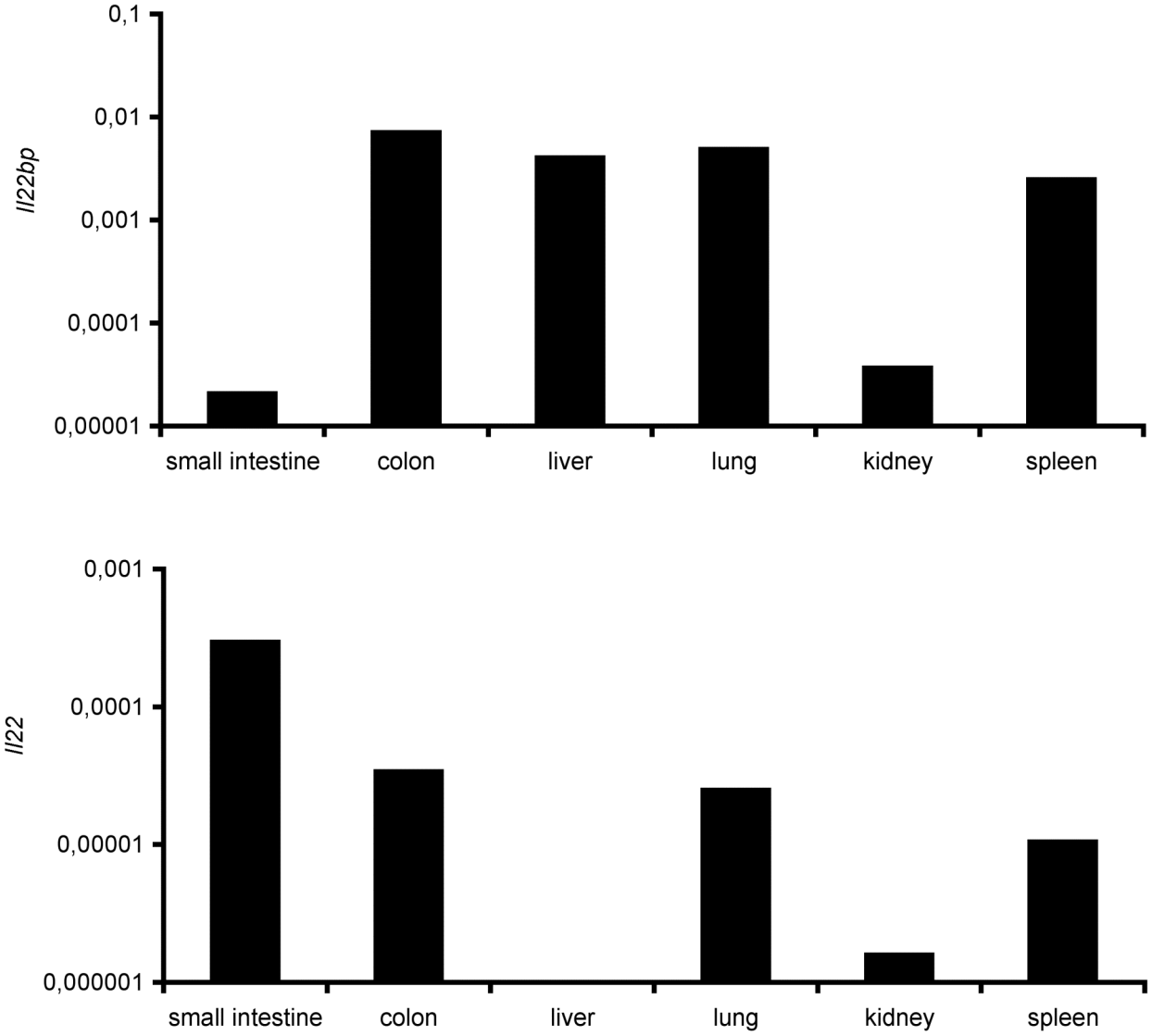
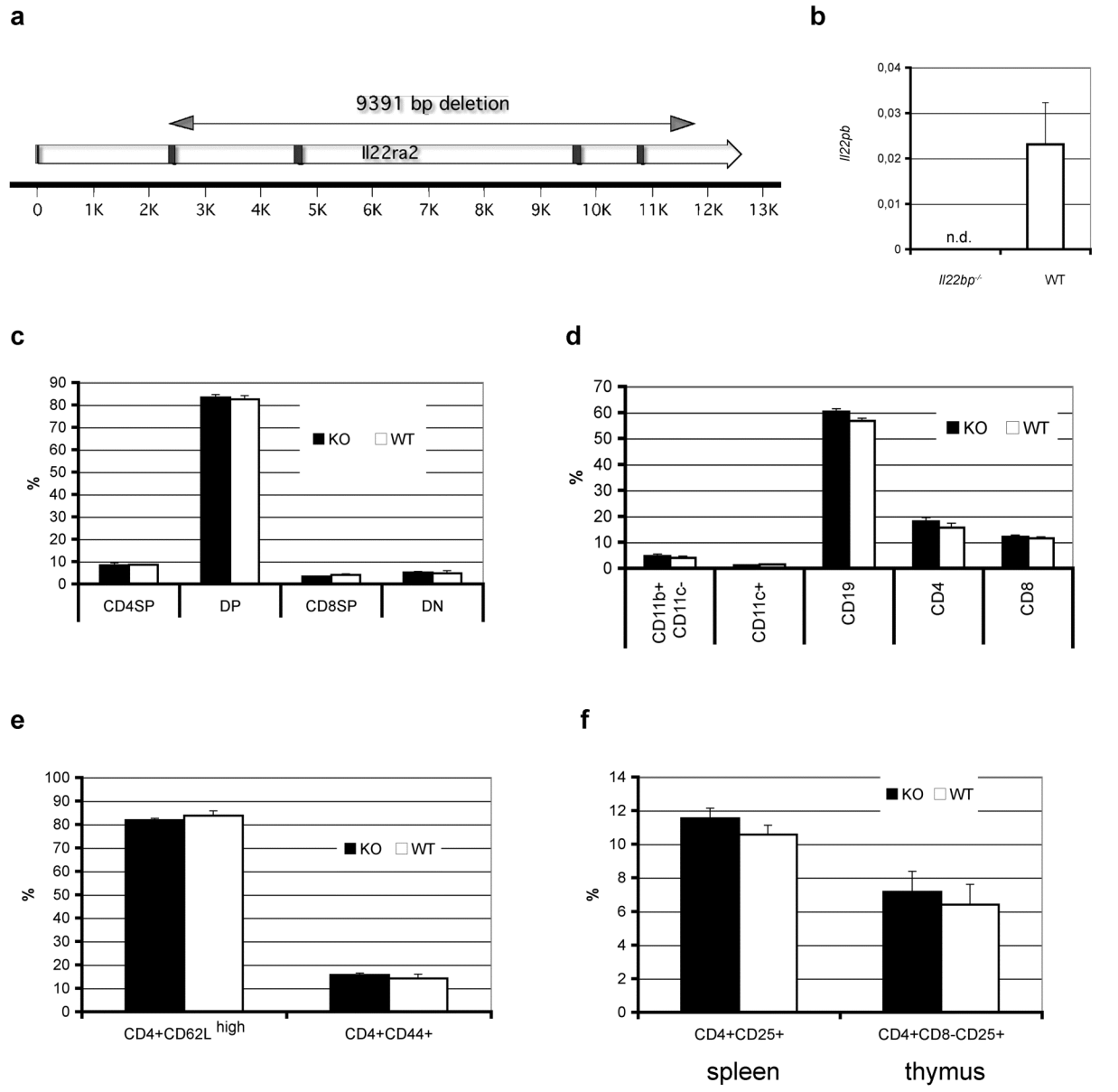
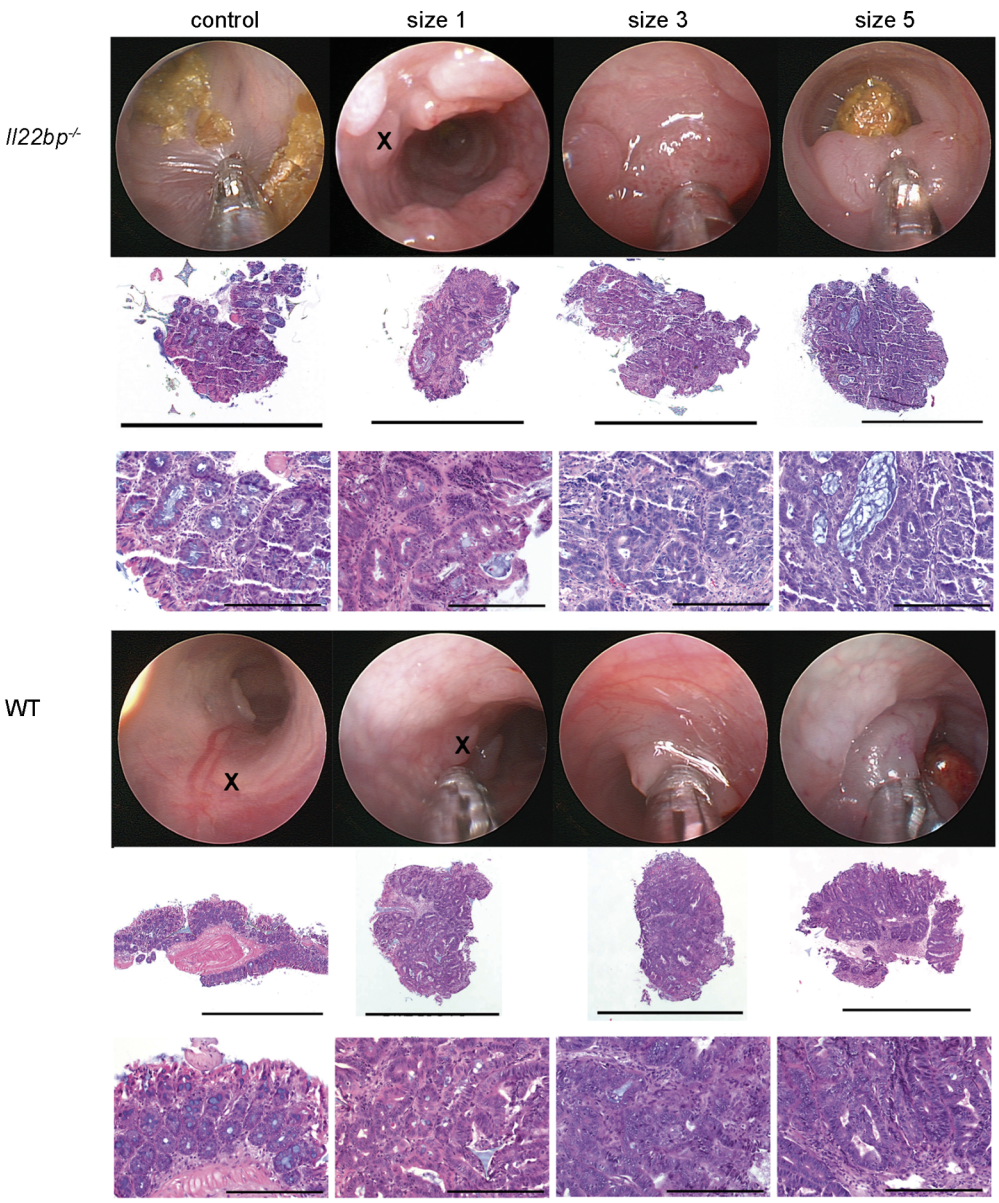


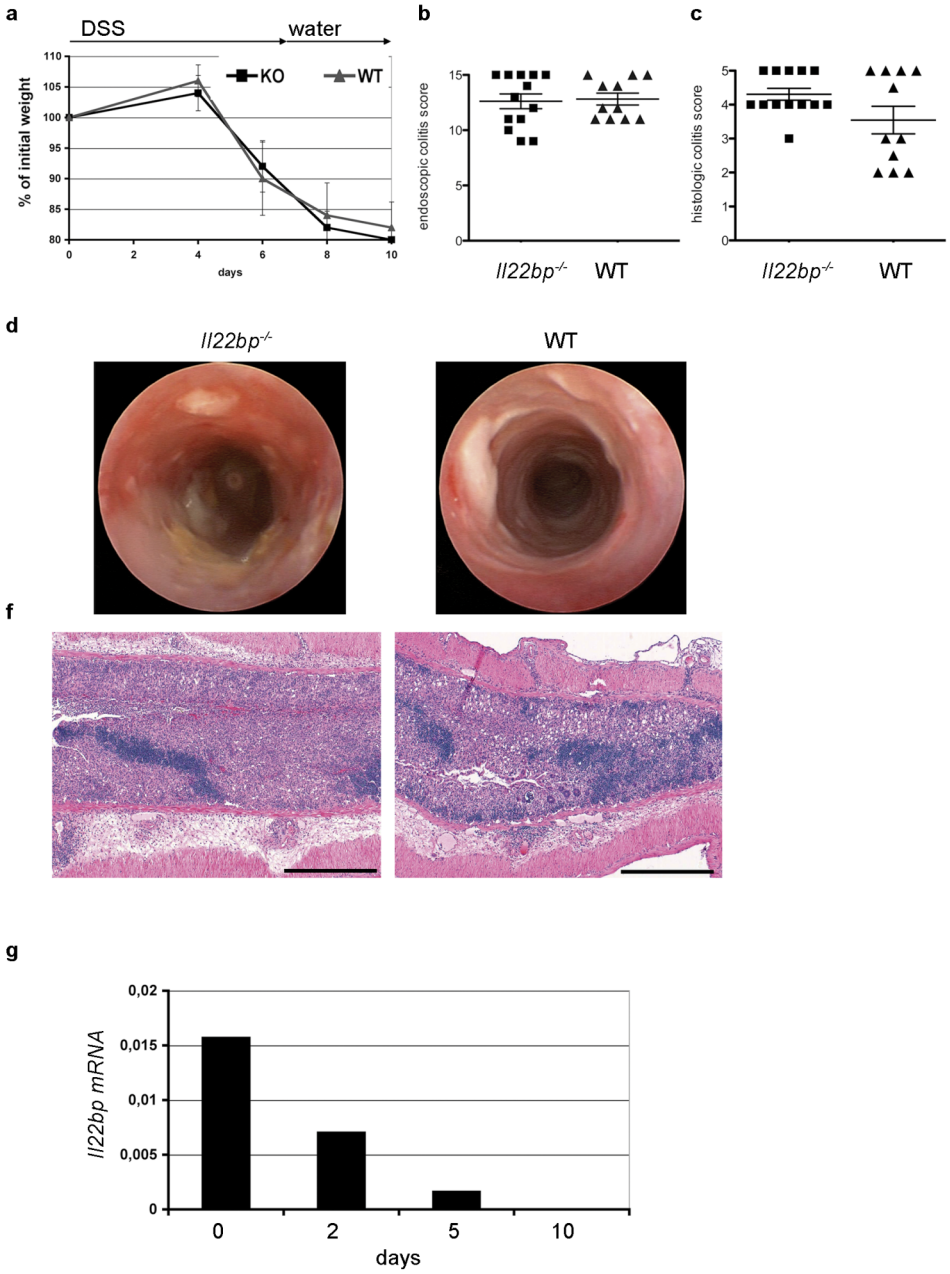
Supplemental Figure 1: *Il22bp* and *Il22* mRNA expression in healthy mice.
Il22bp and *Il22* mRNA expression (normalized to *Hprt*) was analyzed in different tissues using RT-PCR. Results are representative of at least two experiments.



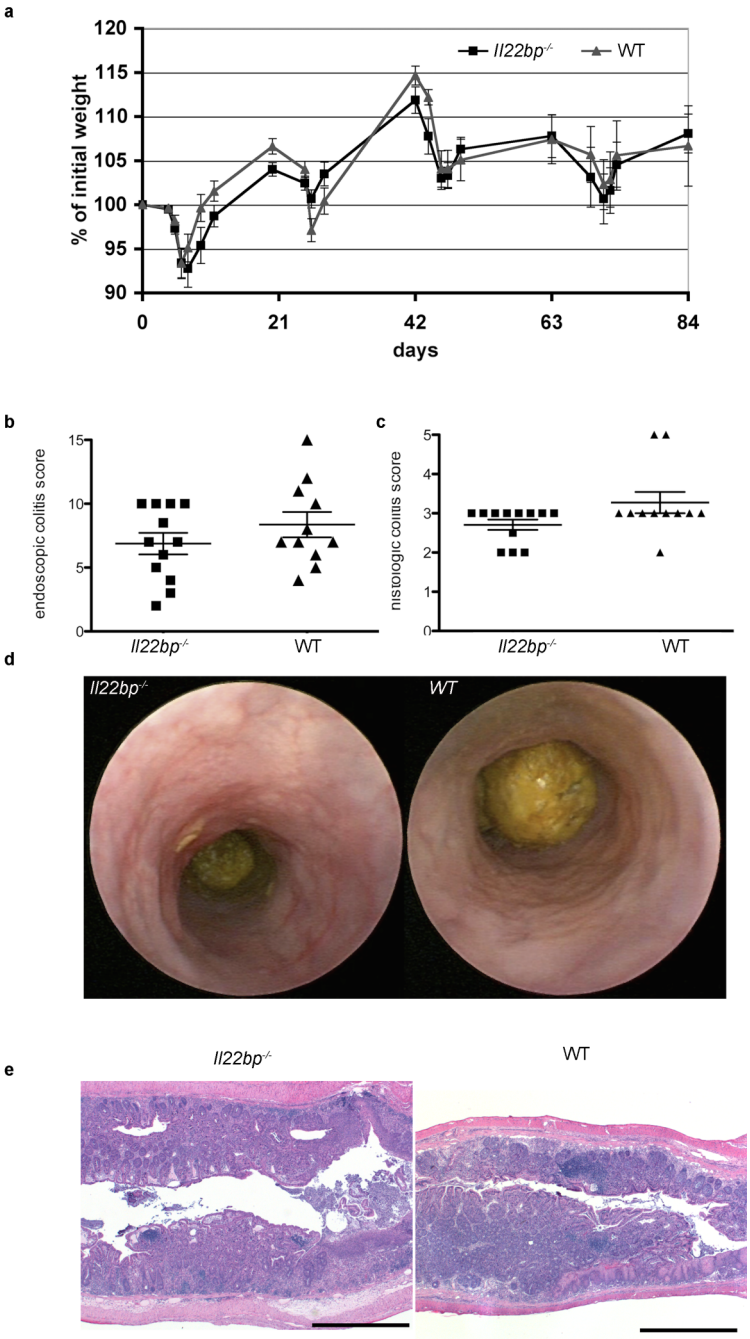
Supplemental Figure 2: Generation and characterization of *Il22bp*$^{-/-}$ mice.
A: The 9.4 kb deletion of the gene encoding *Il22bp* (*Il22ra2*) extends from a position 7 amino acids downstream from the signal sequence into the 3' untranslated region. The deleted sequences are replaced with a TM-lacZ floxed neo cassette. **B:** *Il22bp* mRNA was not detectable in KO mice (results from the colon are displayed). KO mice demonstrate no immunological alterations in thymus (**C**) and spleen (n=5; mean+/- sem) (**D-F**). Data are representative of two independent experiments.



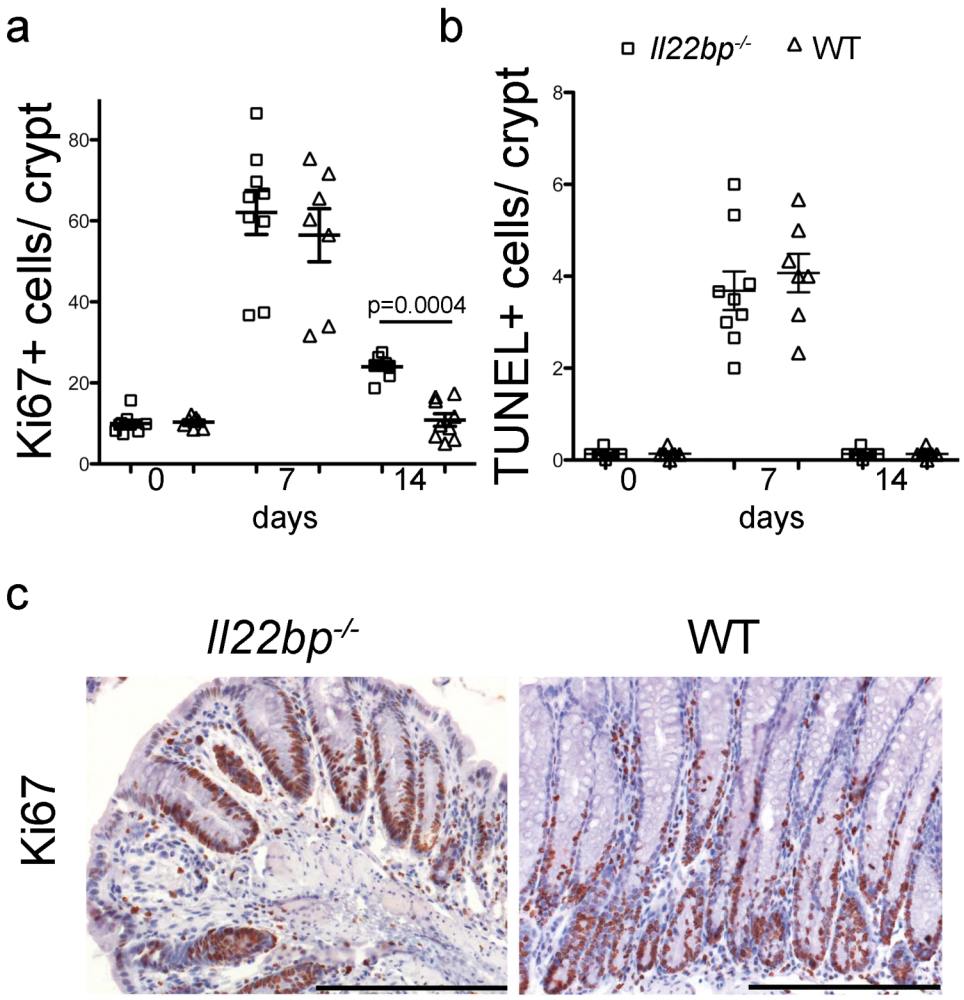
Supplemental Figure 3: Confirmation of endoscopic tumor monitoring using histology of biopsies.
Tumors of different sizes and control regions of the colon from WT and *Il22bp*$^{-/-}$ mice were biopsied using the endoscopic system. Tumors identified with the endoscopy were histologically confirmed to be neoplastic, whereas biopsies from control regions did not show any neoplastic tissue. Bars represent 1000 μm (lower power) and 200μm (higher power) respectively. Pictures are representative of two independent experiments taking a total number of 50 biopsies. X indicates the position where the biopsy was taken.



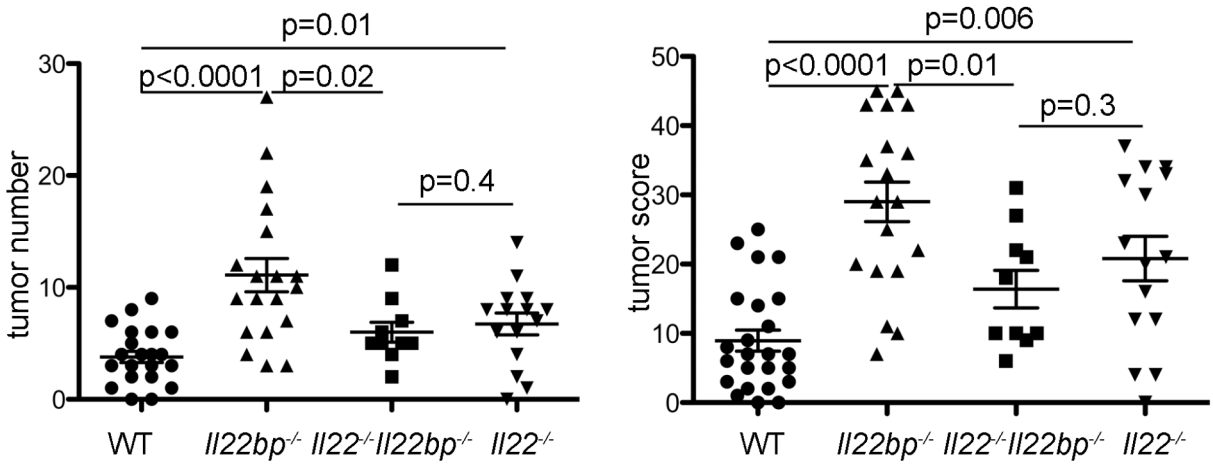
Supplemental Figure 4*: Acute DSS-colitis in *Il22bp*$^{-/-}$ mice
(**A-D**) 2.5% DSS in the drinking water was administered to mice for 7 days, followed by 3 days off water without DSS. No significant changes in weight loss (**A**), endoscopic and histological colitis score (**B+F**) between wild type and *Il22bp*$^{-/-}$ mice could be found. *Il22bp* mRNA levels from total colon decreased during acute DSS colitis and were not detectable on day 10 (**G**). Bars in C represent 500μm. Each dot represents one animal. Lines indicate mean +/- sem. Data are representative of three independent experiments.



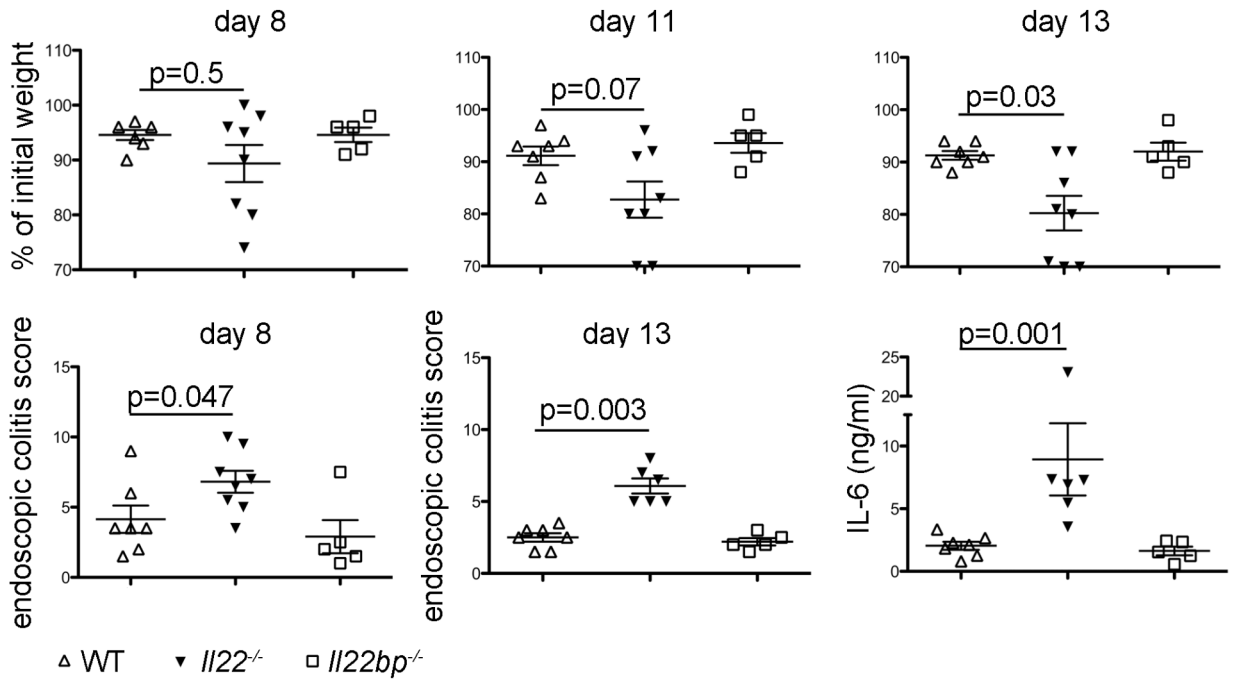
Supplementary Figure 5: Chronic DSS-induced colitis in *Il22bp*$^{-/-}$ mice.
Mice were administered 4 cycles of 2.5% DSS in the drinking water for 5 days followed by 16 days of water. No difference between WT and KO animals in weight loss (**A**), endoscopic and histological colitis score (**B-E**) was found. Bars in E represent 1000μm. Each dot represents one animal. Lines indicate mean+/- sem. Data are representative of three independent experiments.



Supplemental Figure 6: Increased Ki67-positive epithelial cells in *Il22bp*$^{-/-}$ mice in the recovery phase after DSS administration.
2.5% DSS was administered to WT and *Il22bp*$^{-/-}$ mice for 5 days followed by 9 days of water. Mice were sacrificed on day 0, 7 and 14. Ki67- (**A+C**) and TUNEL- (**B**) positive epithelial cells were counted per crypt using light microscopy. Each dot in **A** and **B** represents one animal. Lines indicate mean+/- sem. **C:** Representative examples of Ki67-staining on day 14 of the experiment (bars= 200μm). Results are representative of 3 independent experiments.

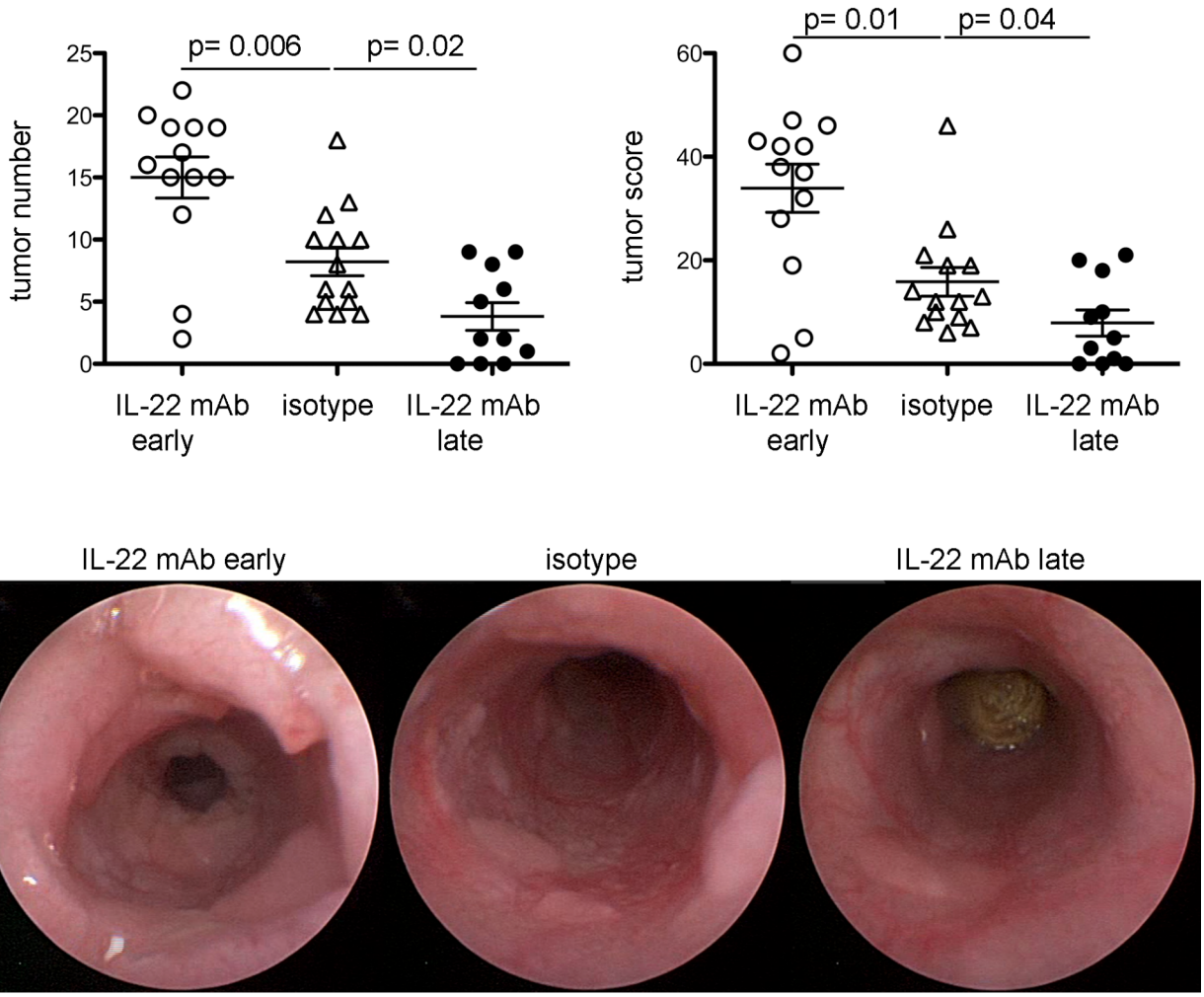


Supplemental Figure 7: Increased tumorigenesis in *Il22bp*$^{-/-}$ mice is dependent on the presence of IL-22.
Colitis-associated colon cancer was induced via injection of AOM followed by the administration of 2% DSS in the drinking water. Tumor score and number were determined on day 63 using endoscopy. Cumulative results from 2 independent experiments are shown. Each dot represents one mouse. Lines indicate mean+/- sem.

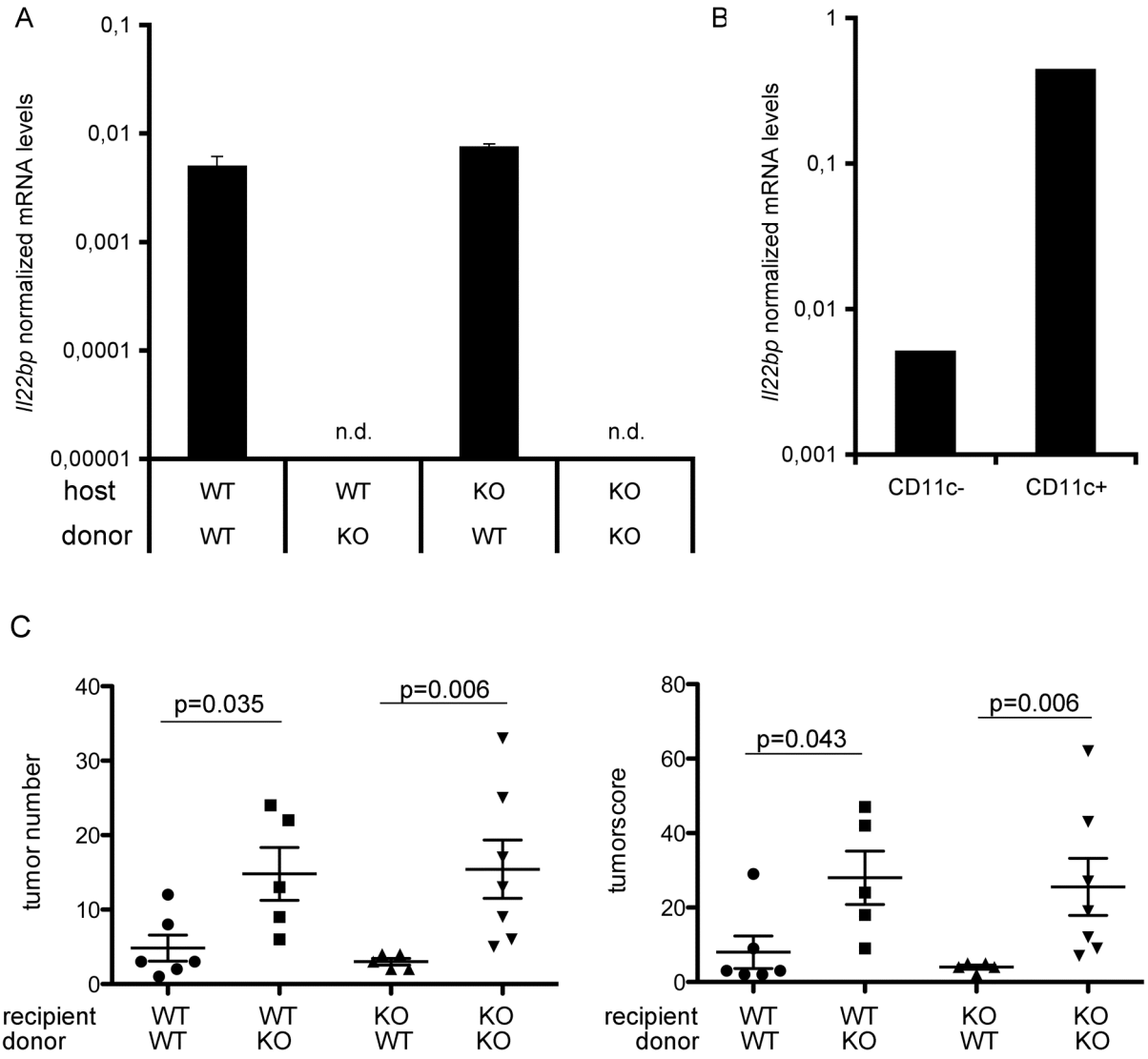


Supplemental Figure 8: Increased susceptibility of *Il22*$^{-/-}$ mice to DSS-induced colitis.

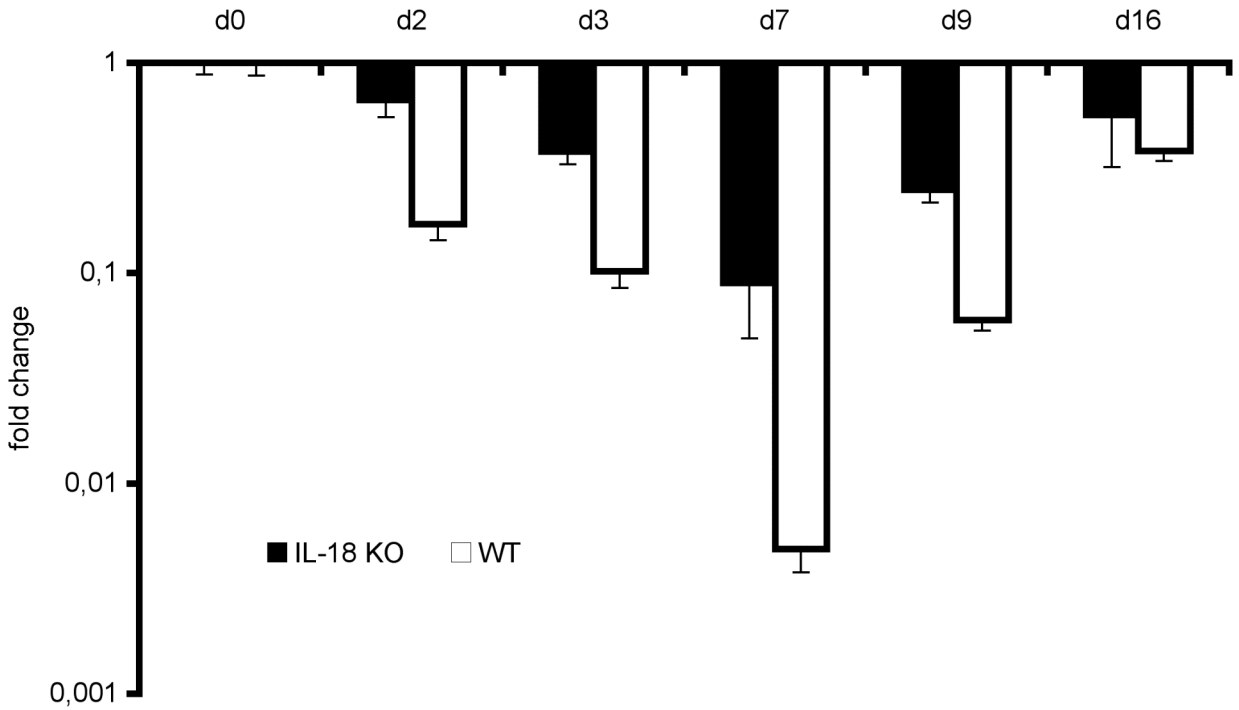
DSS-colitis was induced by the administration of 2% DSS in the drinking water for 5 days followed by regular water. Weight loss and endoscopic colitis score were measured at different time points. Mice were sacrificed at day 13 of the experiments and IL-6 was measured in supernatants of colon explants using CBA. Each dot represents one mouse. Lines indicate mean+/- sem.



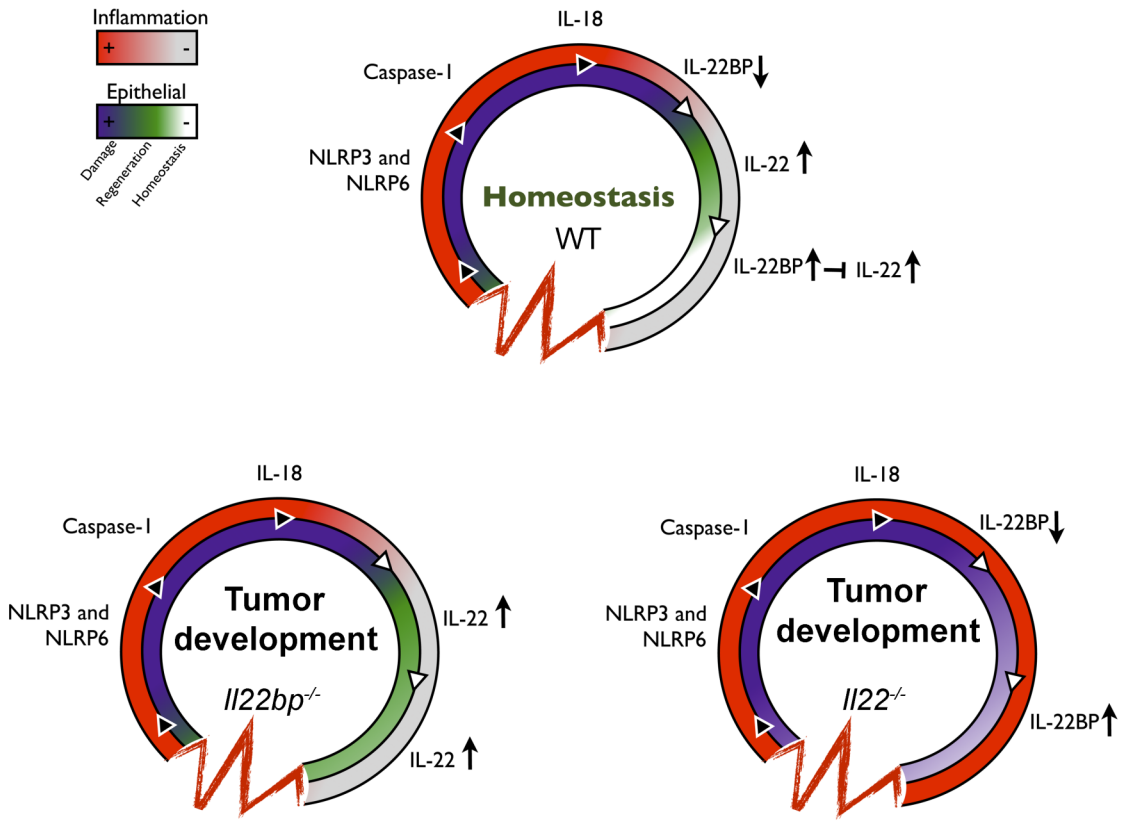
Supplemental Figure 9: Dual role of IL-22 during colitis-associated colon cancer. Colitis-associated colon cancer was induced via injection of AOM followed by the administration of 2% DSS in the drinking water. IL-22 antibody was administered on day 5 (early) or day 12 (late) of each DSS-cycle. Tumor score and number were determined on day 63 using endoscopy. Cumulative results from 2 independent experiments are shown. Each dot represents one mouse. Lines indicate mean+/- sem.



Supplemental Figure 10: IL-22BP is selectively expressed by haematopoietic cells during colitis associated colon cancer. A: Bone marrow chimeras were generated by using WT or *Il22bp*$^{-/-}$ (KO) mice as donors and irradiated *Rag1*$^{-/-}$ or *Rag1*$^{-/-}$*Il22bp*$^{-/-}$ (KO) mice as recipients. Colitis associated colon cancer was induced and *Il22bp* expression in the tumor tissue was measured. **B:** Colitis associated colon cancer was induced in wild type mice *Il22bp* expression was analyzed in different CD45+ haematopoietic cells as indicated. Results are representative of 2 independent experiments. **C:** Bone marrow chimeras were generated by using WT or *Il22bp*$^{-/-}$ (KO) mice as donors and irradiated *Rag1*$^{-/-}$ or *Rag1*$^{-/-}$*Il22bp*$^{-/-}$ (KO) mice as recipients. Colitis associated colon cancer was induced by the administration of AOM followed by the administration of three cycle of DSS. Tumor number and tumor score are shown. Each dot represents one mouse. Lines indicate mean+/- sem.



Supplemental Figure 11: IL-18 is crucial for the complete down regulation of *Il22bp* upon DSS-induced intestinal tissue damage. 2% DSS was administered to WT and *Il18*$^{-/-}$ in the drinking water for 5 days followed by regular water. *Il22bp* mRNA expression was measured in total colon tissue using RT-PCR and normalized to *Cd11c*. Fold change compared to day 0 is shown. At least three WT and KO mice were analyzed at each time point between day 0 – 9. Two KO and three WT mice were analyzed at day 16. Results are representative of 2 independent experiments. Mean and sem are shown.



Supplemental Figure 12: Scheme of the regulation and function of IL-22BP in the intestine. Tissue damage and bacterial ligand triggered NLRP3 and NLRP6 activation leads to caspase 1 mediated IL-18 activation. IL-18 down regulates IL-22BP production by intestinal DC, thereby allowing IL-22 to exert its protective function during tissue repair. Dysregulation of the IL-22 – IL-22BP axis promotes tumorigenesis in the colon: IL-22BP deficiency causes prolonged effects of IL-22 on colon epithelial cells, and promotes tumorigenesis in the colon. IL-22 deficiency leads to delayed wound healing and increased inflammation thereby also promoting tumorigenesis.