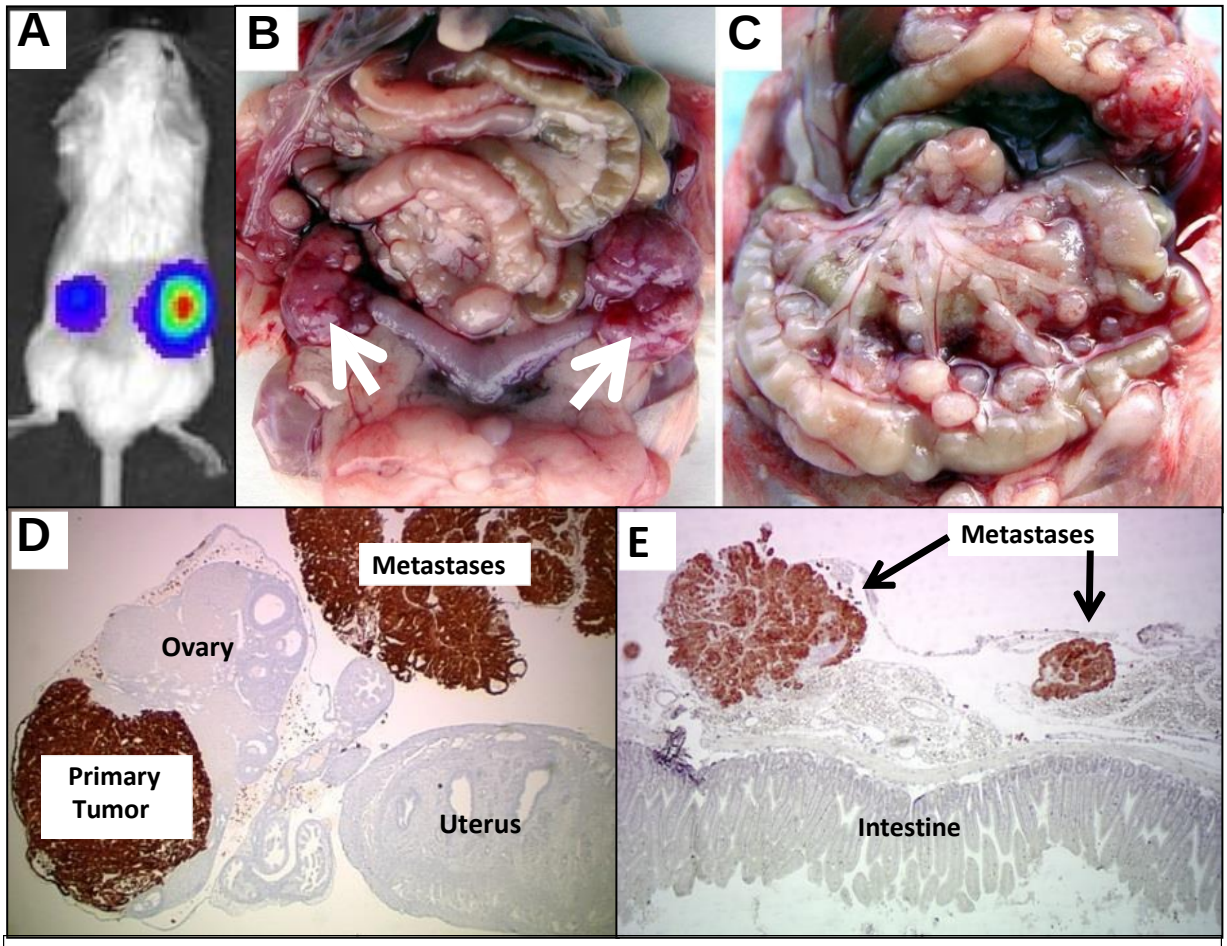
Syngeneic Immunocompetent Mouse Ovarian Cancer Models

The study of ovarian carcinogenesis has been limited by the lack of appropriate immunocompetent syngeneic mouse models that recapitulate genetic changes in human ovarian carcinoma. The Orsulic Laboratory has engineered multiple mouse ovarian cancer cell lines with defined genetic alterations that are frequently present in human high-grade serous ovarian cancer. One example is the FVB-syngeneic mouse ovarian cancer cell line BR-Luc with combinations of genetic alterations in p53, Brca1, myc, and Akt. The tumors in this model are infiltrated with the host stromal cells while the luciferase and HA tags allow for convenient visualization and quantification of cancer cells by whole animal imaging and immunohistochemistry. Several features of this model make it suitable for studying microenvironment dynamics during ovarian cancer progression, such as:

1) the intact immune system

2) tumors form with 100% penetrance and predictable latency

3) the main genetic and pathologic aspects of human ovarian cancer are represented



A mouse syngeneic ovarian cancer model. (A) Small animal imaging visualization of luciferase-tagged cells 10 days after orthotopic implantation of mouse ovarian cancer cells. **(B)** Tumor growth in ovaries. **(C)** Peritoneal metastatic spread. **(D, E)** Visualization of HA-tagged cancer cells with immunohistochemistry in paraffin sections.

We have shown that this ovarian cancer model recapitulates human serous histology, pattern of metastatic spread, and response to standard and targeted therapies [1-14]. In collaboration, we have analyzed immune cell infiltrates, including $CD4^+$ and $CD8^+$ T cells, B cells, NK cells, $CD4^+$ T_{reg} cells, tumor-associated macrophages, and MDSCs, and demonstrated the utility of this model in studying the effects of therapies on the composition of major immune cell types [9, 11-14]. For example, we have shown that targeting the CXCL12/CXCR4 axis results in the selective reduction of intratumoral $FoxP3^+$ T_{reg} cells and a marked increase in T-cell-mediated antitumor immune response [9]. We have also demonstrated that the efficacy of anti-CTLA-4 therapy is greatly potentiated in combination with decitabine, which promotes the differentiation of naïve T cells into effector T cells and prolongs cytotoxic lymphocyte responses [14]. In addition to this FVB-syngeneic model, we have recently developed a C57BL/6-syngeneic mouse ovarian cancer model.

References:

1. Xing D, and Orsulic S (2005). Modeling resistance to pathway-targeted therapy in ovarian cancer. Cell Cycle *4*, 1004-1006.
2. Xing D, and Orsulic S (2005). A genetically defined mouse ovarian carcinoma model for the molecular characterization of pathway-targeted therapy and tumor resistance. Proc Natl Acad Sci U S A *102*, 6936-6941.
3. Sale S, and Orsulic S (2006). Models of ovarian cancer metastasis: Murine models. Drug Discov Today Dis Models *3*, 149-154.
4. Xing D, and Orsulic S (2006). A mouse model for the molecular characterization of brca1-associated ovarian carcinoma. Cancer Res *66*, 8949-8953.
5. Miao J, Wang Z, Provencher H, Muir B, Dahiya S, Carney E, Leong CO, Sgroi DC, and Orsulic S (2007). HOXB13 promotes ovarian cancer progression. Proc Natl Acad Sci U S A *104*, 17093-17098.
6. Miao J, Mu D, Ergel B, Singavarapu R, Duan Z, Powers S, Oliva E, and Orsulic S (2008). Hepsin colocalizes with desmosomes and induces progression of ovarian cancer in a mouse model. Int J Cancer *123*,2041-2047.
7. Ibrahim N, He L, Leong CO, Xing D, Karlan BY, Swisher EM, Rueda BR, Orsulic S, and Ellisen LW (2010). BRCA1- associated epigenetic regulation of p73 mediates an effector pathway for chemosensitivity in ovarian carcinoma. Cancer Res *70*, 7155-7165.
8. Goldberg MS, Xing D, Ren Y, Orsulic S, Bhatia SN, and Sharp PA (2011). Nanoparticle-mediated delivery of siRNA targeting Parp1 extends survival of mice bearing tumors derived from Brca1-deficient ovarian cancer cells. Proc Natl Acad Sci U S A *108*, 745-750.
9. Righi E, Kashiwagi S, Yuan J, Santosuosso M, Leblanc P, Ingraham R, Forbes B, Edelblute B, Collette B, Xing D, Kowalski M, Mingari MC, Vianello F, Birrer M, Orsulic S, Dranoff G, et al. (2011). CXCL12/CXCR4 blockade induces multimodal antitumor effects that prolong survival in an immunocompetent mouse model of ovarian cancer. Cancer Res *71*, 5522-5534.
10. Aspuria PJ, Lunt SY, Varemo L, Vergnes L, Gozo M, Beach JA, Salumbides B, Reue K, Wiedemeyer WR, Nielsen J, Karlan BY, and Orsulic S (2014). Succinate dehydrogenase inhibition leads to epithelial-mesenchymal transition and reprogrammed carbon metabolism. Cancer Metab *2*, 21.
11. Mantia-Smaldone G, Ronner L, Blair A, Gamerman V, Morse C, Orsulic S, Rubin S, Gimotty P, and Adams S (2014). The immunomodulatory effects of pegylated liposomal doxorubicin are amplified in BRCA1--deficient ovarian tumors and can be exploited to improve treatment response in a mouse model. Gynecol Oncol *133*, 584-590.
12. Yuan J, Kashiwagi S, Reeves P, Nezivar J, Yang Y, Arrifin NH, Nguyen M, Jean-Mary G, Tong X, Uppal P, Korochkina S, Forbes B, Chen T, Righi E, Bronson R, Chen H, et al. (2014). A novel mycobacterial Hsp70-containing fusion protein targeting mesothelin augments antitumor immunity and prolongs survival in murine models of ovarian cancer and mesothelioma. J Hematol Oncol *7*, 15.
13. Huang J, Wang L, Cong Z, Amoozgar Z, Kiner E, Xing D, Orsulic S, Matulonis U, and Goldberg MS (2015). The PARP1 inhibitor BMN 673 exhibits immunoregulatory effects in a Brca1(-/-) murine model of ovarian cancer. Biochem Biophys Res Commun *463*, 551-556.
14. Wang L, Amoozgar Z, Huang J, Saleh MH, Xing D, Orsulic S, and Goldberg MS (2015). Decitabine Enhances Lymphocyte Migration and Function and Synergizes with CTLA-4 Blockade in a Murine Ovarian Cancer Model. Cancer Immunol Res *3*, 1030-1041.