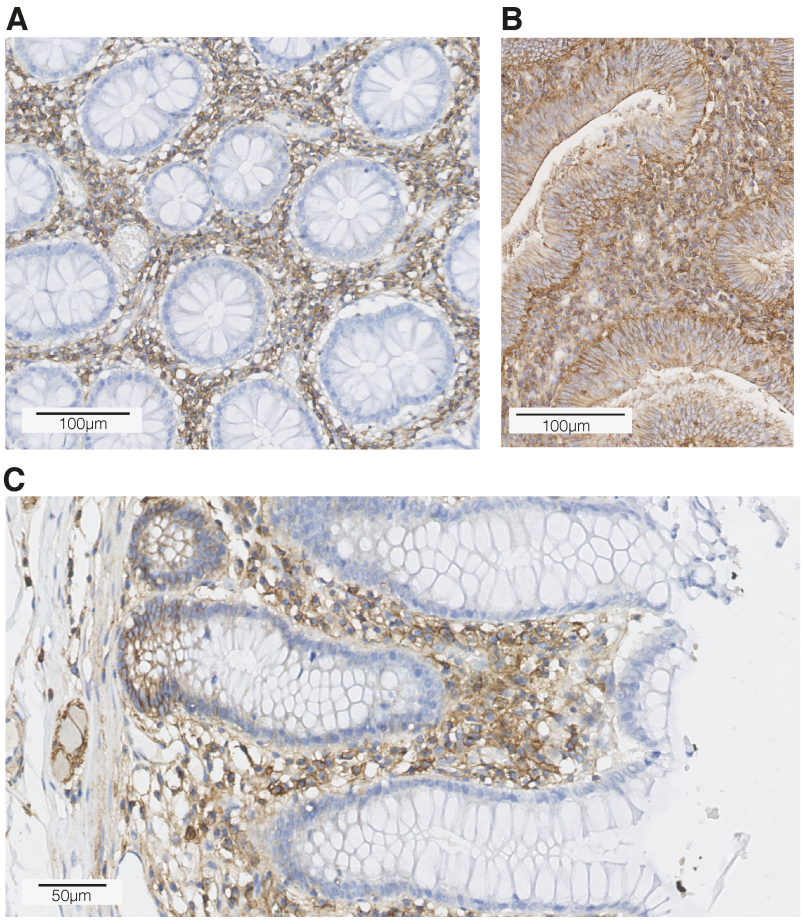

Figure S1. CD44-positive colorectal stromal tissue. Besides the expected staining of the dysplastic cells, we observed positive staining of the surrounding stromal tissue in the majority of samples when using the panCD44 antibody. (**A**) A representative images of a complete healthy colon sample, demonstrating positive CD44 immunostaining of the stromal tissue and absence of CD44 within the colon crypts. (**B**) Representative image of highly positive stromal tissue within an CD44-positive adenomatous polyp. (**C**) Positive CD44 staining at the proliferative base of normal epithelial crypts was observed, which is in accordance to previous reports.(1)

References: (1) Abbasi AM, Chester KA, Talbot IC, et al. CD44 is associated with proliferation in normal and neoplastic human colorectal epithelial cells. Eur J Cancer 1993;29A:1995–2002.

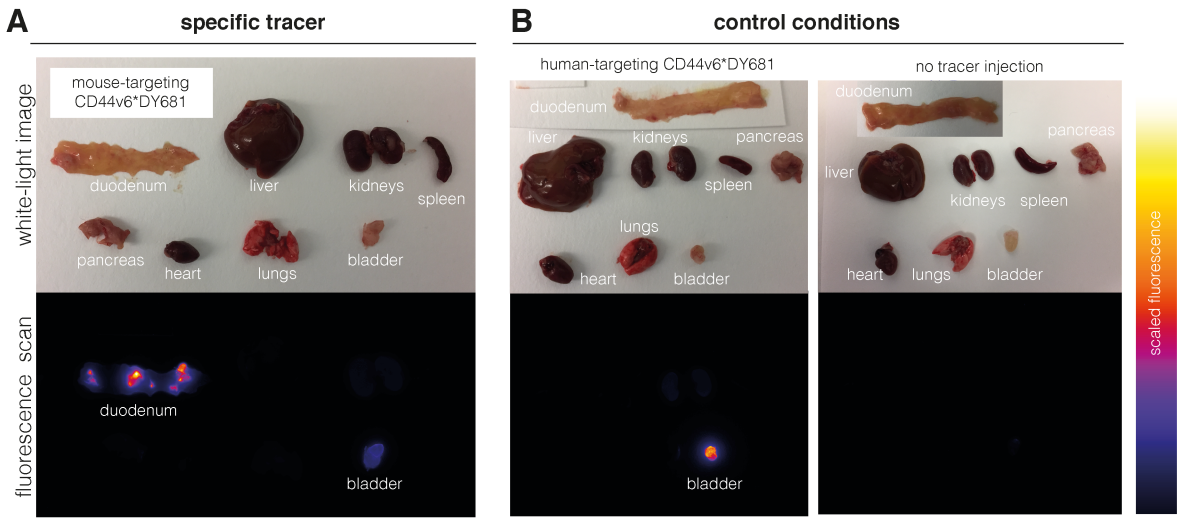

Figure S2 - Tracer distribution. Representative images of *Apc* min/+ mice (n = 5), demonstrating (**A**) specific fluorescence in an adenoma containing intestine, as well as in the bladder. The other imaged organs (incl. liver, lungs, heart, spleen) did not show signficant fluorescence. (**B**) When administering the non-specific (human-targeting) peptide tracer, a high fluorescence signal can be observed in the urine-containing bladder. The other organs, including the intestine, did not show fluorescence at 700 nm (tracer-specific wavelength). The control condition in which no tracer was adminstered did not show any fluorescence. All fluorescent images displayed are scaled to the highest signal observed (derived from the specific tracer).

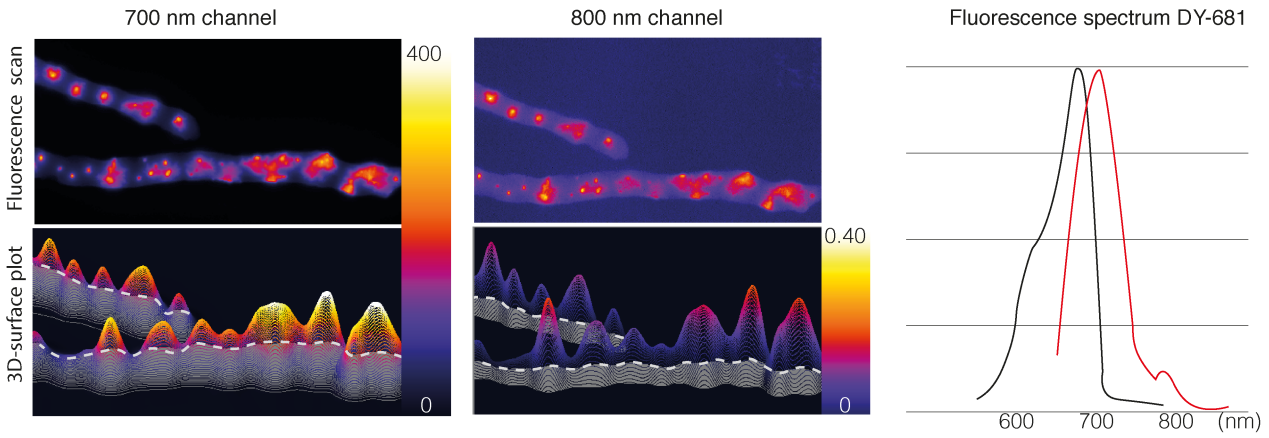

Figure S3. DY-681 specific fluorescence results. The interactive 3D-surface plots illustrate the difference in fluorescence intensity between polyps (spots with high signal peaks) and the surrounding normal intestinal tissue (dotted grey line). In addition to the high fluorescent signals at 700 nm, low fluorescent signals were observed at 800 nm wavelengths, which fit the emission spectrum of fluorophore DY-681 (black represents the excitation and red the emission spectrum, source: www.dyomics.com).

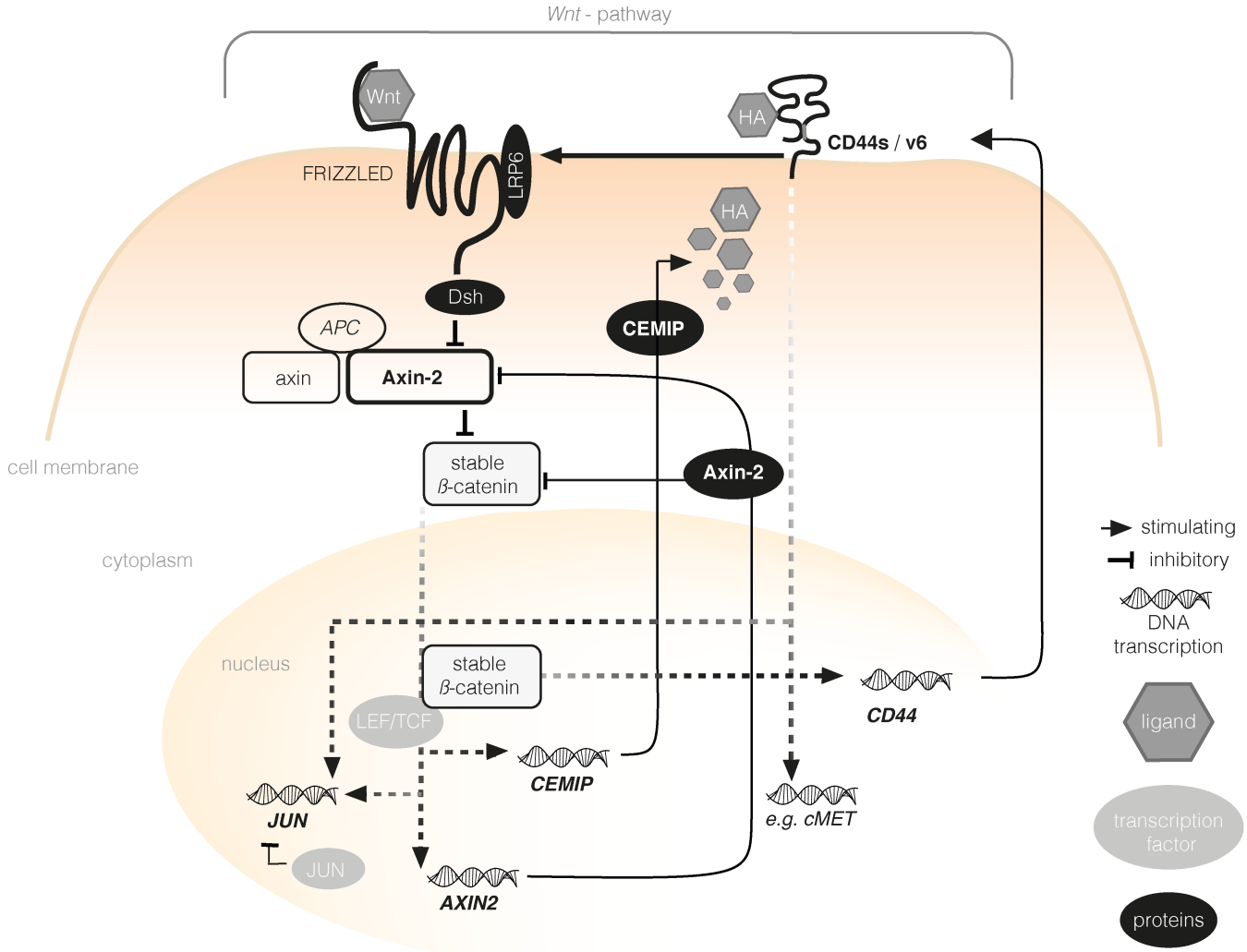

Figure S4. Localization and function of AXIN2, CEMIP, CD44 and JUN. As depicted in this illustration, AXIN2, CEMIP, CD44 and JUN are all part of the Wnt-signalling pathway. Wnt binding to Frizzled receptors and LRP co-receptors activates Dishevelled (Dsh) proteins; these in turn inhibit the destruction complex, including adenomatous polyposis coli (APC) and Axin/Axin-2, which is responsible for degrading ß-catenin. Accumulation of ß-catenin in the cytoplasm prompts its translocation to the nucleus, where it induces the transcription of Wnt target-genes via the LEF/TCF complex (1). AXIN2 has a self-regulatory role and the proto-oncogene JUN, better known from its role in the TGF-ß signalling cascade, is an early response transcription factor. The product of AXIN2, Axin-2, plays an important role in the regulation of the stability of ß-catenin. CEMIP mediates depolymerization of hyaluronic acid (HA), hydrolizing it into intermediate-sized products. Although CD44 has a separate downstream cascade, the two pathways are closely linked as stable ß-catenin, a key downstream component of the Wnt-signalling pathway, is involved in regulating CD44 gene transcription (2). The CD44 protein has an external site that can bind ligands such as HA for anchorage to the basement membrane and an internal side, which fulfills an essential role in Wnt-signalling by regulating the cell surface expression and signalling activity of the Wnt/B-catenin co-receptor LRP6 (3).

References:
(1) Lustig B, Behrens J. The Wnt signaling pathway and its role in tumor development. J Cancer Res Clin Oncol. 2003;129:199–221.
(2) Zeilstra J, Joosten SPJ, Dokter M, Verwiel E, Spaargaren M, Pals ST. Deletion of the WNT Target and Cancer Stem Cell Marker CD44 in Apc(Min/+) Mice Attenuates Intestinal Tumorigenesis. Cancer Research. 2008;68:3655–61.
(3) Schmitt M, Metzger M, Gradl D, Davidson G, Orian-Rousseau V. CD44 functions in Wnt signaling by regulating LRP6 localization and activation. Cell Death Differ. 2014;22:677–89.