In Inflammatory Bowel Disease (IBD), clonal evolution and field cancerisation precedes the development of colitis-associated colorectal cancer (CA-CRC). However, the extent and spread of pre-cancerous clones in the IBD colon remains incompletely determined. Consequently clinical practice is poorly informed of how best to detect these clones at surveillance endoscopy and accurately predict future cancer risk.

**Aims**

- To quantify the number and size of mutant clones arising across the length of the colitic bowel.
- To reveal the mechanism of how they arise and spread.

Through this gain a detailed molecular understanding of the evolutionary dynamics of progression to CA-CRC.

**Methods**

- Three IBD patients undergoing a total panproctocolectomy for multifocal dysplasia or CA-CRC were recruited prospectively.
- Fresh-frozen biopsies were taken at regularly spaced intervals (~2cm) across the entire colon, rectum to caecum, comprising of 118, 108 and 25 biopsies respectively.
- Epithelial tissue was isolated from each biopsy using laser capture microdissection and DNA was extracted.
- Shallow whole genome sequencing (sWGS) was performed to generate genome-wide copy number alteration (CNA) profiles.

**Results**

Analysis from the first 45 samples from colon 1 show:

- Multiple CNA events occur in macroscopically ‘normal’ parts of the colon.
- Recurrent CNAs were shared between biopsies, reveals multiple clonal patches across the length of the colon, both proximal and distal to the cancer, and comprising in normal, inflammed, dysplastic and cancer-associated tissue.
- Clonal expansions ranged from 4-18cm in size, and were separated by distances of 2-20cm.
- Certain CNA events occur more commonly across the colon, both independently and from within different clonal patches, such as losses on chromosomes 4, 5, 8 and 17, and gains on chromosomes 7 and 20.

**Figure 2.** Example of a copy number (CN) plot taken from biopsy point 45. Biopsy 45 is taken from an inflammed area from the ascending colon approximately 8cm distal from the cancer (figure 1). Chromosome region has been marked along the x-axis biopsy position, with corresponding patch size. AC - Ascending colon, TC - Transverse colon, DC - Descending colon, SC - Sigmod colon. Distance between patches is also annotated.

**Figure 3.** CN heat map created after amalgamating all CN profiles taken from the 1-45 samples taken linearly, rectum - caecum biopsy points 1-52 - figure 1). Chromosome region is demonstrated along the y-axis and biopsy position along the x-axis (right). Clonal patch is highlighted along the y-axis biopsy position, with corresponding patch size. AC - Ascending colon, TC - Transverse colon, DC - Descending colon, SC - Sigmod colon. Distance between patches is also annotated.

**Results continued**

- 45 of 122 biopsies processed so far from patient 1.
- CNAs occur in ostensibly ‘normal’ cells, demonstrating evidence of field cancerisation.
- Patches reach up to 18cm in size, and occur across the entire colon.
- Similar CNAs are seen occurring independently throughout the whole colon suggesting patterns of convergent evolution.

**References**