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Review Article

The organoid: A research model for ovarian cancer

*Yu-Hsun Chang[a], Kun-Chi Wu[b], Tomor Harnod[c], Dah-Ching Ding[d,e]**

[a]Department of Pediatrics, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation and Tzu Chi University, Hualien, Taiwan; [b]Department of Orthopedics, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation and Tzu Chi University, Hualien, Taiwan; [c]Department of Neurosurgery, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation and Tzu Chi University, Hualien, Taiwan; [d]Department of Obstetrics and Gynecology, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation and Tzu Chi University, Hualien, Taiwan; [e]Institutes of Medical Sciences, College of Medicine, Tzu Chi University, Hualien, Taiwan

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Abstract

Epithelial ovarian cancer (EOC) is a heterogeneous disease with a variety of distinct clinical and molecular characteristics. The currently available and common research models for EOC include tumor cell lines and patient-derived xenografts. However, these models have certain shortcomings: establishing a cell line is time-consuming, loss of genetic traits after long-term culture is a possibility, and investment is required in terms of animal care facilities. Therefore, better research models are required. Organoid technology was originally developed from colorectal cancer. Tumor organoid is a three-dimensional culture system and can help accurately recapture the tumor phenotype from the original tumor. Tumor organoid systems can overcome the above-mentioned shortcomings of the currently available research models. The organoid model can be used for culturing ovarian cancer subtypes, screening drugs, assessing genomes, and establishing biobanks. However, the currently available organoid models can only culture one type of cells, epithelial cells. Therefore, an organoid-on-a-chip device can be developed in the future to provide a microenvironment for cell–cell, cell–matrix, and cell–media interactions. Thus, organoid models can be used in ovarian cancer research and can generate a simulated *in vivo* system, enabling studies on the heterogeneity of ovarian cancer.

Keywords: *Epithelial cells, Epithelial ovarian cancer, Organoid-on-a-chip, Patient-derived xenografts, Xenograft*

Introduction

Epithelial ovarian cancer (EOC) is a heterogeneous disease, has a wide range of distinct clinical and molecular features [1,2], and is divided into two types (type 1 and type 2 EOC) [1,2]. Type 1 EOC includes endometrial cancer, clear-cell carcinoma, low-grade serous ovarian carcinoma, and mucinous carcinoma, whereas type 2 EOC includes high-grade serous ovarian cancer (HGSOC), carcinosarcoma, and undifferentiated carcinoma [3]. Type 1 EOC shows genetic stability and contains a set of genes, including *KRAS*, *PTEN*, *BRAF*, and *CTNNB1*, that are frequently mutated [4]. The genetic changes in HGSOC include extensive structural genomic (copy number) variations, P53 pathway inactivation, homologous recombination-mediated DNA damage repair (HR DDR, BRCA1 mutation) deficiency, CCNE1 and NOTCH3 activation, and Rb and NF1 inactivation [3]. A previous study has shown that HGSOC originates from the fallopian tube epithelium (FTE) [5].

The currently available, common research models for EOC include tumor cell lines and patient-derived xenografts (PDXs) [6,7]. However, these models have some shortcomings, including the time-consuming nature of cell line establishment processes, loss of genetic traits after long-term culturing, and investment of animal care facilities [8]. Therefore, newer research models are needed [9]. Organoid technology was originally developed from colorectal cancer [10]. The tumor organoid system, a three-dimensional culture system, can help accurately decipher the tumor phenotype from the original tumor [11] and overcome the previously mentioned shortcomings of the currently available research models. This review aims to provide a clear picture of the advantages and disadvantages of the currently available research models and the tumor organoid system used in ovarian cancer research.

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**Address for correspondence:* Dr. Dah-Ching Ding, Department of Obstetrics and Gynecology, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, 707, Section 3, Chung-Yang Road, Hualien, Taiwan.
E-mail: dah1003@yahoo.com.tw

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High-grade serous ovarian cancer development

HGSOC was thought to have originated from the ovarian epithelium; however, recently, it was found to have originated from the FTE. Ovarian cancer originating from the FTE was suspected from the BRCA1/2 germline mutations observed in fallopian tubes [12]. The immediate precursor lesion for HGSOC is serous tubal intraepithelial carcinoma (STIC), which is limited to the FTE and shows nuclear atypia, mitotic figures, abnormal p53 staining, and enhanced Ki-67 staining [13,14]. STIC cells can detach from the fallopian tube and spread to the pelvic cavity. The migrated STIC cells survive via environment selection and progressive nodule formation that leads to ascitic fluid production. Since the ovarian surface is located adjacent to the FTE, it is usually the first site to which STIC cells migrate [15]. p53 signatures are another fallopian tube epithelial lesion and present with intense p53 immunostaining, consistent with a missense TP53 mutation [16].

HGSOC harbors several characteristics, including a higher stage during diagnosis, TP53 mutations, homologous recombination DNA repair deficiency, and CCNE1 amplification, that distinguish it from type 1 EOC [17]. HGSOC development begins at the first ovulation and spans over >30 years [18]: 10 years from normal fallopian tube epithelial cells (FTECs) to p53 signatures, 15 years from p53 signatures to STIC, and 5 years from STIC to HGSOC.

Current research models for ovarian cancer

The currently available common research models for EOC include tumor cell lines and PDXs [6,7]. Both of these have been described below.

Cell lines

To recapture its biological and molecular significance, researchers need genetically and clinically evaluated cell lines to retake HGSOC [19,20]. Without reliable cell lines, it is challenging to translate *in vitro* study findings into *in vivo* studies on HGSOC [8,20,21]. The previous study surprisingly found a genomic dissimilarity between clinical HGSOC and the commonly used HGSOC cell lines [8]. They found that only 12 cell lines, which have been infrequently used, are compatible with HGSOC genotypes [8]. This number of cell lines is too small to efficiently research HGSOC heterogeneity [19,21-24]. Therefore, more cell lines are needed to address the necessity of HGSOC-related research and facilitate ovarian cancer research [1,8,20,25-27].

The current *in vitro* cell culture system precludes suppressed expression of hormone receptors, which may play a role in carcinogenesis:

After long-term *in vitro* culturing of either immortalized FTECs or HGSOC cells, the expression of most steroid hormones is typically silenced, likely via epigenetics [28]. Currently, FTECs (FE25) [29] and ovarian HGSOC cell lines, such as Kuramochi, OVSAHO, OVKATE, OVCAR3, and OVCAR4 [30], which are used in *in vitro* studies do not express estrogen receptor (ER) and progesterone receptor (PR). The cell line FE25 is derived from primary cultured FTECs and transfected by HPV E6 and E7, causing TP53 and Rb loss that mimics the characteristics of HGSOC [31]. In contrast, ER and PR are actually abundantly expressed in the FTE and in primary cultured FTECs, only at early passages [18,29,32]. Therefore, a suitable *in vitro* system is needed to study the role of hormones in the normal physiology and malignant transformation of the FTE.

Patient-derived xenograft model

The PDX model is a new kind of animal model used in cancer research. In the PDX model, a fresh tumor tissue is implanted into an immunodeficient animal, without *in vitro* cell culture. This model can preserve tumor cell heterogeneity and is used in studying various cancers, including breast, endometrial, and cervical [33-38]. It can also be used to explore tumor recurrence and chemosensitivity [39]. Nevertheless, there are many unresolved obstacles with regard to the PDX model. The success rate of PDX establishment is variable as per different studies (18%–100%) [27,40-42]; the factors influencing the success rate are unknown. Due to the lack of standard operating procedures, tumor subtypes, and the gene ontology of the molecular signatures, the role of the PDX model in ovarian cancer research remains to be elucidated [27,43]. Besides, PDX model establishment warrants investments in animal care facilities and a time-consuming animal breeding course. This model is not suitable for genetic manipulations or large-scale drug screening and would precede a mouse-specific tumor evolution process [44]. Therefore, an emerging model is warranted for ovarian cancer research.

The orthotopic (intrabursal) or intraperitoneal animal model

Another animal model for ovarian cancer is orthotopic and intraperitoneal injection model. The intraperitoneal model imitates peritoneal metastasis of ovarian cancer and is used for the evaluation of the efficacy of chemotherapy intraperitoneally [45]. Nevertheless, the limitation of this model is contributed from absence of primary tumor, the short life span of mice, and spontaneous metastasis [46]. The orthotopic model simulates the ovarian microenvironment for ovarian cancer survival. The gene expression pattern, histopathological characteristics, disease progression, and interaction between cancer cells and the microenvironment can be also imitated [47]. Both primary ovarian cancer and metastasis tumor exist in this model and well predicting the subsequent results for patients with metastatic cancer [48]. Nevertheless, this model harbors several disadvantages, including difficult techniques, time-consuming, expensive, and difficult to monitor the tumors [49,50].

Organoid introduction

Organoids are three-dimensional cell aggregates formed *in vitro* and can be derived only from primary tissue or embryonic stem cells. Organoids have self-renewal and self-organization capabilities and exhibit organ functionality [51]. The model has a composition and architecture similar to that of primary tissue. It could also

serve as a relevant model for assessing *in vivo* conditions and as a stable system for extended cultivation [51]. The tumor organoid system was first used in colon cancer research in 2011 [10]. The tumor organoid can accurately recapture the characteristics of the original tumor [11,52-54]. Organoid culture techniques employ cocktail growth factors and matrigel for the long-term effects. An organoid can be derived from a single cell and demonstrates tumor heterogeneity [55]. Organoid models can be used for evaluating genotype–phenotype correlations, drug sensitivity, and for predicting patient treatment response [54,56-58]. Taken together, organoids can be used in cancer research and can help avoid the disadvantages of cell lines and PDX models.

Organoid in fallopian tube epithelial cell research

Because HGSOC may originate from FTECs, an organoid model established from FTECs was developed. FTEC organoids can be derived from the proximal or distal end of the fallopian tube [59]. Fresh fallopian tubes can be used to generate organoids. The organoids will aggregate within 24 h and reach 2.5 mm after 2 weeks of culture [60]. The organoids can be passaged every 2–3 weeks in a ratio of 1:3 and can be maintained in culture for 34–60 days [61]. A previous study used a medium containing 25% of conditioned medium from fibroblasts to provide WNT3A and RSPO1 for fallopian tube organoids [60]. They also achieved a 100% success rate from 52 donors [60]. There was a study previously that reported use of 100 ng/mL of WNT3A and 600 ng/mL of RSPO1 in the organoid culture [62]. Another study used a 10% homemade RSPO1-conditioned medium and 200 ng/mL of WNT3A [63]. Our group also developed the FTEC organoid model. We used low amounts of WNT3A and RSPO1 (50 ng/mL each) to generate FTEC organoids [64]. A previous study found that P53-mutant FTECs could lead to HGSOC [65]. Induced pluripotent stem cells can also be used to generate FTECs and then organoids [66]. Above all, organoid models can be used for studying the transition from FTECs to HGSOC.

Organoids in ovarian cancer research

Organoids derived from ovarian cancers are different from those derived from FTEC. The culture media components and signal transduction are different for both cell types. Neuregulin-1 is considered one of the key factors in the generation of organoids from ovarian cancer [67]. However, the success rate of organoid formation is only 44% [67]. Another study, which contained 56 organoids derived from 32 patients, used the organoid model as a research platform for various types of ovarian cancer [68]. They used the Wnt-conditioned and pure organoid culture media for culturing ovarian cancer organoids, the success rate of which was 85% [68]. The organoid model has been recently used in ovarian cancer DNA repair defect research [69]. Zhang *et al*. reported the use of a genetically defined syngeneic organoid system to develop combination therapy for ovarian cancer [70]. Low Wnt signaling is required for ovarian cancer organoid formation [71]. Taken together, the organoid model used for ovarian cancer research is extremely common.

Advantages of organoids

The success rate of the organoid model is higher than that of spheroid cells and PDXs [72]. The applications of organoids in cancer research include ovarian cancer subtype culturing, drug screening, genomic assessments, and living biobank establishment [54,56-58,73]. An organoid can be derived from a single tumor cell and can recapture the heterogeneity of a tumor [55]. In summary, the organoid model can overcome the disadvantages of cell lines and PDXs.

Disadvantages of organoids

The organoid model harbors several disadvantages. The success rate is not 100% [67], although a previous report demonstrated an 85% success rate using specific culture medium components [68]. Next, the required medium is expensive (3000 USD/month for growth factors and special ingredients). Further, maintaining the organoid culture system is labor-intensive and Western blots cannot be performed to confirm the expression of specific proteins. However, this shortcoming can be conquered using immunohistochemistry. Taken together, the expansive culture medium may be the main disadvantage of the organoid model.

Assembloids in cancer research

Assembloids have recently been introduced to cancer research [74]. The old organoid model can only be used to culture epithelial tumor cells. However, the tumor comprises three germ layers: the endoderm, mesoderm, and ectoderm. The assembloid model overcomes this problem; it can be used to culture epithelial cells, stromal cells, and myoblasts and recapture the composition of the normal bladder and bladder cancer. It needs a three-dimensional printing technique to mix the three types of cells. In the future, we hope to use this technique to establish an ovarian cancer model.

Future perspectives

The organoid model still needs improvements. The current organoid model can only be used to culture epithelial cells and lacks cell–cell interactions. The assembloid model, which mixes three types of cells with three-dimensional bioprinting, will be a huge step forward [74]. However, other types of cells, such as immune cells and endothelial cells, cannot be cultured yet with any of these models. An organoid-on-a-chip may be a possible solution [59]; this system can enable cell–cell, cell–matrix, and cell–media interactions, a feature that the current organoid system lacks. Currently, three-dimensional bioprinting is established in a bioprosthetic ovary [75] and cervical cancer model [76]. The organoid-on-a-chip can use the microfluidic technique to function as a self-assembling and self-organized organoid system. The microfluidic technique is applied on the endocrine loop involving the liver, ovary, fallopian tube, uterus, and cervix, which can communicate with each other within the system [77]. Another study used the microfluidic technique to coculture endometrial cells and endothelial cells and demonstrate steroid responsiveness [78]. Most importantly, the current organoid model needs to be improved. An organoid-on-a-chip system can provide a microenvironment conducive for cell–cell, cell–matrix, and cell–media interactions, and these can be taken up as future developments [Figure 1].

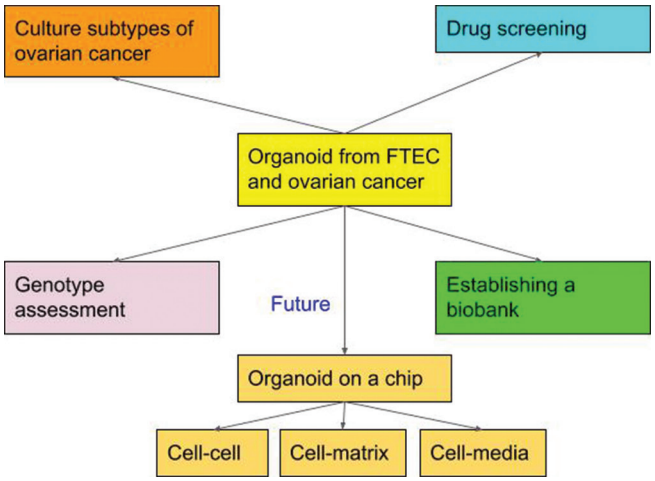

Figure 1: Applications of the organoid model in ovarian cancer research. FTEC: Fallopian tube epithelial cell

Conclusion

The organoid model can serve as a sustainable model for ovarian cancer research. This model overcomes the shortcomings of cell lines and PDX models. Once organoid biobanking is established, this model can be used for ovarian cancer subtype culturing, drug screening, and genomic assessment [Figure 1]. In patients with cancer, this model can be used to test chemosensitivity and radiosensitivity and for improving the treatment response. However, the currently available organoid models possess some disadvantages, such as a moderate success rate, expensive culture media requirements, limited assay runs, and labor intensiveness. Moreover, they can only be used to culture epithelial cells. Therefore, in the future, an organoid-on-a-chip can be developed; this will provide a microenvironment for cell–cell, cell–matrix, and cell–media interactions. In conclusion, organoid models can be used in ovarian cancer research and can generate a simulated *in vivo* system, enabling studies on the heterogeneity of ovarian cancer.

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Conflicts of interest

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References

1. Vaughan S, Coward JI, Bast RC Jr., Berchuck A, Berek JS, Brenton JD, et al. Rethinking ovarian cancer: Recommendations for improving outcomes. Nat Rev Cancer 2011;11:719-25.
2. Bowtell DD, Böhm S, Ahmed AA, Aspuria PJ, Bast RC Jr., Beral V, et al. Rethinking ovarian cancer II: Reducing mortality from high-grade serous ovarian cancer. Nat Rev Cancer 2015;15:668-79.
3. Kurman RJ, Shih IM. The dualistic model of ovarian carcinogenesis: Revisited, revised, and expanded. Am J Pathol 2016;186:733-47.
4. Koshiyama M, Matsumura N, Konishi I. Recent concepts of ovarian carcinogenesis: Type I and type II. Biomed Res Int 2014;2014:934261.
5. Kurman RJ, Shih IM. The origin and pathogenesis of epithelial ovarian cancer: A proposed unifying theory. Am J Surg Pathol 2010;34:433-43.
6. Thu KL, Papari-Zareei M, Stastny V, Song K, Peyton M, Martinez VD, et al. A comprehensively characterized cell line panel highly representative of clinical ovarian high-grade serous carcinomas. Oncotarget 2017;8:50489-99.
7. Kreuzinger C, Gamperl M, Wolf A, Heinze G, Geroldinger A, Lambrechts D, et al. Molecular characterization of 7 new established cell lines from high grade serous ovarian cancer. Cancer Lett 2015;362:218-28.
8. Domcke S, Sinha R, Levine DA, Sander C, Schultz N. Evaluating cell lines as tumour models by comparison of genomic profiles. Nat Commun 2013;4:2126.
9. Jones PM, Drapkin R. Modeling high-grade serous carcinoma: How converging insights into pathogenesis and genetics are driving better experimental platforms. Front Oncol 2013;3:217.
10. Sato T, Stange DE, Ferrante M, Vries RG, van Es JH, Van den Brink S, et al. Long-term expansion of epithelial organoids from human colon, adenoma, adenocarcinoma, and Barrett's epithelium. Gastroenterology 2011;141:1762-72.
11. Gao D, Vela I, Sboner A, Iaquinta PJ, Karthaus WR, Gopalan A, et al. Organoid cultures derived from patients with advanced prostate cancer. Cell 2014;159:176-87.
12. Piek JM, van Diest PJ, Zweemer RP, Jansen JW, Poort-Keesom RJ, Menko FH, et al. Dysplastic changes in prophylactically removed Fallopian tubes of women predisposed to developing ovarian cancer. J Pathol 2001;195:451-6.
13. Kindelberger DW, Lee Y, Miron A, Hirsch MS, Feltmate C, Medeiros F, et al. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: Evidence for a causal relationship. Am J Surg Pathol 2007;31:161-9.
14. Kuhn E, Kurman RJ, Sehdev AS, Shih IM. Ki-67 labeling index as an adjunct in the diagnosis of serous tubal intraepithelial carcinoma. Int J Gynecol Pathol 2012;31:416-22.
15. Soong TR, Kolin DL, Teschan NJ, Crum CP. Back to the future? The fallopian tube, precursor escape and a dualistic model of high-grade serous carcinogenesis. Cancers (Basel) 2018;10:468.
16. Crum CP, Drapkin R, Miron A, Ince TA, Muto M, Kindelberger DW, et al. The distal fallopian tube: A new model for pelvic serous carcinogenesis. Curr Opin Obstet Gynecol 2007;19:3-9.
17. Shih IM, Wang Y, Wang TL. The origin of ovarian cancer species and precancerous landscape. Am J Pathol 2021;191:26-39.
18. Wu NY, Fang C, Huang HS, Wang J, Chu TY. Natural history of ovarian high-grade serous carcinoma from time effects of ovulation inhibition and progesterone clearance of p53-defective lesions. Mod Pathol 2020;33:29-37.
19. Gillet JP, Varma S, Gottesman MM. The clinical relevance of cancer cell lines. J Natl Cancer Inst 2013;105:452-8.
20. Jacob F, Nixdorf S, Hacker NF, Heinzelmann-Schwarz VA. Reliable *in vitro* studies require appropriate ovarian cancer cell lines. J Ovarian Res 2014;7:60.
21. Konstantinopoulos PA, Matulonis UA. Current status and evolution of preclinical drug development models of epithelial ovarian cancer. Front Oncol 2013;3:296.
22. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature 2011;474:609-15.
23. Schwarz RF, Ng CK, Cooke SL, Newman S, Temple J, Piskorz AM, et al. Spatial and temporal heterogeneity in high-grade serous ovarian cancer: A phylogenetic analysis. PLoS Med 2015;12:e1001789.
24. Cooke SL, Ng CK, Melnyk N, Garcia MJ, Hardcastle T, Temple J, et al. Genomic analysis of genetic heterogeneity and evolution in high-grade serous ovarian carcinoma. Oncogene 2010;29:4905-13.
25. Berns EM, Bowtell DD. The changing view of high-grade serous ovarian cancer. Cancer Res 2012;72:2701-4.

26. Korch C, Spillman MA, Jackson TA, Jacobsen BM, Murphy SK, Lessey BA, et al. DNA profiling analysis of endometrial and ovarian cell lines reveals misidentification, redundancy and contamination. Gynecol Oncol 2012;127:241-8.
27. Scott CL, Becker MA, Haluska P, Samimi G. Patient-derived xenograft models to improve targeted therapy in epithelial ovarian cancer treatment. Front Oncol 2013;3:295.
28. Yang S, Jia Y, Liu X, Winters C, Wang X, Zhang Y, et al. Systematic dissection of the mechanisms underlying progesterone receptor downregulation in endometrial cancer. Oncotarget 2014;5:9783-97.
29. Wu NY, Huang HS, Chao TH, Chou HM, Fang C, Qin CZ, et al. Progesterone prevents high-grade serous ovarian cancer by inducing necroptosis of p53-defective fallopian tube epithelial cells. Cell Rep 2017;18:2557-65.
30. Moyle-Heyrman G, Schipma MJ, Dean M, Davis DA, Burdette JE. Genome-wide transcriptional regulation of estrogen receptor targets in fallopian tube cells and the role of selective estrogen receptor modulators. J Ovarian Res 2016;9:5.
31. Huang HS, Chu SC, Hsu CF, Chen PC, Ding DC, Chang MY, et al. Mutagenic, surviving and tumorigenic effects of follicular fluid in the context of p53 loss: Initiation of fimbria carcinogenesis. Carcinogenesis 2015;36:1419-28.
32. Chang YH, Ding DC, Chu TY. Estradiol and progesterone induced differentiation and increased stemness gene expression of human fallopian tube epithelial cells. J Cancer 2019;10:3028-36.
33. Walters DM, Stokes JB, Adair SJ, Stelow EB, Borgman CA, Lowrey BT, et al. Clinical, molecular and genetic validation of a murine orthotopic xenograft model of pancreatic adenocarcinoma using fresh human specimens. PLoS One 2013;8:e77065.
34. Kabos P, Finlay-Schultz J, Li C, Kline E, Finlayson C, Wisell J, et al. Patient-derived luminal breast cancer xenografts retain hormone receptor heterogeneity and help define unique estrogen-dependent gene signatures. Breast Cancer Res Treat 2012;135:415-32.
35. Chaudary N, Pintilie M, Schwock J, Dhani N, Clarke B, Milosevic M, et al. Characterization of the tumor-microenvironment in patient-derived cervix xenografts (OCICx). Cancers (Basel) 2012;4:821-45.
36. Cancer Genome Atlas Research Network, Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, et al. Integrated genomic characterization of endometrial carcinoma. Nature 2013;497:67-73.
37. Topp MD, Hartley L, Cook M, Heong V, Boehm E, McShane L, et al. Molecular correlates of platinum response in human high-grade serous ovarian cancer patient-derived xenografts. Mol Oncol 2014;8:656-68.
38. Weroha SJ, Becker MA, Enderica-Gonzalez S, Harrington SC, Oberg AL, Maurer MJ, et al. Tumorgrafts as *in vivo* surrogates for women with ovarian cancer. Clin Cancer Res 2014;20:1288-97.
39. Vidal A, Muñoz C, Guillén MJ, Moretó J, Puertas S, Martínez-Iniesta M, et al. Lurbinectedin (PM01183), a new DNA minor groove binder, inhibits growth of orthotopic primary graft of cisplatin-resistant epithelial ovarian cancer. Clin Cancer Res 2012;18:5399-411.
40. Dobbin ZC, Katre AA, Steg AD, Erickson BK, Shah MM, Alvarez RD, et al. Using heterogeneity of the patient-derived xenograft model to identify the chemoresistant population in ovarian cancer. Oncotarget 2014;5:8750-64.
41. Ricci F, Bizzaro F, Cesca M, Guffanti F, Ganzinelli M, Decio A, et al. Patient-derived ovarian tumor xenografts recapitulate human clinicopathology and genetic alterations. Cancer Res 2014;74:6980-90.
42. Wu J, Zheng Y, Tian Q, Yao M, Yi X. Establishment of patient-derived xenograft model in ovarian cancer and its influence factors analysis. J Obstet Gynaecol Res 2019;45:2062-73.
43. Kortmann U, McAlpine JN, Xue H, Guan J, Ha G, Tully S, et al. Tumor growth inhibition by olaparib in BRCA2 germline-mutated patient-derived ovarian cancer tissue xenografts. Clin Cancer Res 2011;17:783-91.
44. Ben-David U, Ha G, Tseng YY, Greenwald NF, Oh C, Shih J, et al. Patient-derived xenografts undergo mouse-specific tumor evolution. Nat Genet 2017;49:1567-75.
45. Shaw TJ, Senterman MK, Dawson K, Crane CA, Vanderhyden BC. Characterization of intraperitoneal, orthotopic, and metastatic xenograft models of human ovarian cancer. Mol Ther 2004;10:1032-42.
46. Karakashev S, Zhang RG. Mouse models of epithelial ovarian cancer for preclinical studies. Zool Res 2021;42:153-60.
47. Céspedes MV, Casanova I, Parreño M, Mangues R. Mouse models in oncogenesis and cancer therapy. Clin Transl Oncol 2006;8:318-29.
48. Francia G, Cruz-Munoz W, Man S, Xu P, Kerbel RS. Mouse models of advanced spontaneous metastasis for experimental therapeutics. Nat Rev Cancer 2011;11:135-41.
49. Bibby MC. Orthotopic models of cancer for preclinical drug evaluation: Advantages and disadvantages. Eur J Cancer 2004;40:852-7.
50. Guo J, Cai J, Zhang Y, Zhu Y, Yang P, Wang Z. Establishment of two ovarian cancer orthotopic xenograft mouse models for *in vivo* imaging: A comparative study. Int J Oncol 2017;51:1199-208.
51. Lancaster MA, Knoblich JA. Organogenesis in a dish: Modeling development and disease using organoid technologies. Science 2014;345:1247125.
52. Fujii M, Shimokawa M, Date S, Takano A, Matano M, Nanki K, et al. A colorectal tumor organoid library demonstrates progressive loss of niche factor requirements during tumorigenesis. Cell Stem Cell 2016;18:827-38.
53. Boj SF, Hwang CI, Baker LA, Chio II, Engle DD, Corbo V, et al. Organoid models of human and mouse ductal pancreatic cancer. Cell 2015;160:324-38.
54. van de Wetering M, Francies HE, Francis JM, Bounova G, Iorio F, Pronk A, et al. Prospective derivation of a living organoid biobank of colorectal cancer patients. Cell 2015;161:933-45.
55. Roerink SF, Sasaki N, Lee-Six H, Young MD, Alexandrov LB, Behjati S, et al. Intra-tumour diversification in colorectal cancer at the single-cell level. Nature 2018;556:457-62.
56. Vlachogiannis G, Hedayat S, Vatsiou A, Jamin Y, Fernández-Mateos J, Khan K, et al. Patient-derived organoids model treatment response of metastatic gastrointestinal cancers. Science 2018;359:920-6.
57. Sachs N, de Ligt J, Kopper O, Gogola E, Bounova G, Weeber F, et al. A Living biobank of breast cancer organoids captures disease heterogeneity. Cell 2018;172:373-86.e10.
58. Verissimo CS, Overmeer RM, Ponsioen B, Drost J, Mertens S, Verlaan-Klink I, et al. Targeting mutant RAS in patient-derived colorectal cancer organoids by combinatorial drug screening. Elife 2016;5:e18489.
59. Semertzidou A, Brosens JJ, McNeish I, Kyrgiou M. Organoid models in gynaecological oncology research. Cancer Treat Rev 2020;90:102103.
60. Kessler M, Hoffmann K, Brinkmann V, Thieck O, Jackisch S, Toelle B, et al. The Notch and Wnt pathways regulate stemness and differentiation in human fallopian tube organoids. Nat Commun 2015;6:8989.
61. Lawrenson K, Notaridou M, Lee N, Benjamin E, Jacobs IJ, Jones C, et al. *In vitro* three-dimensional modeling of fallopian tube secretory epithelial cells. BMC Cell Biol 2013;14:43.
62. Xie Y, Park ES, Xiang D, Li Z. Long-term organoid culture reveals enrichment of organoid-forming epithelial cells in the fimbrial portion of mouse fallopian tube. Stem Cell Res 2018;32:51-60.
63. Boretto M, Maenhoudt N, Luo X, Hennes A, Boeckx B, Bui B, et al. Patient-derived organoids from endometrial disease capture clinical heterogeneity and are amenable to drug screening. Nat Cell Biol 2019;21:1041-51.
64. Chang YH, Chu TY, Ding DC. Human fallopian tube epithelial cells exhibit stemness features, self-renewal capacity, and Wnt-related organoid formation. J Biomed Sci 2020;27:32.
65. Zhang S, Dolgalev I, Zhang T, Ran H, Levine DA, Neel BG. Both fallopian tube and ovarian surface epithelium are cells-of-origin for high-grade serous ovarian carcinoma. Nat Commun 2019;10:5367.

66. Yucer N, Holzapfel M, Jenkins Vogel T, Lenaeus L, Ornelas L, Laury A, et al. Directed differentiation of human induced pluripotent stem cells into fallopian tube epithelium. Sci Rep 2017;7:10741.
67. Maenhoudt N, Defraye C, Boretto M, Jan Z, Heremans R, Boeckx B, et al. Developing organoids from ovarian cancer as experimental and preclinical models. Stem Cell Reports 2020;14:717-29.
68. Kopper O, de Witte CJ, Lõhmussaar K, Valle-Inclan JE, Hami N, Kester L, et al. An organoid platform for ovarian cancer captures intra- and interpatient heterogeneity. Nat Med 2019;25:838-49.
69. Hill SJ, Decker B, Roberts EA, Horowitz NS, Muto MG, Worley MJ Jr., et al. Prediction of DNA repair inhibitor response in short-term patient-derived ovarian cancer organoids. Cancer Discov 2018;8:1404-21.
70. Zhang S, Iyer S, Ran H, Dolgalev I, Gu S, Wei W, et al. Genetically defined, syngeneic organoid platform for developing combination therapies for ovarian cancer. Cancer Discov 2021;11:362-83.
71. Hoffmann K, Berger H, Kulbe H, Thillainadarasan S, Mollenkopf HJ, Zemojtel T, et al. Stable expansion of high-grade serous ovarian cancer organoids requires a low-Wnt environment. EMBO J 2020;39:e104013.
72. Maru Y, Hippo Y. Current status of patient-derived ovarian cancer models. Cells 2019;8:505.
73. Liu HD, Xia BR, Jin MZ, Lou G. Organoid of ovarian cancer: Genomic analysis and drug screening. Clin Transl Oncol 2020;22:1240-51.
74. Kim E, Choi S, Kang B, Kong J, Kim Y, Yoon WH, et al. Creation of bladder assembloids mimicking tissue regeneration and cancer. Nature 2020;588:664-9.
75. Laronda MM, Rutz AL, Xiao S, Whelan KA, Duncan FE, Roth EW, et al. A bioprosthetic ovary created using 3D printed microporous scaffolds restores ovarian function in sterilized mice. Nat Commun 2017;8:15261.
76. Zhao Y, Yao R, Ouyang L, Ding H, Zhang T, Zhang K, et al. Three-dimensional printing of Hela cells for cervical tumor model *in vitro*. Biofabrication 2014;6:035001.
77. Xiao S, Coppeta JR, Rogers HB, Isenberg BC, Zhu J, Olalekan SA, et al. A microfluidic culture model of the human reproductive tract and 28-day menstrual cycle. Nat Commun 2017;8:14584.
78. Gnecco JS, Pensabene V, Li DJ, Ding T, Hui EE, Bruner-Tran KL, et al. Compartmentalized culture of perivascular stroma and endothelial cells in a microfluidic model of the human endometrium. Ann Biomed Eng 2017;45:1758-69.