

CANCER

Electroporation-based mouse models provide new insights into ovarian cancer and response to therapy

Paffenholz, S.V. et al. *Proc. Natl. Acad. Sci. USA* **119**, e2117754119 (2022)

High-grade serous ovarian carcinoma (HGSOC), the most prevalent histotype of ovarian cancer, is difficult to treat because tumors develop resistance to platinum/taxane-based chemotherapy, the first-line treatment for this disease. A study in *PNAS* used advanced models of HGSOC to identify the factors that influence the response of ovarian tumors to therapy.

Current mouse models of HGSOC present important limitations, hindering our knowledge of the disease and the development of efficient therapies. Patient-derived xenografts grown in immune-deficient mice recapitulate the genomic feature of patient tumors, but they cannot reproduce the interaction between cancer cells and immune cells; genetically engineered mouse models (GEMMs) allow for the study of gene function *in vivo*, but the generation of germline GEMMs can be time-consuming.

To overcome these limitations, Paffenholz and colleagues at the Memorial

Sloan Kettering Cancer Center used *in vivo* electroporation (EPO) to deliver CRISPR-Cas9-mediated genome editing and transposon/transposase-based systems and introduce selected mutations into the ovary of wild-type C57BL/6 mice. Histological and transcriptomic analysis revealed that mice electroporated with various combinations of sgRNAs targeting tumor suppressor genes (such as *Trp53*) and oncogene (*Myc*)-expressing transposon vectors develop tumors similar to human HGSOC. “These results validate the EPO-GEMM approach as a flexible platform to model HGSOC tumors of varying genotypes that resemble the metastatic, histological, genomic, and transcriptomic properties of the human disease,” explain the investigators in their report.

HGSOC can also harbor inactivating mutations in genes important for homologous recombination (HR) DNA repair, such as *BRCA1* and *BRCA2*. Given that HR-deficient ovarian tumors

are highly sensitive to platinum-based therapies, the team generated and characterized a *Myc;Trp53;Brca1* mouse model (MPB1) to investigate the role of *Brca1* in response to therapy. MPB1 mice showed improved survival following cisplatin therapy compared with *Myc;Trp53* mice (MP), and further experiments revealed that tumor cell senescence was increased in MPB1 ovarian tumors compared to MP tumors.

In conclusion, the EPO-GEMM platform enabled the modeling of a clinically important HR-deficient ovarian cancer and provided new insights into the senescence program triggered by chemotherapy in *Brca1*-deficient ovarian tumors that is associated with improved response to therapy.

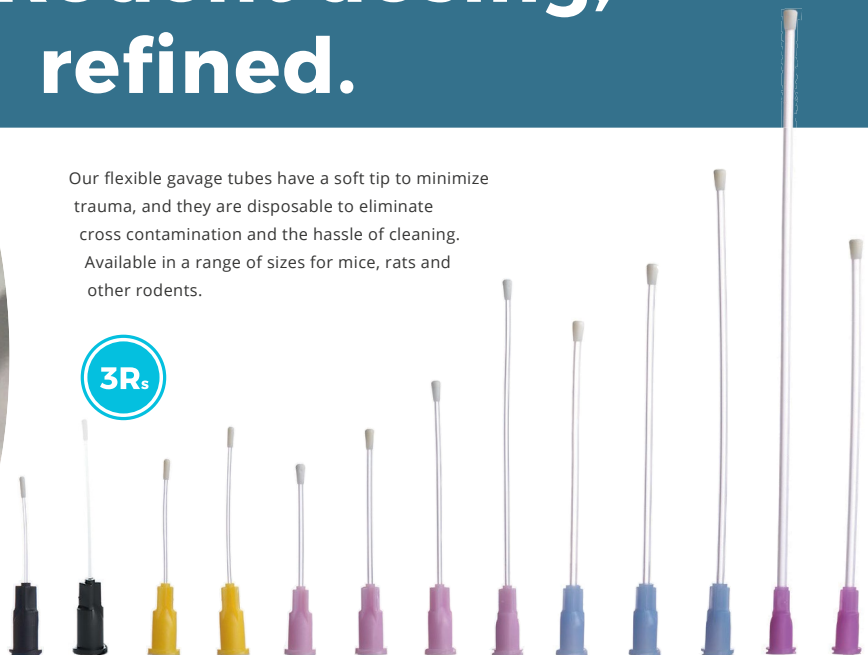
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