High-grade serous ovarian carcinoma (HGSOC) is an aggressive cancer that has had minimal improvement in survival rates over the last few decades. It is somewhat of a misnomer, with much data now suggesting that the cell of origin typically resides in the fallopian tube rather than the ovaries. It mostly affects women above the age of 40 and has a peak incidence at the age of 70. Genetically HGSOC is characterised by a high prevalence of \( TP53 \) mutations, seen in virtually all cases. About 80% of tumours have undergone whole genome duplication (WGD) and the majority have highly rearranged genomes. Ovarian cancer is one of the defining tumours seen in carriers of \( BRCA1/2 \) germline variants, associated with a lifetime risk of ~50%.

Interestingly, a recent analysis of 2778 cancer genomes has revealed that the HGSOC has a very long latency of the disease with many WGD and other driver mutations dating back more than 20 years prior to diagnosis (Gerstung, 2017; Figure 1). The long latency of ovarian cancer is also implied by epidemiological data showing that oral contraceptives and pregnancies protect against ovarian cancer, linking the mostly post-menopausal presentation of tumours to pre-menopausal events. Finally, p53 immunostaining suggests that stabilised p53 variants can be seen in normal fallopian tube cells, indicative of early driver mutations and microscopic clonal expansions (Figure 2; Eckert, 2016).

A latency of decades for such an aggressive malignancy raises the intriguing possibility that we might be able to detect the earliest clones in the fallopian tubes before they progress to an incurable, invasive cancer. In other tissues, such as healthy skin for example, we can detect microscopic clones containing the typical somatic driver mutations seen in skin cancers. The prevalence of cancer-like mutations in healthy tissues will shed new light on clonal evolution in somatic cells and their
transformation to malignancy, but will also address whether acquisition of driver mutations at younger age predicts further malignant evolution.

Here we propose to systematically analyse and sequence tissues of the fallopian tubes from individuals from BRCA1/2 carriers and from normal subjects; and from patients with ovarian cancer and those without. We have developed protocols for sequencing microbiopsies from histologically normal tissue using laser capture microdissection. Such studies promise the ability to evaluate a number of critical unanswered questions about the earliest stages of ovarian cancer development:

1. What is the mutation burden in normal fallopian cells and how does this change with age and contraception / pregnancy history?
2. Do carriers of BRCA1/2 germline mutations exhibit different signatures and burden of mutations compared to wild-type individuals?
3. Are the earliest driver mutations evident in normal fallopian cells?
4. What are the clonal dynamics of normal fallopian tube cells, and what are the implications for normal stem cell biology in this organ?

This will provide an unprecedented view on the precancerous evolution the fallopian tube epithelium in normal conditions and under BRCA deficiency. It will shed light on the earliest stages of HGSOC evolution and help establish whether genomic biomarkers exist that distinguish normal and malignant evolution.

References

