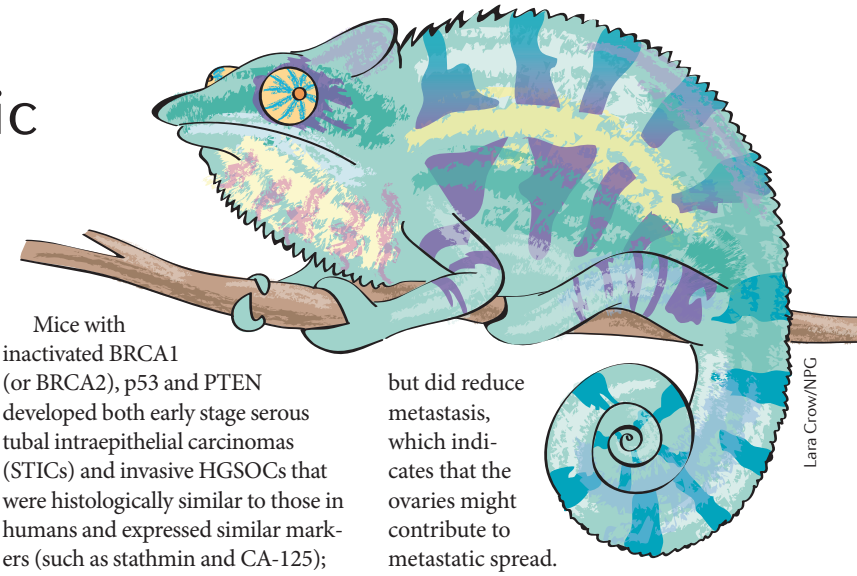
OVARIAN CANCER

A better mimic



Lara Crow/NPG

Several recent studies have suggested that high-grade serous ovarian carcinoma (HGSOC) does not arise from the ovarian surface epithelium (OSE) but rather from the fallopian tube secretory epithelial cells (FTSECs). However, these studies are primarily correlative, and direct proof is lacking owing to a paucity of both effective early detection methods in women and *de novo* mouse models.

In order to determine whether HGSOC can arise from FTSECs, Ruth Perets and Gregory Wyant, working in the laboratories of Ronny Drapkin and Daniela Dinulescu, respectively, developed mouse models in which tumour suppressors that are commonly lost or mutated in human HGSOC were specifically inactivated in FTSECs but not in the OSE. To do this, the authors used the paired box 8 (*Pax8*) promoter, which they showed is expressed in FTSECs but not in the OSE. Mice with *Pax8*-driven expression of reverse tetracycline-dependent transactivator (*rtTA*) were crossed with mice that expressed a tetracycline-driven Cre recombinase (*tetO–Cre*), and these *Pax8–Cre* mice were shown to express Cre only in the fallopian tubes (and not in the ovaries) following administration of doxycycline. *Pax8–Cre* mice were then used to generate mice that lacked various combinations of inactivated or mutated genes, including *Brca1* (or *Brca2*), *Trp53* and *Pten*.

> “this mouse model ... successfully mimics human HGSOC.”

Mice with inactivated BRCA1 (or BRCA2), p53 and PTEN developed both early stage serous tubal intraepithelial carcinomas (STICs) and invasive HGSOCs that were histologically similar to those in humans and expressed similar markers (such as stathmin and CA-125); the pattern of metastatic spread of these HGSOCs was also similar to that in humans and included frequent metastasis to the ovaries. Genomic analyses showed that HGSOCs from these mice had many copy-number alterations that overlapped with those reported in human HGSOCs by The Cancer Genome Atlas, and many recurrent alterations were shared between human and mouse tumours. Overall, these data indicate that this mouse model, in which tumours arise from FTSECs, successfully mimics human HGSOC.

To further confirm the origin of HGSOC in mice with inactivated BRCA1 (or BRCA2), p53 and PTEN, the authors removed the ovaries, uterus or fallopian tubes. The removal of the uterus had no effect on tumour growth or spread, whereas the removal of the fallopian tubes completely prevented HGSOC. The removal of the ovaries did not prevent the development of STIC but did reduce metastasis, which indicates that the ovaries might contribute to metastatic spread.

Interestingly, mice that only had inactivated PTEN and p53 but not inactivated BRCA developed STICs, but they did not develop invasive HGSOCs, which suggests that the inactivation of a BRCA gene is necessary for progression. Furthermore, mice that lacked BRCA2 and p53 but not PTEN had a longer disease latency, and tumorigenesis was inefficient in these mice.

Although it is possible that FTSECs are not the only cell of origin for HGSOC, these mouse models confirm that these tumours can indeed arise from the FTSEC. Furthermore, this mouse model of HGSOC may be useful not only for preclinical testing of potential therapeutics but also for developing early detection strategies.

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ORIGINAL RESEARCH PAPER Perets, R. *et al.* Transformation of the fallopian tube secretory epithelium leads to high-grade serous ovarian cancer in *Brca;Tp53;Pten* models. *Cancer Cell* **24**, 751–765 (2013)