Humanized Preclinical Mouse Models for Endometrial Cancer Reflecting Patient Tumor Growth, Pathology, and Metastatic Progression

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ABSTRACT SUMMARY
New preclinical endometrial cancer mouse models were developed by direct transplantation of patient-derived tumor tissues. These humanized models illustrate the diversity of endometrial cancer including metastatic progression and retain crucial pathological characteristics of the original human tumor specimens. This unique animal model will serve as a tool to facilitate the evaluation of new therapeutic agents and development of personalized medicine.

INTRODUCTION
Endometrial cancer is the most common gynecologic cancer and accounting 6% of all cancers in women, with an incidence of 47,130 new cases diagnosed and over 8,000 deaths in the United States this year alone [1]. Despite the vast investment in oncological research and an improved understanding of cancer biology, the translation of research advancements into clinical practice still progress at a slow pace. More than 90% of newly developed anticancer therapeutic agents fail to produce the preclinically predicted improvement of current treatments during the translational process into the clinic [2,3]. The scarcity of truly predictive in vivo models, which are capable of authentically reproducing tumor progression and metastasis, is one major obstacle of translational research [4]. In this study, we developed a humanized endometrial cancer mouse model that retains crucial pathological and molecular characteristics of the original, patient-derived tumor specimen and a tissue bank of serially transplantable, orthotopic, clinical, endometrial tumors is establishing for future translational investigation.

EXPERIMENTAL METHODS
Patient derived tissue was obtained freshly from Huntsman Cancer Institute Tissue Resource and Applications Core (TRAC) facility and a single tissue fragment was surgically implanted into the uteri of 6-8 week old female nude mice. Following orthotopic implantation, mice body weights and abdominal circumferences were captured weekly. Palpation was performed to check tumor growth. Once the palpable tumor mass approached endpoint diameter, animals were sacrificed and tumors were harvested. At this point metastases were also evaluated in regards to quantity and location. Patient-derived xenografts grown in mice were histologically validated staining for human specific Vimentin, H&E and CD31 to obtain information regarding morphology, vasculature and origin. The status of hormone expression was immunohistochemically evaluated to verify that mouse tumors resembled features of the original human tumors. Sections of mouse tumors were isolated and minced into smaller pieces to be transplanted to groups of five mice, denoted as 2nd generation. The same study procedures were performed to confirm that our humanized mouse model successfully retained original characteristics of patient-derived tumor specimen following serial transplantation in vivo.

RESULTS AND DISCUSSION
Tumor tissues from 5 patients, received as fresh primary or recurrent endometrial tumors were surgically transplanted into mouse uteri. Four out five samples (80%) successfully developed orthotopic, endometrial tumors in vivo (Figure 1).
All of these humanized mouse models formed distant metastases with the metastatic spread occurring in a characteristic pattern similar to common clinical metastatic sites of endometrial cancer including liver, spleen as well as inguinal and supraclavicular lymphnodes (Figure 2).
Immunohistochemical staining validated that the tumors formed in mice resembled the original patient tumor samples. Further tumor
characterization to confirm that our tumor grafts retain their molecular characteristics as well as other features of human tumors is currently still ongoing.

Figure 1. Humanized mouse models produced the diversity of endometrial cancer and recapitulate patient tumor growth. (A) Control uterus; (B-D) Representative examples of different stages of endometrial cancer generated by direct transplantation of patient-derived tumor tissues. Scale bars, 1 cm.

Figure 2. Distant metastases formed in a characteristic pattern similar to common clinical metastatic sites. (A) Liver; (B) Spleen; (C) Inguinal node; (D) Supraclavicular node. Yellow arrows indicate tumor nodules. Scale bars, 1 cm.

CONCLUSION
This study reports the successful generation of humanized, endometrial cancer mouse models by direct transplantation of patient-derived tumor tissues to nude mice. These humanized endometrial cancer mouse models successfully retain crucial characteristics, including metastatic spread, of the original human tumor specimens and are serially transplantable. This type of animal model is a step towards personalized models for the individual investigation of tumor progression, metastasis and drug screening. This unique tumor tissue bank will serve as a tool to facilitate strategies for early disease diagnosis, development and evaluation of new therapeutic agents, and the pre-, and clinical realization of personalized medicine.

REFERENCES

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