Intestinal stem cells are located at the base of the intestinal crypt, marked by Lgr5 gene expression. Interacting signalling pathways such as the Wnt and bone morphogenetic protein (BMP) pathway normally regulate cell division, maturation and death as intestinal cells migrate. Secreted BMP antagonists expressed exclusively from stromal cells below the crypt and act on the stem cell niche to maintain stem cell function.

WHAT WAS KNOWN
- Intestinal stem cells are located at the base of the intestinal crypt, marked by Lgr5 gene expression
- Interacting signalling pathways such as the Wnt and bone morphogenetic protein (BMP) pathway normally regulate cell division, maturation and death as intestinal cells migrate
- Secreted BMP antagonists expressed exclusively from stromal cells maintain the stem cell niche
- Crypt base stem cells were thought to be the sole cell of origin of colorectal cancer

WHAT WE DID
- Mapped and defined a genetic defect in the rare condition Human Hereditary Mixed Polyposis Syndrome (HMPS)
- Developed an animal model to test cancer pathogenesis in these patients by overexpressing Grem1 throughout the mouse intestinal epithelium (Vil1-Grem1 mouse)

WHAT THIS ADDS
- HMPS is caused by a germline duplication of the gene regulatory regions upstream of the BMP antagonist GREM1
- This mutation changes GREM1 tissue expression from stromal cells to the epithelium itself, disrupting the signalling pathway balance
- Aberrant epithelial GREM1 expression causes an expansion in the progenitor cell population of the intestinal crypt
- The expanded population of progenitor cells divide, form ectopic crypt structures and acquire somatic mutations leading to carcinogenic change
- A subtype of sporadic human polyps called traditional serrated adenomas (TSAs) with hitherto unknown pathogenesis, share the same carcinogenic pathway
- First studies to show that a subtype of human colorectal cancer arises from cells outside the crypt base stem cell niche, suggesting a basis for tumour resistance to chemotherapy and potential new drug targets

REFERENCES
Hereditary mixed polyposis syndrome (HMPS) is caused by a 40-kb duplication of chromosome 15 including the upstream gene regulation region of the GREM1 gene. The duplication causes a massive increase in GREM1 production and switches expression from the intestinal fibroblasts underneath the crypt to the epithelium (mRNA in situ expression).