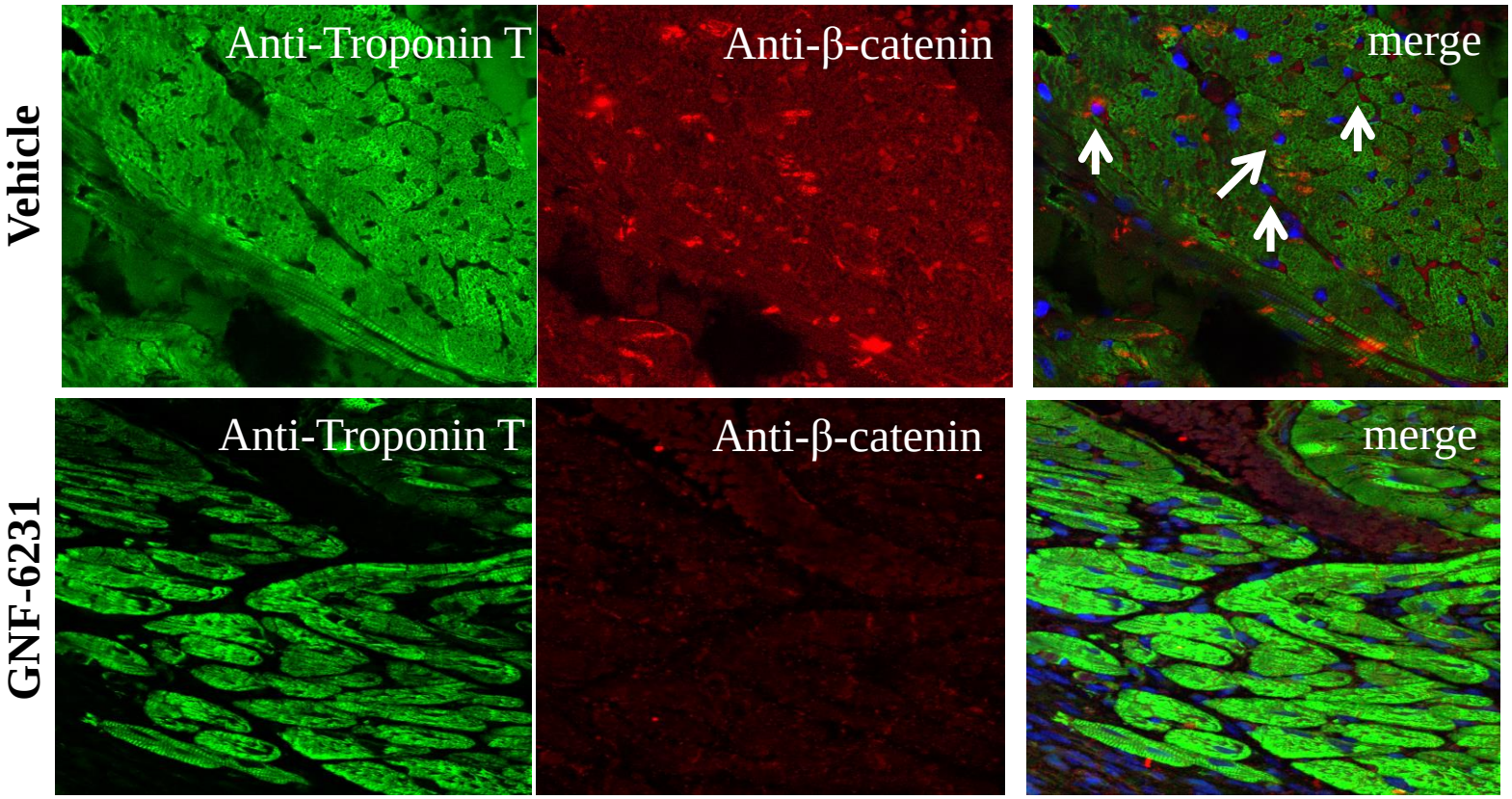
Supplementary Figure 1: GNF-6231 causes no detectable toxicity in Wnt-dependent tissues. Representative **(A)** H&E stained sections, and **(B)** β-catenin immunostained sections of the colon depicted that GNF-6231 treatment had no effect on colon morphology and β-catenin protein level and localization in the tissue. **(C)** Representative H&E stained sections of skin from GNF-6231 or vehicle-treated animals. Scale bars in A and B equal 50µm. Images are representative of at least 4 sections from $N \geq 3$ mice.

Supplementary Figure 2.



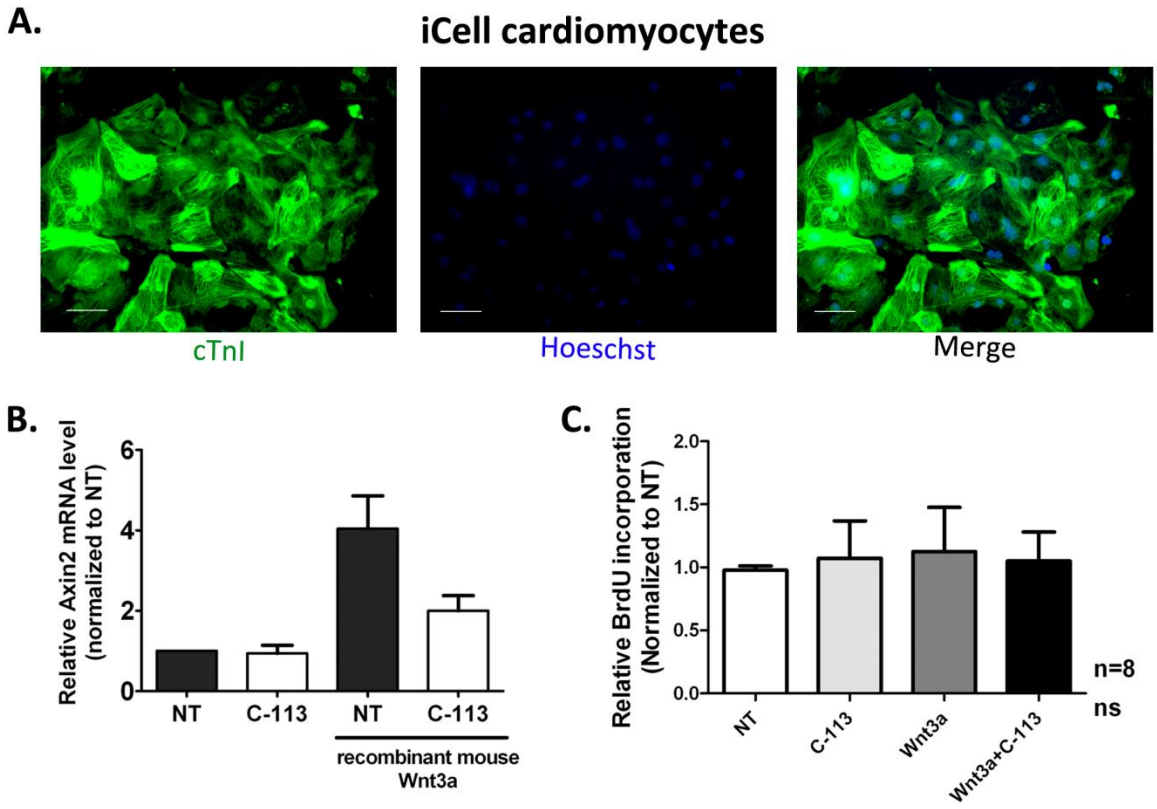
Supplementary Figure 2: C-113 inhibits Wnt target gene expression. Graph showing relative Axin2 mRNA expression detected by qRT-PCR in $Sca1^{+}$ progenitors treated with recombinant WNT3A or with recombinant WNT3A and Wnt inhibitor C-113. Bars represent mean±SD. *N=3* replicates from independent experiments*; **P≤0.01* and **P≤0.001;* Kruskal-Wallis test with Dunns correction for multiple comparisons.

Supplementary Figure 3.



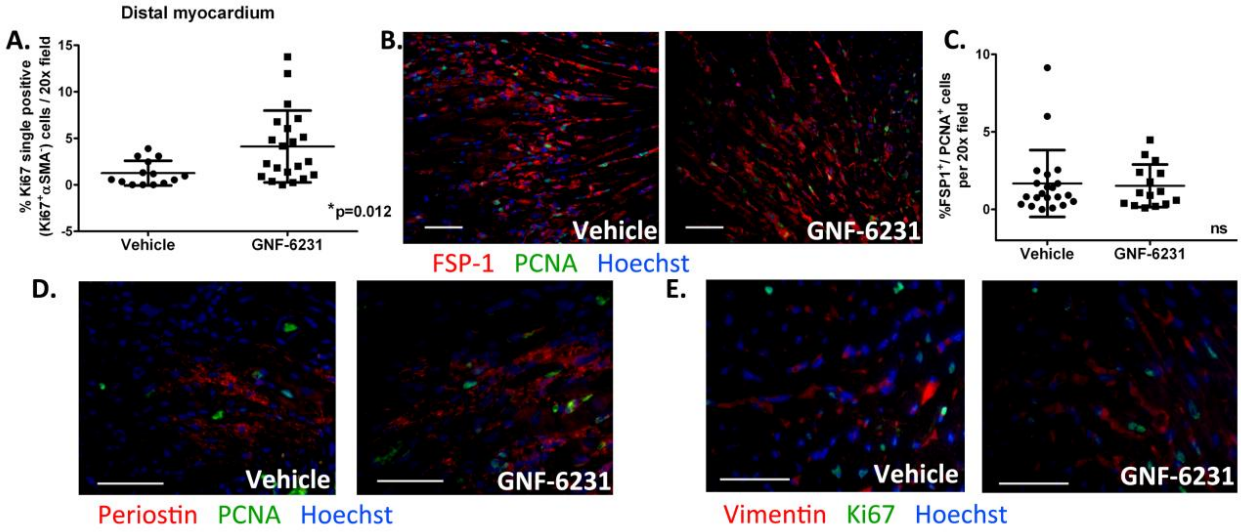
Supplementary Figure 3: GNF-6231 causes reduction in Wnt activation in cardiomyocytes. Representative figures showing paraffin sections from mouse hearts 7 days after MI treated with GNF-6231 (bottom panel) vs. vehicle (top panel) dual stained with anti troponin T to mark cardiomyocytes (green), anti-β-catenin (red), and DAPI (blue) to identify nuclei. Post MI, myocytes exhibit increased nuclear (active) β-catenin . Treatment with GNF-6231 virtually eliminates nuclear β-catenin in cardiomyocytes.

Supplementary Figure 4.



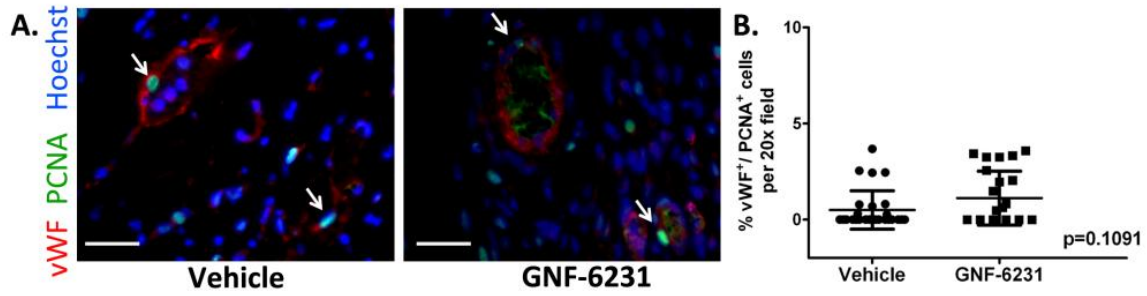
Supplementary Figure 4: iCell cardiomyocytes express the cardiomyocyte marker cTnI, and Wnt pathway modulation does not affect proliferation of HL-1 cardiomyocytes. (A) Representative images of iCell^2 Cardiomyocytes immunostained with the cardiomyocyte marker, cTnI (green). Sections were counterstained with Hoechst (blue). Scale bars equal 50µm. Images are representative of at least 4 sections from *N=3* replicate cell lines. **(B)** Relative Axin2 mRNA expression in HL-1 mouse cardiomyocytes treated with recombinant mouse Wnt3a and/or C-113. Bars represent mean±SD; *N*=3 replicates from independent experiments. **(C)** Relative proliferation measured by BrdU incorporation by HL-1 cardiomyocytes treated with recombinant Wnt3a or Wnt3a and C-113, showing that Wnt pathway modulation did not affect their proliferation. *N=8* replicates from independent experiments.

Supplementary Figure 5.



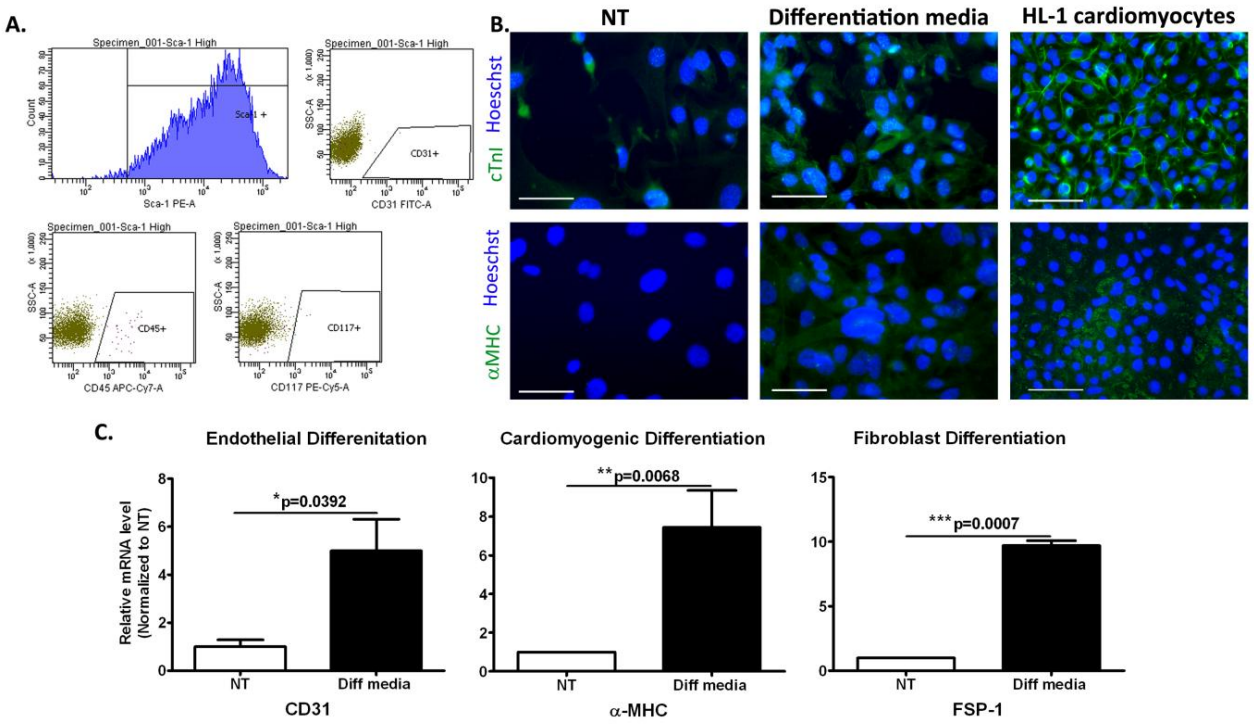
Supplementary Figure 5: Wnt inhibition augments proliferation of Alpha SMA negative cells in the distal myocardium, but does not affect proliferation of other fibroblast subtypes. (A) Quantification of $Ki67^{+}\alpha SMA^{-}$ cells in the distal myocardium showing higher proportion of proliferating αSMA negative cells in GNF6231-treated hearts. *N≥14* obtained from at least 4 sections imaged from *N≥3* mice per group*;*P=0.0120*; Unpaired t-test. **(B)** Co-immunostaining for PCNA and fibroblasts marker FSP-1; quantification is presented in **(C)** showing no difference in percent double positive ($FSP\text{-}1^{+}PCNA^{+}$) cells between GNF-6231 and vehicle treated hearts. *N≥15* obtained from at least 5 sections imaged from *N≥3* mice per group*;* Mann-Whitney test. Representative co-immunostaining for **(D)** PCNA and Periostin, and **(E)** Ki67 and Vimentin; no significant difference in percent double stained cells between GNF-6231 and vehicle-treated sections were observed for both Periostin and Vimentin. Scale bars in B, D and E equal 50µm.

Supplementary Figure 6.



Supplementary Figure 6: GNF-6231 treatment does not affect proliferation of vWF$^+$ endothelial cells in the infracted heart. (A) Representative vWF (red) and PCNA (green) immunostained sections of LV treated with GNF-6231 or vehicle. Sections were counterstained with Hoechst (blue); white arrows mark double stained cells. Scale bars equal 50µm. **(B)** Quantification of vWF and PCNA double positive cells showed no significant difference in percent double positive cells between vehicle and GNF-6231-treated hearts. *N≥20* obtained from at least 4 sections imaged from *N≥5* mice per group; *P=0.1091;* Mann-Whitney test.

Supplementary Figure 7.



Supplementary Figure 7: Conditionally immortalized mouse heart-derived Sca1+ cells are negative for CD31, CD45 and c-kit expression, and can upregulate myocyte, endothelial and stromal markers in specific culture conditions. (A) FACS of $Sca1^{+}CD31^{-}CD45^{-}CD117^{-}$ cardiac progenitor cells. **(B)** Images showing immunostaining for αMHC and cTnI of $Sca1^{+}$ cells (untreated, left panels), cultured in cardiomyocyte differentiation media (middle panels) or HL-1 cardiomyocytes as control (right panel) demonstrated that conditionally immortalized murine $Sca1^{+}$ cells retain capacity to express cardiomyocyte markers in culture. Scale bars equal 50µm. **(C)** Relative gene expression of CD31 (left chart), αMHC (middle chart) and FSP-1 (right chart) in untreated $Sca1^{+}$ cells and following culture in endothelial cell-, cardiomyocyte-, and fibroblast-specific differentiation media, respectively to demonstrate their multilineage potential. *N≥3* replicates from independent experiments; **P=0.0392, **P=0.0068,* and ****P0.0007;* Mann-Whitney test.

Table S1. List of q-RT-PCR primers

Gene	Forward	Reverse
Axin2	GGACAGTAGCGTAGATGGAG	CGGAAAATGAGGTAGAGACA
Col1α1	GCCAGATGGGTCCCCGAGGT	GGGGGTCCAGCAGCACCAAC
CD31	GTGAAGGTGCATGGCGTATC	CACAAAGTTCTCGTTGGAGGT
αMHC	CCACTGTGGTGCCTCGTTC	GCGTCCGTCATTCTGTCACTC
FSP1	CGGTTACCATGGCAAGACCC	TGTGCGAAGCCAGAGTAAG
18S	CGCCGCTAGAGGTGAAATTCT	GAACCTCCGACTTTCGTTCCT