**Colorectal cancer can arise from cells situated outside the crypt base stem cell niche**

**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.

A. The rare autosomal dominant 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. B. 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).