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14. ABSTRACT Despite a common outstanding response to primary therapy, most ovarian cancer patients will experience recurrence due to what is often microscopic undetectable disease. One possible cause of this is a chemoresistant population of cells with stem cell characteristics. We have examined one potential population in particular, the ALDH-positive population. We have shown that ALDH1A1-positive cells are more tumorigenic than ALDH1A1-negative cells, contribute to poor patient outcomes, and contribute to chemoresistance. These effects can be reversed by downregulating ALDH1A1 expression with nanoparticle-delivered siRNA. Additionally, we have shown that CSCs are clinically significant, in that chemoresistant tumors have increased density of ALDH and CD133 cells. Importantly, they do not seem to explain the entire story, as there are still many CSC-negative cells present at the conclusion of treatment. Specifically, endoglin (CD105) and hedgehog family members (Gli1 and Gli2) appear to play important roles in chemotherapy resistance, and when targeted enhance response to chemotherapy. To further identify other important players, we have further developed the patient-derived xenograft (PDX) model where patient samples are directly implanted into mice, and when formed, treated with chemotherapy. The treated tumors, like patient specimens, are enriched with ALDH1-positive cells. Further characterization of the surviving population is underway, in conjunction with separately-funded protocols.					
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Characterization and targeting of the ALDH subpopulation in ovarian cancer

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University of Alabama at Birmingham, Birmingham, AL

Ovarian Cancer Academy OC093443 July 2012- June 2013 Annual Report

INTRODUCTION:

While most ovarian cancer patients initially respond to chemotherapy, most will ultimately recur and succumb to disease, suggesting that there is a subpopulation of cells within a heterogeneous tumor that has either inherent or acquired resistance to chemotherapy¹. Recently subpopulations of cancer cells in solid tumors have been observed to have properties of stem cells, and therefore designated as “cancer stem cells” (CSC’s) or tumor initiating cells (TIC’s)^{2,3}. The intent of this project is to characterize whether ovarian cells that express aldehyde dehydrogenase (ALDH1A1) have cancer stem cell properties, and if targeting ALDH1A1 would lead to a reversal of the chemoresistant properties. Characteristics of cancer stem cell that will be assessed include tumorigenicity experiments, evidence of multipotentiality, and enhanced resistance to chemotherapeutics. The effects of ALDH1A1 downregulation will be determined both *in vitro* and *in vivo*, using small interfering RNA (siRNA) encapsulated in nanoparticles that allow efficient *in vivo* delivery. If our hypotheses are confirmed, we will have identified a subpopulation of ovarian cancer cells that might survive initial chemotherapy and contribute to resistance, and furthermore may find a clinically feasible novel methodology to target these cells to improve outcomes in this devastating disease. If ALDH1 cells are not explaining the full population of chemoresistant cells, these studies will provide the opportunity to more fully characterize which cells are mediating survival of primary therapy.

BODY:

Task 1: Determine tumorigenicity of ALDH1A1 subpopulations

The goal of task 1 was to determine the tumorigenicity of ALDH1A1 subpopulations. In a prior annual report, we described results published in *Molecular Cancer Therapeutics*⁴ showing tumorigenicity of ALDH1A1-positive cells compared to ALDH1A1-negative cells from the A2780cp20 cell line.

Task 2: Determine if ALDH1-positive cells survive chemotherapy in the tumor microenvironment.

We have previously reported on IHC performed on these for ALDH1, CD44, and CD133 to determine whether recurrent tumors, which are generally more chemoresistant, are predominantly composed of these populations. We found that tumors collected immediate after receiving primary therapy, the time at which cells surviving would ultimately cause recurrent disease, were higher in both ALDH1 (2-fold) and CD133 (24-fold) cells.

To examine whether this is also noted in a setting where chemotherapy administration and tumor collection is more controlled, we have established protocols for development of primary xenografts in SCID mice, termed “patient-derived xenografts” (PDX). We previously reported that growth in the subcutaneous site was most efficient, and that the tumors growing in

mice have similar expression patterns as patient tumors. This was shown by qPCR for 84 oncogenes considered targets for therapy.

In the interim, we have asked the question whether tumors growing intraperitoneally are similar to those growing subcutaneously. This is important, as models of orthotopic growth are considered by many to be more relevant than those grown in extraperitoneal sites. However, IP models are difficult to use in evaluation of therapeutics, since they rapidly cause morbidity in mice, preventing time to determine efficacy of therapeutics. We performed qPCR array on IP and SQ tumors derived from the same patient, and found that they too have very similar expression patterns (Figure 1). Future studies plant to perform RNA-Seq analysis on such tumors to determine ways in which growth in these sites are different.

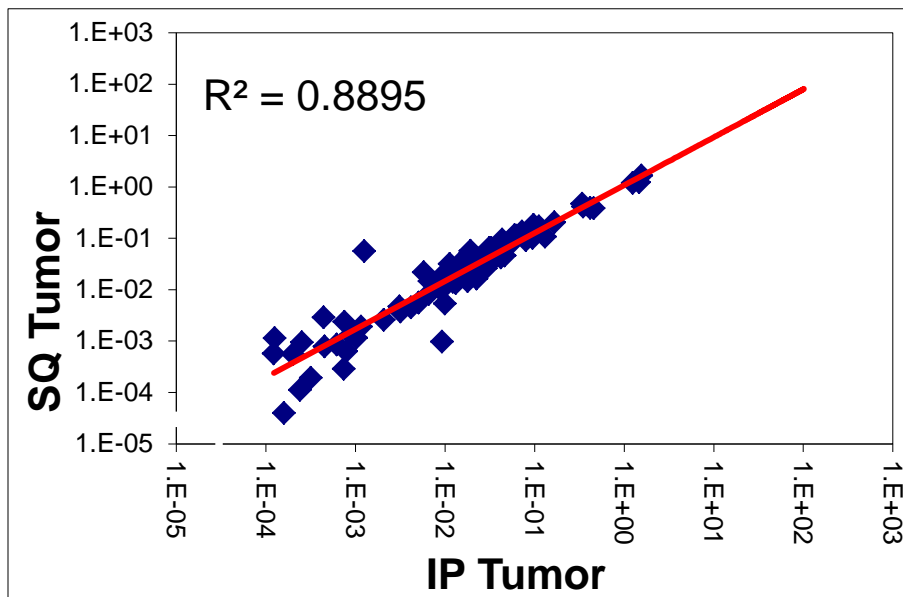


Figure 1. Quantitative PCR array comparing PDX tumors from the same patient grown in IP and SQ sites

Task 3: Target ALDH1 with siRNA *in vivo*

We previously reported use of a method for delivery of siRNA *in vivo* using DOPC nanoparticles to target ALDH1A1 *in vivo*. Immunohistochemical analysis confirmed reduced ALDH1A1 expression with ALDH1A1-siRNA/DOPC treatment compared to controls but not with chemotherapy alone. The combination of ALDH1A1 siRNA and docetaxel resulted in significantly reduced growth, by 93.6% compared to control siRNA ($p < 0.001$), by 89.8% compared to docetaxel plus control siRNA ($p = 0.003$), and by 91.4% compared to ALDH1A1 siRNA ($p = 0.002$).

Task 4: Evaluate mechanisms of ALDH1-mediated chemoresistance

We previously reported completion of microarray studies performed on ALDH1-positive and negative populations in order to identify which pathways may be overexpressed and targetable. In conjunction with this list, as well as genes identified in stem cell pathway analysis

of patient primary/recurrent pair, two genes have been further characterized for their contribution to chemotherapy resistance – the endoglin pathway and the hedgehog pathway.

There are no new results under this task to report, primarily due to delays in being able to pursue this line investigation while arrangements associated with a change institutions have been made. Administrative tasks have been completed, including MTAs for cell lines to be used, transferring the grant from UAB to UVA, and hiring research staff to perform experiments.

KEY RESEARCH ACCOMPLISHMENTS:

- ALDH-positive cells from the A2780cp20 and SKOV3TRip2 cell lines have approximately 50-fold increased tumorigenicity compared to ALDH-negative cells.
- Tumors treated with chemotherapy are enriched in the ALDH1 And CD133 CSC population, compared to matched samples collected prior to therapy.
- Efficient establishment of primary xenografts directly from patient tumors is feasible, and mimic patient tumors in histologic make-up, CSC density, and response to chemotherapy.
- Xenograft tumors from mice treated with chemotherapy are similarly enriched in ALDH1 and CD133 CSCs.
- Treatment of tumor-bearing mice with ALDH1A1-targeting siRNA in DOPC sensitized normally-resistant cell lines to cisplatin or paclitaxel.
- Stem cell pathway genes endoglin and hedgehog mediators Gli1 and Gli2 contribute to chemotherapy resistance, and targeting these genes restores sensitivity to chemotherapy.
- Successful physical and administrative transfer of personnel and grant to UVA

REPORTABLE OUTCOMES:

- Publications 2014-2015:
 1. Bradley A, Zheng H, Ziebarth A, Sakati W, Branham-O'Connor M, Blumer JB, Liu Y, Kistner-Griffin E, Rodriguez-Aguayo C, Lopez-Berestein G, Sood AK, **Landen CN** Jr, Eblen ST. EDD enhances cell survival and cisplatin resistance and is a therapeutic target for epithelial ovarian cancer. *Carcinogenesis*. 35(5): 1100-9, 2014. PMID 24379240
 2. Shah MS and **Landen CN**. Ovarian Cancer Stem Cells: Are They Real and Why are they Important? *Gynecol Oncol*, 132(2): 483-89, 2014. PMID 24321398
 3. Arend RC, Londoño-Joshi AL, Samant RS, Li Y, Conner M, Hidalgo B, Alvarez RD, **Landen CN**, Straughn JM, DJ Buchsbaum. Inhibition of Wnt/ β -catenin pathway by niclosamide: a therapeutic target for ovarian cancer. *Gynecol Oncol*. 134(1): 112-20, 2014. PMID:24736023
 4. Shah MM, Dobbin ZC, Nowsheen S, Wieglos M, Katre AA, Alvarez RD, Konstantinopoulos PA, Yang ES, **Landen CN**. An ex-vivo assay of XRT-induced Rad51 foci formation predicts response to PARP-inhibition in ovarian cancer. *Gynecol Oncol*, 134(2): 331-7, 2014. PMID 24844596.
 5. Steg AD*, Burke MR*, Amm HM, Katre AA, Dobbin ZC, Jeong DH, **Landen CN**. Proteasome inhibition reverses hedgehog inhibitor and taxane resistance in ovarian cancer. *Oncotarget*, Aug 30;5(16):7065-80, 2014. PMID 25216523.

6. Dobbin ZC, Katre AA, Steg AD, Erickson BK, Shah MM, Alvarez RD, Conner MG, Schneider D, Chen D, **Landen CN**. Using heterogeneity of the patient-derived xenograft model to identify the chemoresistant population in ovarian cancer. *Oncotarget*. 5(18): 8750-64, 2014. PMID 25209969.
 7. Erickson BK, Kinde I, Dobbin ZC, Wang Y, Martin JY, Alvarez RD, Conner MG, Huh WK, Roden RBS, Kinzler KW, Papadopoulos N, Vogelstein B, Diaz LA, **Landen CN Jr**. Detection of Somatic TP53 Mutations in Tampons of Patients With High-Grade Serous Ovarian Cancer. *Obstet Gynecol*, 124(5): 881-5, 2014. PMID 25437714.
 8. Desai A, Xu J, Aysola K, Qin Y, Okoli C, Hariprasad R, Chinemerem U, Gates C, Reddy A, Danner O, Franklin G, Ngozi A, Cantuaria G, Singh K, Grizzle W, **Landen C**, Partridge EE, Rice VM, Reddy ES, Rao VN. Epithelial ovarian cancer: An overview. *World J Transl Med*. 2014 Apr 12;3(1):1-8. PMID: 25525571
 9. Chien J and **Landen CN**. Summary of the 2015 American Association for Cancer Research (AACR) Annual Meeting. *Gynecol Oncol*, in press.
- Abstracts presented 2014-2015:
 1. Meredith R, Torgue J, Shen S, Banaga E, Bunch P, **Landen CN**. Phase I Trial of Intraperitoneal Alpha Radioimmunotherapy with ^{212}Pb -TCMC-trastuzumab. *12th International Congress of Targeted Anticancer Therapies*, Washington, DC, March 2014.
 2. Walters Haygood CL, Arend RC, Londono-Joshi A, Kurpad C, Katre AA, Conner MG, **Landen Jr. CN**, Straughn JM, Buchsbaum DJ. *Ovarian Cancer Ascites Stem Cell Population Compared to Primary Tumor. Annual Meeting of the Society of Gynecologic Oncologists*. Tampa, FL. March 2014.
 3. Erickson BK, Dobbin ZC, Kinde I, Martin JY, Wang Y, Roden R, Huh WK, Vogelstein B, Diaz LA, **Landen Jr CN**. Testing the Accuracy of Mutation detection for the Prevention of Ovarian Neoplasia: the TAMPON study. *Annual Meeting of the Society of Gynecologic Oncologists*. Tampa, FL. March 2014.
 4. Dobbin ZC, Katre AK, Shah MM, Erikson BK, Chen H, Alvarez RD, Conner MG, Chen D, and **Landen CN**. An ovarian patient-derived xenograft model to identify the chemoresistant population. *10th Biennial Ovarian Cancer Research Symposium*. Seattle, WA. September, 2014.
 5. Arend RC, Gangrade A, Walters Haygood CL, Kurpad C, Metge BJ, Samant RS, Li PK, Li Y, Bhasin D, **Landen CN**, Alvarez RD, Straughn JM, Buchsbaum DJ. Overcoming Platinum Resistance in Ovarian Cancer with Niclosamide. *10th Biennial Ovarian Cancer Research Symposium*. Seattle, WA. September, 2014.
 6. Garcia AA, Makker V, Spitz DL, Matei DE, Nick AM, **Landen CN**, Alvarez EA, Mendelson DS, Strother RM, Seon BK, Alvarez D, Adams BJ, Theuer CP, Gordon M. TRC105 (Anti-endoglin Antibody) in Combination with Bevacizumab (BEV) and as a Single Agent for Platinum Resistant Ovarian Cancer. *ESMO*. Madrid, Spain. September, 2014.
 7. Dobbin ZC, Katre AA, Jeong DJ, Erickson BK, Alvarez RD, Schneider DA, **Landen Jr CN**. Post-chemotherapy tumors in the PDX model identify ribosomal synthesis as a novel targeting strategy in ovarian cancer. *Annual Meeting of the Society of Gynecologic Oncologists*. Chicago, IL. March 2015.
 8. Kreitzburg KM, Dobbins Z, Katre A, Anwer T, Alvarez R, Landen CN, Yoon KJ. Developing targeted therapy for the treatment of drug-resistant ovarian cancer. *Proceedings of the American Association of Cancer Research*, 2015.

- Grants awarded for which data generated by this work contributed preliminary data:
 - Principle Investigator. *Identifying mediators of chemoresistance in ovarian cancer*. The Norma Livingston Foundation. 50,000, 5/1/2012-4/30/2014.
 - Principle Investigator. *Development of a Personalized Therapy Model in Cervical Cancer*. Pilot Project, SPORE in Cervical Cancer. 9/1/2012 – 8/31/2013. \$30,000.
 - Co-Principle Investigator. *Predicting response of ovarian cancers to PARP Inhibitors*. The ROAR Foundation. 12/14/2012 – 12/13/2014. \$100,000.
 - Principal Investigator, *Targeting Ribosomal RNA Synthesis for Treatment of Ovarian Cancer*, RSDP Seed Grant Program. 9/1/2014 – 8/31/2015, \$25,000.
 -
- Funding applied for with decision pending:

Investigator Initiated Award
Sponsor: CDMRP

Role: PI

Overcoming Chemotherapy Resistance by Targeting Ribosomal RNA Synthesis

Major Goals of Project: To determine the potential of targeting ribosomal synthesis as a strategy to overcome chemoresistance, and determine the mechanisms involved in such observations.

CONCLUSIONS:

Our data demonstrate that ALDH1A1-positive cells are more tumorigenic than ALDH1A1-negative cells, contribute to poor patient outcomes, and contribute to chemoresistance. Importantly, these effects can be reversed by downregulating ALDH1A1 expression with nanoparticle-delivered siRNA. Additionally, we have shown that increased tumorigenicity is not only an important *ex vivo* assessment of CSCs, but that they are clinically significant as well, in that chemoresistant tumors have increased density of ALDH and CD133 cells. This suggests that they represent at least part of the chemoresistant population within a heterogeneous tumor. Importantly, they do not seem to explain the entire story, as there are still many CSC-negative cells present at the conclusion of treatment. Further evaluation of the mechanism stem cell pathways have on chemotherapy resistance have found that endoglin (CD105) and hedgehog mediators Gli1 and Gli2 are strongly associated with resistance. Targeted either of these pathways restored sensitive to paclitaxel or carboplatin *in vitro* and *in vivo*. Although response to chemotherapy in PDX models is highly variable at the individual gene level, pathway analysis reveals multiple pathways that commonly altered in many tumors. The immune system also appears to mediate a robust response in some tumors. Future work will attempt to delineate which of these pathways is most contributory, and how they may be best targeted to kill the final chemotherapy resistant population in ovarian cancer.

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2. Dalerba P, Cho RW, Clarke MF. Cancer stem cells: models and concepts. *Annu Rev Med* 2007;58:267-84.
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4. Landen CN, Jr., Goodman B, Katre AA, *et al.* Targeting aldehyde dehydrogenase cancer stem cells in ovarian cancer. *Mol Cancer Ther* 2010;9(12):3186-99.
5. Steg AD, Bevis KS, Katre AA, *et al.* Stem cell pathways contribute to clinical chemoresistance in ovarian cancer. *Clin Cancer Res* 2012;18(3):869-81.

APPENDICES:

- Appendix 1: Publications
 - Dobbin ZC, Katre AA, Steg AD, Erickson BK, Shah MM, Alvarez RD, Conner MG, Schneider D, Chen D, **Landen CN**. Using heterogeneity of the patient-derived xenograft model to identify the chemoresistant population in ovarian cancer. *Oncotarget*. 5(18): 8750-64, 2014. PMID 25209969.
- Appendix 2: Curriculum Vitae, Charles N. Landen, Jr.

Using heterogeneity of the patient-derived xenograft model to identify the chemoresistant population in ovarian cancer

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Keywords: Ovarian Cancer, Patient-derived xenograft, cancer stem cells, chemoresistance, animal models of cancer

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ABSTRACT

A cornerstone of preclinical cancer research has been the use of clonal cell lines. However, this resource has underperformed in its ability to effectively identify novel therapeutics and evaluate the heterogeneity in a patient's tumor. The patient-derived xenograft (PDX) model retains the heterogeneity of patient tumors, allowing a means to not only examine efficacy of a therapy, but also basic tenets of cancer biology in response to treatment. Herein we describe the development and characterization of an ovarian-PDX model in order to study the development of chemoresistance. We demonstrate that PDX tumors are not simply composed of tumor-initiating cells, but recapitulate the original tumor's heterogeneity, oncogene expression profiles, and clinical response to chemotherapy. Combined carboplatin/paclitaxel treatment of PDX tumors enriches the cancer stem cell populations, but persistent tumors are not entirely composed of these populations. RNA-Seq analysis of six pair of treated PDX tumors compared to untreated tumors demonstrates a consistently contrasting genetic profile after therapy, suggesting similar, but few, pathways are mediating chemoresistance. Pathways and genes identified by this methodology represent novel approaches to targeting the chemoresistant population in ovarian cancer

INTRODUCTION

Although most ovarian cancer patients present with advanced-stage disease, response to front-line platinum-based chemotherapy is high, on the order of 75%. The combination of surgery and adjuvant chemotherapy will allow remission in most patients, and about 40% of advanced stage patients will live at least 5 years [1]. However, absolute cures are uncommon, with 80% of patients eventually having a recurrence [2]. The clinical profile of high rates of positive responses yet high recurrence rates suggests the presence of a subpopulation of cells within the heterogeneous tumor that survives

initial chemotherapy, to lie dormant and eventually regrow with chemoresistant disease. Only by targeting this subpopulation can we achieve durable cures [3, 4].

Pre-clinical models used in drug discovery have predominately used clonal ovarian cancer cell lines, which cannot account for tumor heterogeneity, and evolve through selective growth and time to become very different from tumors growing in patients. Recently some of the most commonly used ovarian cell lines used were reported to have profiles more like endometrioid than papillary serous carcinoma, as defined by TCGA expression profiling[5]. Studying tumors preclinically that more closely resemble human tumors may increase the likelihood that

Table 1: Patient demographics of implanted and growing patient-derived xenograft (PDX) lines

Characteristic	Percent or Average (range)	
Age at diagnosis	61.7 (47-87)	
Stage	Stage IIIC	83%
	Stage IV	17%
Race	Caucasian	76%
	African American	24%
Procedure		
	Tumor Reductive Surgery	Optimal TRS 52%
		Suboptimal TRS 45%
	Laparoscopic Biopsy prior to neoadjuvant chemotherapy	3%
Histology		
	Papillary Serous Adenocarcinoma	79%
	Endometrioid	3%
	Mixed Epithelial	9%
	Mucinous	3%
Chemotherapy Treatment	Extra-ovarian in origin	6%
	Carboplatin	4%
	Carboplatin/Avastin	4%
	Carboplatin/Paclitaxel	56%
	Carboplatin/Paclitaxel/Avastin	7%
	Carboplatin/Taxotere	19%
	Cisplatin/Docetaxel	4%
	Cisplatin/Paclitaxel	4%
	Cisplatin/Taxotere	4%

medications effective in preclinical studies are effective in clinical trials. The patient-derived xenograft (PDX) model, whereby tumors are collected from patients and immediately implanted into mice, has recently been characterized and may allow such an advantage[6-8].

We set out to further characterize the PDX model and determine whether the heterogeneity seen in ovarian cancer is recapitulated, in order to explore the cell populations responsible for chemoresistance. One potential subpopulation with chemotherapy resistance is the cancer stem cell (CSC) population. CSC's have been shown to have increased tumorigenicity in mice, chemotherapy resistance, and are enriched in recurrent ovarian cancer [9-11]. In developing and characterizing the PDX model our goals were to 1) optimize methods to allow a high success rate of implantation, 2) examine retention of heterogeneity, 3) determine if PDX tumors respond to chemotherapy similarly to patient tumors, 4) assess whether treatment with chemotherapy results in

survival of just CSC populations, and 5) identify pathways that are amplified in resistant tumors. We demonstrate that the PDX model can be established with a high success rate, have similar expression profiles and biologic activities as patient tumors, and can be used as a model to identify the chemoresistant population.

RESULTS

Implantation success rate and establishment of the ovarian PDX model

Here we report outcomes on the first 34 patient samples implanted into SCID mice. Demographics for patients from whom tumors were collected are presented in Table 1. All patients had stage IIIC or IV high-grade epithelial ovarian cancers, and tumors were collected prior

to any chemotherapy.

Tumor collected and implanted into mice was either from an omental metastasis or peritoneal implant, since they are plentiful, composed of grossly-identifiable tumor, and most relevant to recurrent disease.

Different sites of implantation in the mouse were tested to identify the best location for growth. Subcutaneous (SQ) and mammary fat pad (MFP) sites were tested as their location allows for tumor growth to be monitored with caliper-measurements. Intraperitoneal (IP) injection was examined, to provide an orthotopic location for model establishment. The subrenal capsule (SRC) was evaluated given previous reports of high take rates in this site [12]. Implantation for all 4 sites was conducted as

described in the methods. Therefore both site and method of processing were controlled for each patient. The rates for PDX tumor development in each site, including individual implants are presented in Figure 1A. In the first 34 patients, a PDX line was established in 85.3% of SQ implants. This is compared to 63.64% in the MFP, 22.2% IP, and 8.3% in the SRC. SQ xenografts almost always visually disappeared in the weeks after implantation before regrowing and being detectable at a mean of 78.4 days after implantation (range 17-174 days, Figure 1C) compared to 77.3 days for the MFP (range 29 to 129 days, NS). The success of a PDX being established is highest in the SQ site in part due to the increased number of implants per patient. Based on this data, and subsequent

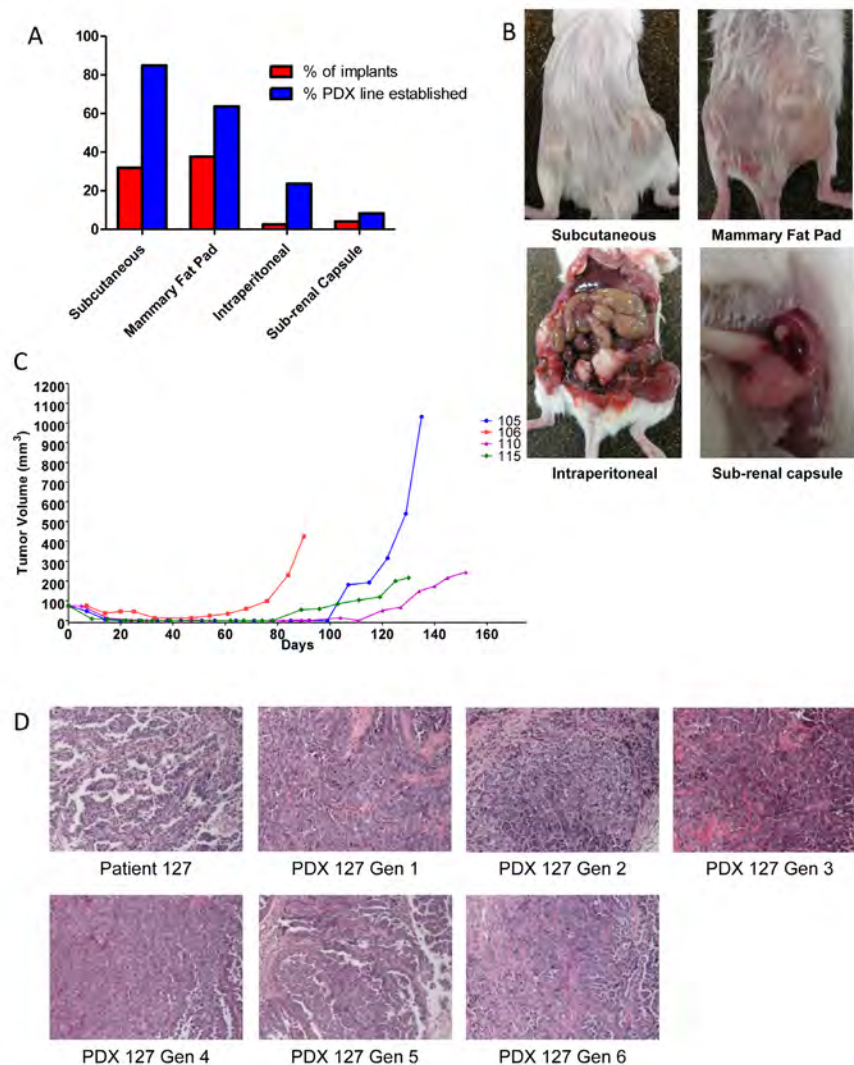


Figure 1: Take rates of different sites for implantation and maintenance PDX histology . (A) Tumors were implanted subcutaneously (SQ), in the mammary fat pad (MFP), intraperitoneal (IP), or sub-renal capsule. The success of implantation was similar comparing SQ to MFP, however more PDX lines were established from SQ implant due to number of implants. IP and SRC implants are not effective for establishing a PDX line. (B) Representative pictures of implanted tumors at either SQ, MFP, IP, or SRC. (C) After implantation, tumor volume decreased to an undetectable size then re-grew after a dormancy period. This implicate the small population of tumorigenic cells survive and re-capitulate the tumor after implantation. Representative growth chart showed of 4 different PDX lines after implantation. (D) Histology of the original tumor is maintained throughout subsequent generations. Patient 127 had a histology of papillary serous adenocarcinoma that has been maintained for 6 generations in the corresponding PDX.

studies showing similar expression profiles in tumors from the SQ site and original patient tumors (described below), continued development of the PDX model was done in the SQ site. PDX tumors were examined for histologic characteristics by a gynecologic pathologist. In all cases and in up to six generations of reimplantation, the original histology was maintained (Figure 1D). Interestingly, in the few cases where a mixed epithelial-type ovarian cancer was implanted, both histologies were present in each of the subsequent PDX generations.

Heterogeneity of PDX tumors

One potential advantage of the PDX model is that it may maintain patient heterogeneity, as opposed to the clonality that ultimately characterizes cell lines. However, a growing body of evidence suggests that certain cell subpopulations have enhanced ability to initiate tumors, often termed tumor-initiating cells (TIC's) or sometimes CSC's if additional attributes are demonstrated [10]. We examined whether resulting PDX tumors maintained tumor heterogeneity from a tumor-initiating cell standpoint.

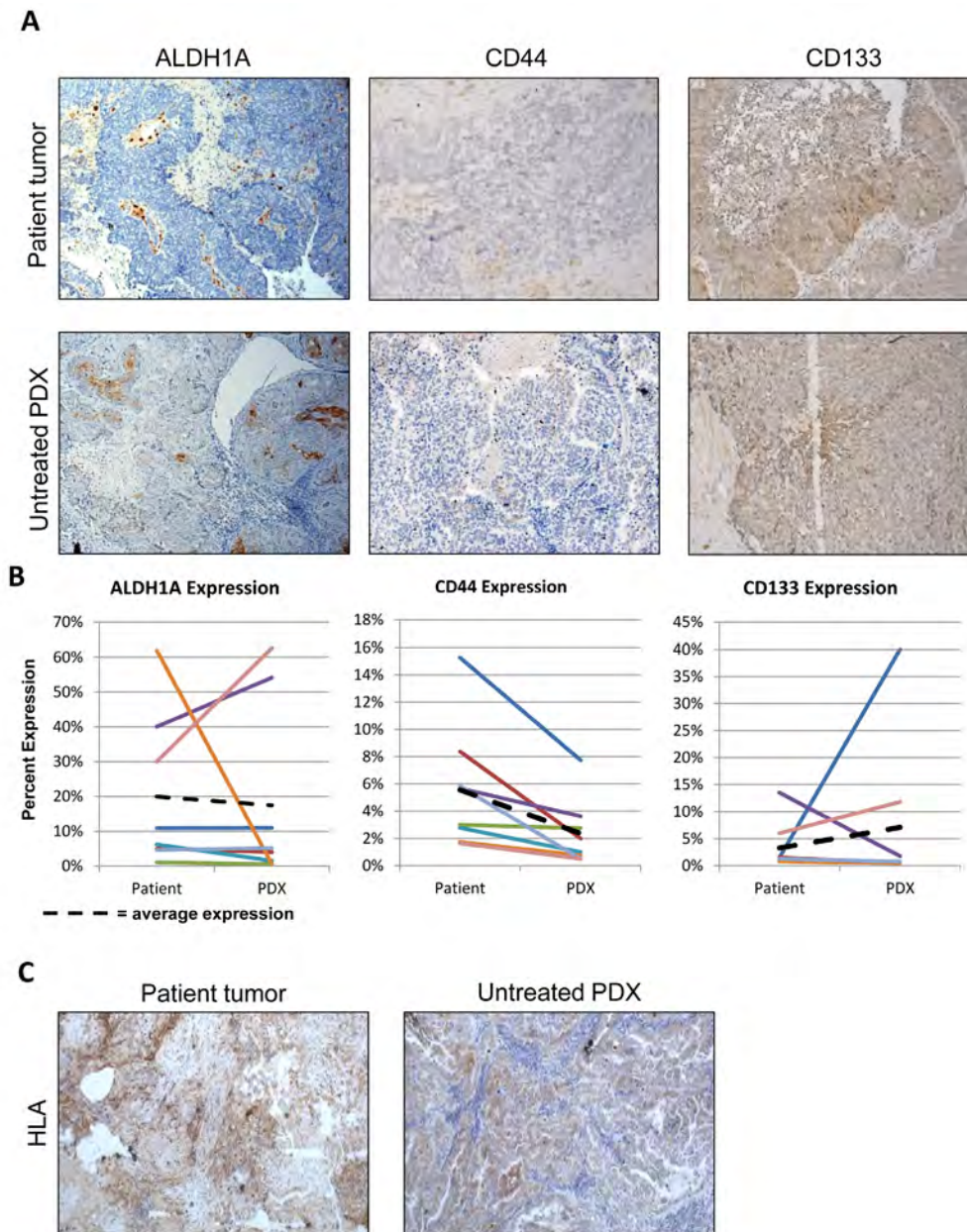


Figure 2: Establishment of the PDX line does not enrich for the tumorigenic cell population and human stroma is replaced in the implanted PDX. (A) Representative staining for ALDH1A1, CD133, and CD44 on the patient sample and untreated PDX. (B) Quantification of change in expression of ALDH1A1, CD133, and CD44 between the patient sample and the untreated PDX. Only CD44 had a significant decrease in expression (p-value <0.05). ALDH1A1 and CD133 had no significant change in expression. (C) Human HLA expression in patient and untreated PDX tumors, demonstrating replacement of human stroma with murine cells.

PDX tumors and original patient tumors were subjected to IHC for the TIC markers ALDH1A1 [11, 13, 14], CD133 [15-17], and CD44 [18, 19]. For ALDH1A1, CD44, and CD133, the patient samples averaged expression of 19.95%, 5.56%, and 3.27% respectively. The PDX tumors had similar expression of ALDH1A1 and CD133 at 17.4%, and 7.1% respectively ($p=0.80$ and 0.49 , Figure 2A, 2B). There was a significant change in expression of CD44, but it was actually a decrease, from 5.54% to 2.36% ($p=0.014$). If TICs in ovarian cancer are indeed the cells mediating xenograft formation, these data suggest that they subsequently differentiate into marker-positive and -negative cells and recapitulate tumor heterogeneity, in keeping with the CSC hypothesis [10, 20].

Related to heterogeneity, the human/murine component of PDX tumor would have implications to the

biologic relevance of this model. IHC for human HLA antigen was conducted to identify the species-specific composition of the PDX tumor. Interestingly, all stromal cells in the PDX tumors were of murine origin (Figure 2C). This was consistent across 100% of the tumor specimen, and in all of the first 15 PDX tumors established.

Biological and clinical characterization of PDX tumors

To begin to evaluate the biologic characteristics of PDX tumors compared to original patient tumors, we examined oncogenic expression, proliferation, and response to chemotherapy. Weroha *et al* have previously demonstrated similar amplification and deletion patterns

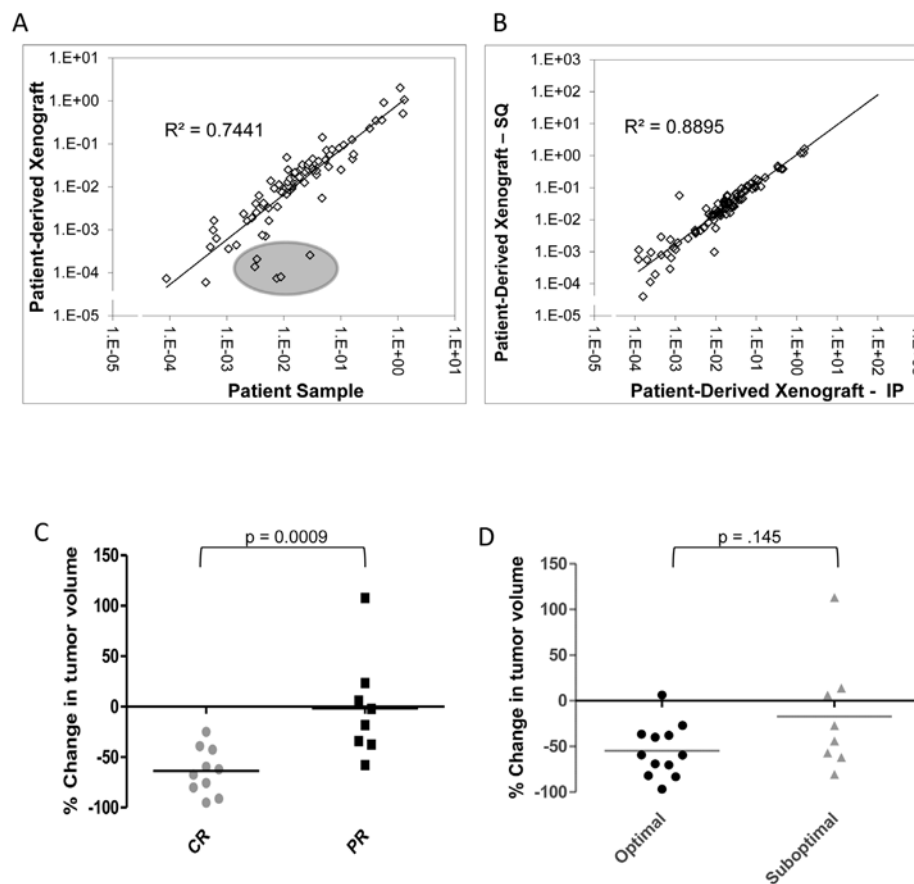


Figure 3: Cancer drug targets are maintained in the PDX line and the PDX response to treatment correlates to the patient's response to primary chemotherapy. (A) The SABiosciences RT² qPCR array for cancer drug targets was run on the patient's tumor and their matched untreated PDX tumor. Differences in relative gene expression for each target was calculated and the 2^{ΔCt} value was determined. Most of the 84 cancer drug target genes had similar expression in the PDX and the original patient sample. 5 gene were down-regulated in the PDX sample, though all 5 are related to VEGF and PDGF signaling (circled in grey). (B) The SABiosciences RT² qPCR array for cancer drug targets was run on matched subcutaneous PDX tumors and intraperitoneal PDX tumors. Differences in relative gene expression for each target was calculated and the 2^{ΔCt} value was determined. All 84 cancer drug target genes showed a strong correlation between the IP and SQ PDX tumors. (C) PDX lines were treated with combination carboplatin and paclitaxel IP weekly. The percent change in tumor volume at 30 days was compared to the patient's response to primary therapy. PDX lines with the greatest decrease in volume significantly correlated to patients with a complete response to therapy ($p=0.0009$) (D) Classifying reduction in tumor volume by outcome of tumor reductive surgery (optimal debulking vs suboptimal) shows a trend towards PDX with the greatest reduction in volume correlating to optimal debulking for the patient (p -value = NS).

between PDX and patient tumors using aCGH [6]. To characterize whether expression of key oncogenes are similarly expressed in PDX tumors, an RT² PCR array on four pair of patient samples and matched PDX tumors was used. This array quantifies mRNA levels of 84 genes that are recognized targetable oncogenes[21]. There was a strong correlation of expression in 79 of the cancer drug targets, with an overall R²-value of .744 (Figure 3A). This correlation was also present in individual samples (Supplemental Figure 1). The five genes that exhibited the poorest correlation had expression in the patient with near-zero mRNA expression in the PDX. These genes were platelet-derived growth factor receptor, alpha and beta polypeptide (PDGFRA, PDGFRB) and vascular endothelial growth factor receptor one, two, and three (VEGFR1, VEGFR2, VEGF3). These genes were expected to be decreased in the PDX tumor, since they are produced by the host, and the primers are human-specific. Therefore, there is strong consistency in expression of targetable oncogenes intrinsic to malignant cells, despite the fact that these tumors are growing in the subcutaneous compartment. In addition, we profiled the genetic difference of oncogene expression using the RT² PCR array comparing PDX tumors from the IP location versus the SQ implant. There was a strong correlation of expression among the 84 genes in the oncogene drug target array, with an overall R²-value of .8895 (Figure 3B). This indicates that the SQ tumor has similar expression to a tumor growing in the orthotopic location.

While expression at the single-gene level is important, biologic similarity regarding response to treatment is equally important. Mice with measurable tumors from 19 PDX models were treated with IP carboplatin (90 mg/kg/week) and paclitaxel (20 mg/kg/week) in combination for 4 weeks. After 4 weeks, percent-reduction in tumor volume was calculated and compared to the patient's response to therapy, categorized as complete (CR, no evidence of disease at completion of 6 cycles of primary chemotherapy) or partial (PR, residual disease present at completion of 6 cycles of primary therapy). Patients that had a CR to therapy had an average reduction in volume of 63.73% (range 95.04% to 24.87%) compared to an average reduction of just 1.53% (range 57.77% reduction to 107.9% increase) in patients that had a PR (p = 0.0009, Figure 3C). There was also a differential, but not significant, response between patients who had an optimal or suboptimal tumor reductive surgery (Figure 3D). While not definitive, this suggests that patients presenting with disease unable to be optimally debulked are more aggressive and resistant to chemotherapy.

Biologic mediators of chemotherapy resistance in the PDX

With evidence showing that the PDX model accurately replicates the biology and clinical properties of the original patient tumor, we sought to explore differences between matched untreated and treated tumors. Mice were treated as described above, with tumors harvested 6 days after the 4th weekly dose, to minimize acute tumoral effects that might occur after chemotherapy administration. Ki-67 was examined to measure proliferation, and was not significantly different in untreated PDX tumors compared to the original patient tumor (Figure 4A,B). However, treated tumors had significant decrease in Ki-67 positivity (33.6% compared to 64.9% in untreated tumors p=0.0013). Examining the trend of each tumor individually (Figure 4C), two pair actually showed an increase in Ki-67, one of which had a 107% increase in tumor size on therapy, but the other with a 70.9% reduction. Despite these aberrations, the overall decrease in proliferating fraction suggests that dormancy is either being induced by chemotherapy, or some cells are already in a dormant state at presentation, and have intrinsic resistance to chemotherapy.

For analysis of which subpopulations have enhanced survival with chemotherapy, we assessed the density of the CSC populations expressing ALDH1A1, CD44, and CD133. If these populations were important to survival in the presence of chemotherapy, they should be more densely present after treatment, as noted in human specimens [11]. Treatment resulted in the significant enrichment of ALDH1A1-positive cells (increased from 16.2 to 36.1%, p=0.002) and CD133-positive cells (increased from 9.5% to 33.8%, p=0.011) (Figure 4D). Mean CD44 expression increased, but this was driven by two samples, and was not significant. These data suggests treated tumors are enriched in CSC populations.

Differential expression of genes due to chemotherapy treatment

Although cells with CSC properties were increased in treated specimens, they did not make up the entirety of the tumor. To globally examine which other genes and pathways are significantly altered during chemotherapy treatment, RNA-Seq was conducted on 6 pairs of treated and untreated PDX tumors. Across all six pairs, 299 genes were found to be significantly differentially expressed in the treated PDX samples compared to untreated (Supplementary Table 1), 137 of which have known roles in cancer. The top up-regulated genes and down-regulated genes are in Table 2. When principal component analysis was performed, an interesting trend emerged. Four of the samples clustered together, and the remaining two were separated in the 3D space. All the treated samples showed a

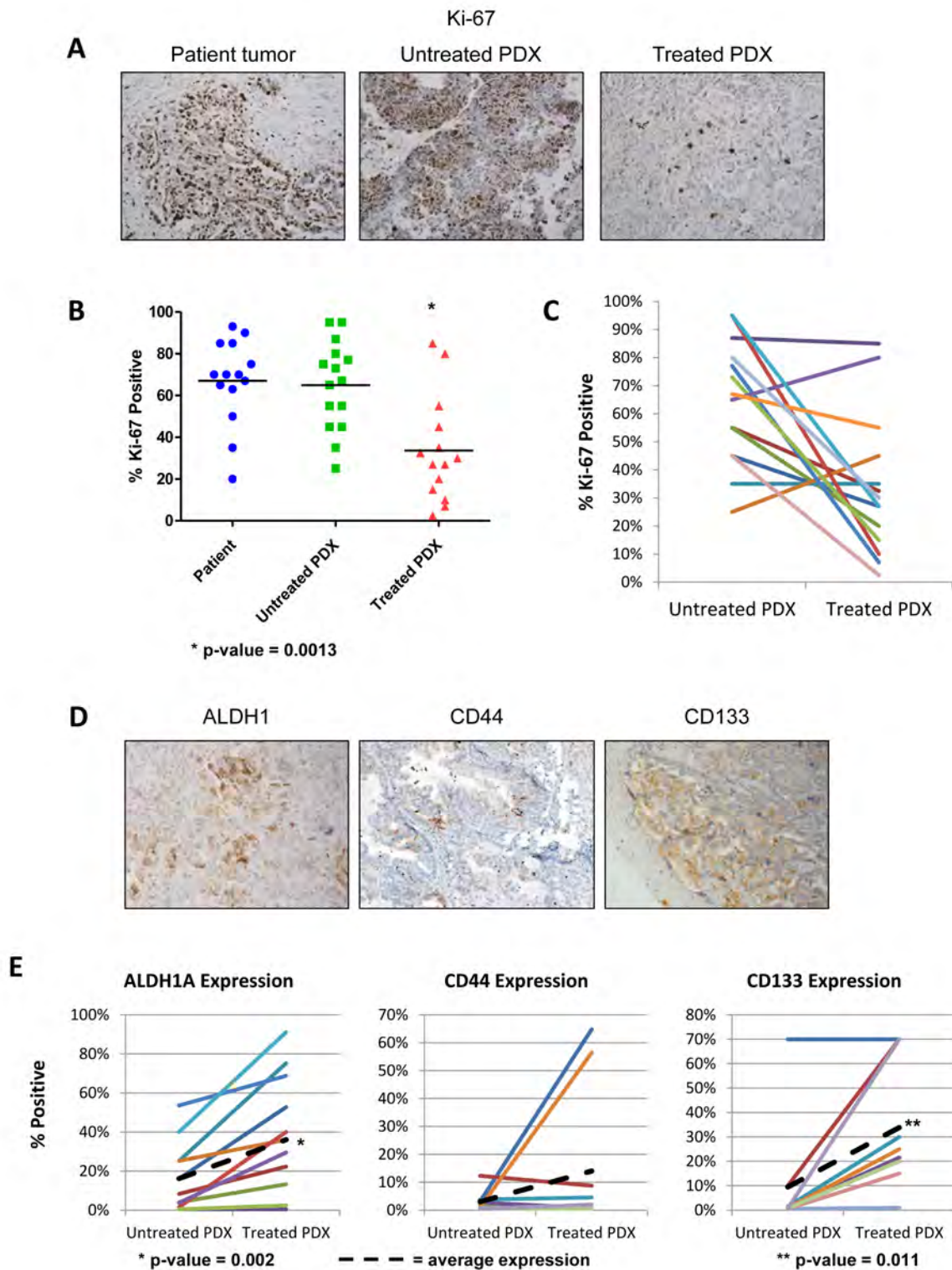


Figure 4: Chemotherapy treatment reduces proliferation and enriches the PDX for cancer stem cells. Tumor cell proliferation was quantified using the Ki67 marker on original patient samples, untreated PDX samples, and chemotherapy treated PDX samples. Change in cancer stem cell marker expression was analyzed after chemotherapy treatment. (A) Representative IHC of Ki67 staining in the patient sample, untreated PDX, and treated PDX. (B) On average, proliferation decreases with chemotherapy treatment in all PDX lines tested. There is no significant change in proliferation between the patient and the untreated PDX. (C) Proliferation rates for each treated and matched untreated pair show that the majority of tumors have a reduced proliferation rate after chemotherapy treatment (D) Representative IHC of CSC markers ALDH1A1, CD133, and CD44 of PDX treated with carboplatin and paclitaxel for 4 weeks. (E) In the treated PDX, expression of ALDH1A1 and CD133 are significantly increased (p-value = 0.0023 and p-value = 0.011 respectively).

Table 2: RNAseq analysis on PDX comparing 6 pairs of treated versus untreated samples.

Top Canonical Pathways	P-Value
Protein Kinase A Signaling	3.58E-05
GNRH Signaling	2.74E-04
Sphingosine-1-phosphate signaling	5.4E-04
α -Adrenergic signaling	9.39E-04
Cholecystokinin/Gastrin-mediated signaling	1.91E-03
Molecular and Cellular Functions	
Lipid Metabolism	1.33E-04 to 3.80E-02
Molecular Transport	1.33E-04 to 3.80E-02
Small Molecule Biochemistry	1.33E-04 to 3.80E-02
Cell Morphology	1.64E-04 to 3.80E-02
Cellular Assembly and Organization	1.64E-04 to 3.75E-02
Top Up-Regulated Molecules	Fold-Change Expression
ZNF750	2.441
ACP5	2.294
HIST2H2BE	2.141
CPEB3	2.117
DNM3	2.028
MPC1	1.980
ABCG1	1.938
MGLL	1.924
TLR5	1.884
Top Down-Regulated Molecules	Fold-Change Expression
APOC1	-2.488
GPHA2	-2.262
POLR3G	-1.862
TES	-1.759
PLCE1	-1.738
PUS7	-1.618
ARNT2	-1.607
MECOM	-1.570
CKAP4	-1.564
KLF5	-1.554

shift in the same direction away from their untreated PDX pair (Figure 5). This indicates that while the majority of genes are similar before and after treatment, all six tumors were affected similarly by therapy. IPA pathway analysis identified 5 major pathways that were significantly altered with treatment and key changes in molecular and cellular function (Table 2). Changes in these biological functions and pathways are consistent with the visualized phenotype of tumors responding to chemotherapy and reorganizing cellular function to adapt for survival.

DICUSSION

We demonstrated the feasibility of an ovarian PDX model that closely models the heterogeneity of the original patient's tumor and maintains clinical relevance. Ovarian PDX tumors form at a high rate when placed in the subcutaneous location. Growing tumors recapitulate the heterogeneity of the original patient tumor, and are not composed of just TICs, though the stromal component is murine. The PDX tumors have similar oncogene expression as the patient tumor, and respond

to chemotherapy in a similar manner as the patients from which they were harvested. These similarities make the PDX model an attractive platform for pre-clinical testing of therapies that will hopefully correlate with a clinical response better than noted in cell lines. Finally, using this model has allowed identification of pathways mediating survival after chemotherapy that are attractive targets for future study.

In most malignancies, preclinical studies have primarily utilized cell lines to assess novel therapies and biologic processes. Cell lines are still ideal for carefully controlled studies on mechanisms and pathways. However, in terms of translating results to the clinic, these models have underperformed [22]. The clonal nature of cell lines limits the ability to study both intratumoral and interpatient heterogeneity [8, 23]. In addition, new genomic studies indicate that commonly-used ovarian cancer cell lines do not accurately represent high-grade serous ovarian cancers when compared to profiling performed on the TCGA dataset[5].

Development of PDX models have been demonstrated in a few malignancies, including ovarian, colorectal, medulloblastoma, pancreatic, breast, and non-small cell lung cancers [6, 24-29], and have consistently been found to be similar to patient samples. One well-established program in pediatric malignancies has demonstrated prediction of response in the clinic is higher when the PDX model is used [30]. However, there are drawbacks to the model. The time for PDX tumors to grow is variable, but usually on the order of months, making experiments slow and expensive. Historically, rates for

success of PDX establishment have been low, with the most successful models having 37% establishment rate [28, 31, 32], until Weroha's recent report of 74% overall success in ovarian cancer[6]. In this study, we had 85.29% success rate of establishing a PDX in the first 34 patients we implanted in the SQ. We believe the higher success rate is due to several factors. Given similar success of Weroha's report, this may be disease-specific. Strong working relationships with clinicians and pathologists allow for implantation within one hour of removal. We used two different processing methods that could be directly compared - one where solid tumors were implanted (SQ and SRC), and one where tumors were dissociated (MFP and IP). With both methods, the take rate was more dependent on the site implanted than the processing method. A crucial factor is the starting material. Other groups have reported that higher engraftment rates are associated with more aggressive tumors [6, 8, 29]. Instead of using the primary tumor from the ovary, we have implanted omental or peritoneal metastatic implants. The reasons for this are both biologic and practical. From a practical standpoint, omental implants are easily distinguished from normal tissue, reducing the risk of implanting normal tissue. A portion of "tumor" taken from the ovary, a complex tissue with normal solid components, may more likely be misinterpreted grossly as tumor, when in fact was benign. Because the omentum is well-vascularized, tumors are very "healthy", giving additional confidence that the portion implanted is not necrotic. Finally, it has been demonstrated that other factors produced in the omental microenvironment are

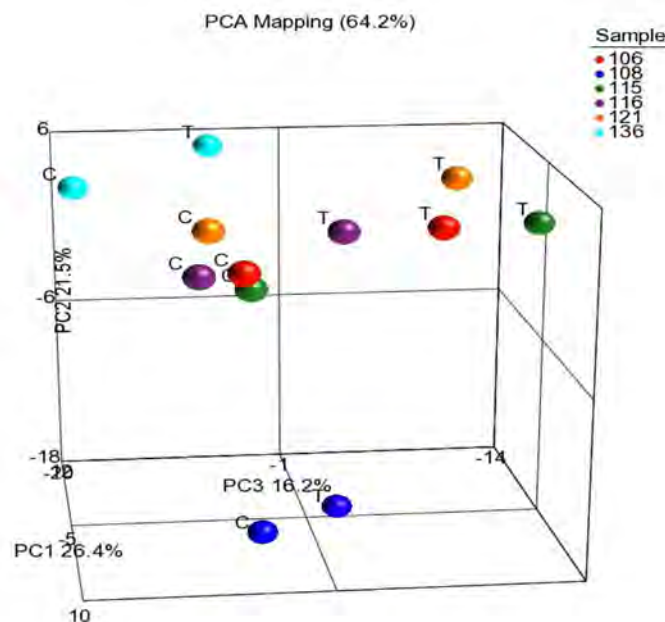


Figure 5: RNAseq comparing the treated PDX lines to the untreated PDX lines. Principal component analysis of genes expression in the treated and untreated PDX tumors. While matched treated and untreated PDX tumors clustered together, most treated PDX tumors had change of expression in the same direction indicating a small subset of genes responding to chemotherapy.

pro-tumorigenic, and are likely implanted with these tumors[33]. The biologic rationale for using metastatic implants is that these sites are more relevant to the portions of tumors that recur. Therefore it may be more clinically relevant to characterize the metastatic site.

The site of implantation is an important consideration as there are benefits and drawbacks from using an orthotopic or heterotopic site. Heterotopic locations allows for easier monitoring of the tumor while orthotopic preserves the appropriate microenvironment [24]. However, in developing this model, use of the intraperitoneal orthotopic location had practical limitations of lower engraftment rates and difficulty in assessment of growth. In several instances mice become moribund with ascites before there was appreciable tumor volume, even when following with micro-CT imaging. This limits the ability to measure response to a therapy, and provides less tissue for analysis and propagation into the next generation of PDX. However, the Weroha study demonstrated an ability for high take rate using the intraperitoneal injection with large volumes of tumor-cells [6]. Like our study, their mice also demonstrated development of ascites but by using ultrasound, were able to more accurately follow tumor progression than using a micro-CT. By using the heterotopic location, tumor growth can be easily monitored for establishment, growth, and response to therapy [8]. However, biologic relevance has to be demonstrated. With our findings that subcutaneous tumors have similar oncogene expression profiles to patient tumors and the orthotopic intraperitoneal PDX tumors, and respond to chemotherapy similarly, the subcutaneous model appears relevant. This information helps alleviate the primary concern of not using the orthotopic location and provides a mechanism for decreasing the technical complexity of establishing and using a PDX model. While in our hands, not enough intraperitoneal tumors developed to evaluate their correlation to the clinical response, based on our oncogene data comparing SQ and IP tumors and the Weroha study, it appears both models are equivalent. Not enough intraperitoneal tumors developed to demonstrate whether they would be equivalent, or superior, to the subcutaneous model. While previous groups have reported a high rate of success using the subrenal-capsule for tumor establishment [12], we did not see these successes. The ultimate proof of the importance of location in the PDX model will require testing numerous compounds, and relating the response in PDX tumors to responses in patients. PDX models in other malignancies have demonstrated a similar response rate between mice and the corresponding clinical trial [34-36]. Such studies in ovarian cancer are ongoing. But our analysis of the oncogene expression profiles, and their consistent similarity to patient tumors (Figure 3A), suggest that differences in targetable oncogenes between orthotopic PDX tumors and patient tumors are minimal.

We also demonstrate that the ovarian PDX model

maintains the heterogeneity of the original patient tumor, at least from a TIC standpoint. Studies of CSC and TIC populations have shown that some cells are more capable of forming xenograft tumors than other[37]. Our analysis of density of ALDH1A1, CD44, and CD133 cells, the most consistent markers of TICs in ovarian cancer, demonstrates that PDX tumors are not only composed of these subpopulations (Figure 2B). It is possible that these subpopulations are the drivers of tumor formation, but as they grow they produce differentiated tumors with both CSC and non-CSC populations. This in fact would be predicted by the CSC model.

Potential limitations to the PDX model in ovarian cancer have been identified through our analysis. We saw that of 84 oncogenes examined, 5 were under-expressed in PDX tumors: receptors for platelet-derived growth factors and VEGF receptors. The fact that all members of these receptor families strengthens the validity of the association. Analysis of the species making up tumor stroma showed it to be composed purely of murine origin. The reduced content of human stromal genes is expected [38] as a result of the replacement of the human stroma with mouse stromal cells after implantation. Prior reports in pancreatic cancer have suggested that human stromal cells are maintained for several generations[39], although Weroha *et al* also found that IP ovarian PDX tumors had murine stroma. Whether murine stroma impacts the validity of the model will depend on the specific agent and pathway targeted.

The heterogeneity demonstrated in ovarian PDX tumors makes it uniquely positioned to investigate the key clinical problem of chemoresistance and recurrence. Ovarian cancer has a high rate of response to primary chemotherapy followed by an equally high rate of recurrence. One hypothesis is that this population is the same as the tumorigenic CSC population. While we have seen an increase in CSC density in the treated PDX tumors, and previously in treated patients[11], the persistent/recurrent tumors were by no means completely composed of these populations. Either the CSC populations had already begun to give rise to repopulating daughter cells negative for the CSC marker, or (more likely) other chemoresistant populations exist that cannot be identified by ALDH1A1, CD44, or CD133 alone. Going beyond CSCs, we have shown that surviving tumors have more cells in dormancy, decreasing from a baseline of 65% to 34%. RNA-seq analysis resulted in 299 genes being significantly different between the treated and untreated tumors with principal component analysis indicating that the changes in gene expression represent a small subset of the entire genetic makeup of the tumor (Figure 5, Supplementary Table 1). Most remarkable and encouraging is that the changes were similar in all pairs tested, providing hope that there may be common pathways to be targeted in most patients. One of the top up-regulated genes was ABCG1 (BCRP1), a member

of the White family of ATP-Binding cassette (ABC) transporters. Expression of ABCG1 has been shown to identify a side population of cancer cells that demonstrate CSC properties and chemoresistance [40]. Interestingly, one of the top activated pathways identified by IPA Ingenuity pathway analysis was Sphingosine-1-phosphate signaling. This pathway has been shown to protect oocytes from apoptosis induced by chemotherapeutic agents *in vitro* and *in vivo* [41, 42]. Taken together, the enrichment of CSC markers in the treated population, decrease in cell proliferation, and increase in genes and signaling pathways predicted to play a role in chemoresistance, it appears that treatment of the ovarian PDX results in the survival of a cell population that is chemoresistant to primary therapy. The global analysis by RNAseq provides a snapshot of possible pathways that are responsible for the development of chemoresistance. These will be important targets for therapy in future studies. With the development of an ovarian PDX model that recapitulates the clinical response and the heterogeneity of ovarian cancer, investigators are positioned to more effectively evaluate novel therapeutics and use the model to improve our understanding of the mechanisms of chemotherapy resistance. Hopefully targeting these pathways will sensitize cells to chemotherapy and lead to more durable cures.

CONCLUSION

Development of an ovarian PDX model to study *de novo* chemotherapy resistance provides a unique use of the xenograft model beyond testing pre-clinical compounds, allowing for possible novel understandings of tumoral responses to therapy that may lead to new strategies for targeting the residual survival population after primary therapy.

MATERIALS AND METHODS

Collection and Implantation of tumor specimens

Under IRB and IACUC approval, patients with suspected ovarian cancer that were being treated by the Division of Gynecologic Oncology at UAB were consented for this study. At the time of primary tumor reductive surgery, a specimen from an omental metastasis or peritoneal implant that was not required for pathologic diagnosis was collected and transported to the laboratory for processing. Specimens were sectioned and a portion submitted for formalin-fixed-paraffin embedding; placed in RNAlater (Qiagen, Frederick, MD); snap frozen in liquid nitrogen, and slow freezing in Optimal Cutting Temperature (OCT) Medium, and stored at -80°C . Remaining tumor was isolated for implantation into

SCID mice (NCI-Frederick, Frederick MD) into four sites: subcutaneous (SQ), subrenal capsule (SRC), intraperitoneally (IP), and mammary fat pad (MFP). To discover the optimal site for tumor growth, of the first 22 patients, 22 were implanted SQ and MFP, 18 IP, and 12 SRC. When enough tumor was available, all four sites were implanted to allow direct comparison of growth rates. After it was evident that the subcutaneous implantation site was optimal, an additional 11 patients had tumors implanted only SQ.

For SQ implants, 5mm^2 tumor pieces ($n=20$ per patient) adjacent to the slice used for confirmation of histology were sectioned. 5 mice were implanted with four tumors each. The dorsal surface of the mouse was shaved and prepped with betadine solution. A 1cm midline incision was made and with blunt dissection, four pockets were created in four quadrants of the flank of the SCID mouse. One 5mm^2 tumor implant was placed in each quadrant and the incision was closed with staples.

For SRC implantation, five 3mm^2 tumor sections were prepared for implantation into five mice, one kidney per mouse. An incision was made in the body wall along the long axis of the kidney. The kidney was gently exposed through the incision, a 4 mm incision was made in the renal capsule, and an implant was inserted. The kidney was gently placed back into the body cavity and incision was closed with chromic gut sutures. For both SQ and SRC implantation, mice were anesthetized using isoflurane with 5% for induction of anesthesia and 1.5% for maintenance. Mice were administered carprofen (7mg/kg, Pfizer) prior to incision to reduce post-operative pain.

For injection into the MFP and IP sites, an adjacent portion of tumor was manually dissociated until fine enough to pass through a 21g needle. Prior to injection, the suspension was added to an equal volume of BD Matrigel (BD Biosciences, Cat#356234), mixed, and injected intraperitoneally (500,000 cells) or into bilateral MFPs (250,000 cells). Five mice were injected IP, and five mice had cells injected into the left and right MFP.

Treatment of PDX lines with chemotherapy

Once SQ or MFP tumors reached 500mm^2 in volume, chemotherapy treatment was initiated in mice from 21 patients. Mice were injected IP with 90 mg/kg of carboplatin and 20 mg/kg of paclitaxel weekly or with vehicle, doses which approximate the maximal tolerated dose used in weekly dose-dense schedule of carboplatin and paclitaxel in patients. Tumors were measured biweekly using calipers. Volume of tumor was calculated using the formula $(\text{Length} \times \text{Width}^2)/2$. After 5 weeks of treatment (4 weekly doses, then one week after last chemotherapy dose in order to minimize acute tumor effects of chemotherapy), mice were euthanized by CO_2 asphyxiation and cervical dislocation. Samples of treated and mice treated with vehicle were stored for

future analysis. Any remaining tumor was reimplanted for maintenance of the PDX.

Immunohistochemistry of patient samples and tumors from PDX tumors

Samples in FFPE were cut into 5 μm sections and placed on positively-charged slides. Hematoxylin and eosin stained tissue was analyzed by a gynecologic pathologist to confirm histology. For IHC of ALDH1A1, CD133, CD44, Ki-67 and human-HLA, slides were deparaffinized and rehydrated. Antigen retrieval was with 10 mM sodium citrate at pH 6.0 under pressure. Slides were washed in PBS. Endogenous peroxidases were blocked with 3% H_2O_2 in methanol. For ALDH1A1, CD133, and CD44, slides were blocked with Ctyo-Q immune-diluent (Innovex Biosciences Cat#NB307) followed by primary antibody incubation in Ctyo-Q immune diluent. Antibody concentrations were as follows: ALDH1A1 – 1:500 (BD Biosciences, Cat#611195) CD133 – 1:500 (Cell Signaling, Cat#3663S), CD44 – 1:500 (Cell Signaling, Cat# 3570S). After primary antibody, slides were washed in PBS. Primary antibody detection was achieved with Mach 4 HRP polymer (Biocare Medical), followed by 3,3'-diaminobenzidine incubation. Slides were counterstained with Gill's Hematoxylin then washed in water and PBS. Slides were sealed with Universal Mount (Open Biosystems, Cat#MBI1232). For Ki-67 (Abgent cat# AJ1427b) and human HLA (Proteintech Group Cat#15240-1), primary antibodies were used at concentrations of 1:200 in 10% normal goat serum. After incubation, slides were washed and blocked with 5% goat serum in 1X PBS. Primary antibody detection was visualized using an anti-rabbit HRP secondary at 1:500 in 5% goat serum (Vector Labs, Cat# PI-1000) and DAB substrate. Slides were counterstained as described above.

Scoring of IHC for TIC makers and Ki67

Two examiners (AK and CNL) visually estimated the percent of cancer cells staining for ALDH1A1, CD133, CD44, and Ki-67. A 3rd examiner (MGC) was included if there was a >20% discrepancy. The examiners were blinded to the experimental condition for each slide, and a 4th investigator (ZCD) averaged the scores for each specimen and decoded samples for analysis. To be consistent with prior identification of CSCs with flow cytometry, for CD133 and CD44 only expression at the surface membrane was considered. The average number of positive tumor cells for each marker was compared between the untreated PDX tumor and the patient's tumor, and between the treated and untreated PDX, with Student's t-test.

RT2-qPCR Arrays

RNA extracted from stored samples was converted to cDNA and amplified using the RT² First Strand cDNA Synthesis Kit (SABiosciences). Gene expression was then analyzed using the Cancer Drug Targets RT² Profiler PCR Array (SABiosciences), which profiles the expression of 84 genes that are potential oncogenic targets for anticancer therapeutics [21]. PCR amplification was conducted on an ABI Prism 7900HT and gene expression was calculated using the comparative C_T method as previously described [43].

High throughput sequencing of untreated and treated PDX tumors

Sample preparation, raw data preprocessing, quality control were conducted in UAB Genomics Core and preliminary analysis was conducted in the UAB Biostatistics Core. For RNA-seq, total RNA quality was assessed and the rRNA depleted and concentrated. The RNA-Seq libraries were prepared, validated and quantified. The raw fastq files were aligned to human genome hg19 of a local instance of Partek Flow software package (Saint Louis, MO). Pre-alignment was conducted to determine if trimming is needed based on reads quality score. Aligner STAR was used for best recovery[44]. The BAM files were loaded into Partek Genomics Suite 6.6 (Saint Louis, MO) for further analysis [45]. The reads per kilobase of exon model per million mapped reads (RPKM)-normalized reads were calculated and the expression levels of genes were estimated [46]. Additional filter was applied to exclude genes of low expression. The differential expressions were determined by using paired t-test [47]. Further functional analysis was conducted by using Ingenuity Pathway Analysis (IPA, Redwood City, CA).

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Conflict of Interest Statement

The authors have no conflict of interests to disclose.

Editorial Note

This paper has been accepted based in part on peer-review conducted by another journal and the author's response and revisions as well as expedited peer-review in Oncotarget.

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- and Gallick GE. Generation of orthotopic and heterotopic human pancreatic cancer xenografts in immunodeficient mice. *Nat Protocols*. 2009; 4(11):1670-1680.
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 35. Fichtner I, Slisow W, Gill J, Becker M, Elbe B, Hillebrand T and Bibby M. Anticancer drug response and expression of molecular markers in early-passage xenotransplanted colon carcinomas. *European Journal of Cancer*. 2004; 40(2):298-307.
 36. Fiebig HH, Maier A and Burger AM. Clonogenic assay with established human tumour xenografts: correlation of *in vitro* to *in vivo* activity as a basis for anticancer drug discovery. *European Journal of Cancer*. 2004; 40(6):802-820.
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45. Trapnell C, Williams BA, Pertea G, Mortazavi A, Kwan G, van Baren MJ, Salzberg SL, Wold BJ and Pachter L. Transcript assembly and quantification by RNA-Seq reveals unannotated transcripts and isoform switching during cell differentiation. *Nature biotechnology*. 2010; 28(5):511-515.
46. Wagner GP, Kin K and Lynch VJ. Measurement of mRNA abundance using RNA-seq data: RPKM measure is inconsistent among samples. *Theory in biosciences = Theorie in den Biowissenschaften*. 2012; 131(4):281-285.
47. Hochberg Y and Benjamini Y. More powerful procedures for multiple significance testing. *Statistics in medicine*. 1990; 9(7):811-818.

CURRICULUM VITAE

CHARLES N. LANDEN, JR., M.D., M.S.

PRESENT POSITION

Primary Appointment: Associate Professor, Department of Obstetrics and Gynecology,
Division of Gynecologic Oncology, University of Virginia, Charlottesville, VA

Secondary Appointments: Associate Leader, Women's Oncology Program, UVA Cancer Center
Associate Professor, Department of Pathology
Graduate Faculty, UVA Graduate School
Member, UVA Cancer Center

OFFICE ADDRESS

Division of Gynecologic Oncology
University of Virginia
PO Box 800712
Charlottesville, VA 22908
Admin Office: (434) 243-9414
Admin Office Fax: (434) 982-1840
Email: clanden@virginia.edu

LAB ADDRESS

345 Crispell Dr.
Carter Harrison Bldg, Rm B704
Charlottesville, VA 22908
Lab Office Phone: (434) 243-6131
Lab Phone: (434) 924-5390

EDUCATION

Degree-Granting Education

University of North Carolina at Chapel Hill, Chapel Hill, NC, B.S., Biology, 1992
University of North Carolina School of Medicine, Chapel Hill, NC, M.D., 1998
University of Texas Graduate School of Biomedical Sciences, Houston, TX, M.S., 2005

Postgraduate Training

Resident, Obstetrics and Gynecology, Medical University of South Carolina, Charleston, SC
William Creasman (Chairman) and Peter Van Dorsten (Program Director), 7/1998 – 6/2002

Postdoctoral fellow, Microbiology and Immunology, Medical University of South Carolina, Charleston, SC
James Norris (Chairman), 7/2002 – 6/2003

Fellow, Gynecologic Oncology, MD Anderson Cancer Center, Houston, TX
David Gershenson (Chairman) and Diane Bodurka (Program Director), 7/2003 – 6/2007

PRIMARY FACULTY APPOINTMENTS

Clinical Instructor, Department of Obstetrics and Gynecology University of South Carolina School of Medicine	7/2002 – 6/2003
Assistant Professor, Research, Department of Gynecologic Oncology University of Texas MD Anderson Cancer Center	7/2007 – 6/2009
Assistant Professor, Department of Obstetrics and Gynecology University of Alabama at Birmingham	6/2009 – 10/2012
Associate Professor, Department of Obstetrics and Gynecology University of Alabama at Birmingham	10/2012 – 7/31/2014
Associate Professor, Department of Obstetrics and Gynecology University of Virginia	8/1/2014 – current

BOARD CERTIFICATION

Board certified, American Board of Obstetrics and Gynecology, 12/2003
Board certified, Gynecologic Oncology, 4/2011

LICENSES

Current:	Virginia	Avail on request	7/22/2014-current
	DEA	Avail on request	3/25/2005-current
Inactive:	South Carolina	21944	2002-2004
	Texas	M0466	2/04/2005-8/31/2010
	Alabama	29546	5/27/2009-7/31/2014

HONORS AND AWARDS

Medical School – *University of North Carolina School of Medicine, Chapel Hill, NC*

Dean's List, 1994-1996

Class Co-President, University of North Carolina School of Medicine, 1994-1996

University of North Carolina School of Medicine Merit Scholarship, 1995

NIH Summer Research Fellowship, University of North Carolina SOM, 1995

Residency – *Medical University of South Carolina, Charleston, SC*

First Place, Resident Oral Presentations, District IV Annual Meeting, ACOG, 2000

Donald F. Richardson Memorial Prize Paper Award, ACOG, 2001

Golden Apple Nominee, Medical University of South Carolina, 2002

Outstanding Resident Teaching Award, MUSC, Dept of OB/GYN, 1999 and 2001

First Place, Resident Oral Presentations, SC/GA Section, ACOG, 2001

Ortho-McNeil Award for Best Resident in Laparoscopy, MUSC, 2002

Resident Research Award for Outstanding Research in Women's Health, MUSC, 2002

Fellowship – *University of Texas MD Anderson Cancer Center, Houston, TX*

J.G. Moore Award, Best Presentation by Fellow or Resident, WAGO, 2004

Del and Dennis McCarthy Award for Advances in Surgery, MDACC, 2004

ASCO Fellows Travel Grant, 2005

AACR Scholar-in-Training Award, 2005

Trainee Excellence Award, MD Anderson Alumni and Faculty Association, 2005

Gynecologic Cancer Foundation / Carol's Cause Outstanding Paper Award, 2006

The Diane Denson Tobola Fellowship in Ovarian Cancer Research, MD Anderson Alumni and Faculty Assn, 2007

Bristol-Myers Squibb Poster Award in Clinical/Translational Research, MD Anderson Trainee Research Day, 2007

Faculty – *University of Texas MD Anderson Cancer Center, Houston, TX*

Listing in "Guide to America's Top Obstetricians and Gynecologists", 2007-2009

Reproductive Scientist Development Program Phase I Scholar, 2007-2009

Julie and Ben Rogers Award for Excellence Nominee, 2008

Faculty – *University of Alabama at Birmingham, Birmingham, AL*

Listing in "Best Doctors in America", 2010-2014

Reproductive Scientist Development Program Phase II Scholar, 2010-2012

John R. Durant Award for Excellence in Cancer Research, UAB CCC, 2009

Ovarian Cancer Academy Award Scholar, Department of Defense, 2010-2015

CCTS Scientific Symposium award, 1st place, UAB CCTS, 2010

Listing in Cambridge Who's Who among Executives and Professions in Research, Medicine, and Healthcare, 2011

Faculty – *University of Virginia, Charlottesville, VA*

Excellence in Reviewing, *Gynecologic Oncology* Case Report, 2014

Excellence in Reviewing, *Gynecologic Oncology*, 2014

Donald Swartz Travel Award, AAOGF/AGOS, 2014

NIH CBSS Study Section, Invited reviewer, 2014

NCI Special Emphasis Panel, ZCA1 RPRB – C: SPORE proposals; Invited reviewer, 2015

NIH CBSS Study Section, Standing member, 2015-2020

EXPERIENCE/SERVICE

PROFESSIONAL SOCIETY MEMBERSHIPS

American College of Obstetricians and Gynecologists – Fellow
Society of Gynecologic Oncology – Full Member
American Association for Cancer Research – Full Member
American Society of Clinical Oncology – Full Member
NRG / Gynecologic Oncology Group – Member
The Gynecology and Obstetrics Society, Medical University of South Carolina, 2002-present
UAB Griffin Society, University of Alabama at Birmingham, 2009-2014
The Felix Rutledge Society, MD Anderson Cancer Center, 2007-present

PROGRAMS

Director of Resident Research, Dept of OB/GYN, UAB, 2010-2014
Co-Director, Molecular Tumor Board (Precision Medicine initiative), UAB Comprehensive Cancer Center, 2013-14
Co-Leader, Women's Oncology Program, University of Virginia Cancer Center

COMMITTEES

National / International

Marketing and Publications Committee, Society of Gynecologic Oncologists (SGO), 2009-2011
Annual Meeting Program Committee, Society of Gynecologic Oncologists (SGO), 2010-2011
Awards Committee, Foundation for Women's Cancer (FWC), 2010-2013
Education Committee, Society of Gynecologic Oncologists (SGO), 2011-2015
Website Development Task Force, Foundation for Women's Cancer (FWC), 2011
Board of Directors, Foundation for Women's Cancer (FWC), 2011-current
Outcome Research Institute, Society of Gynecologic Oncology (SGO), 2014-current
Annual Meeting Program Committee, Society of Gynecologic Oncologists (SGO), 2014-2015

Regional / Institutional

Clinical Ethics Committee, MUSC, 1998-2003
Academic Program coordinator, MUSC, 2001-02
Fellowship Admissions Committee, MDACC, Dept of Gynecologic Oncology, 2005-2006
Fellowship Planning Committee, MDACC, Dept of Gynecologic Oncology, 2005-2006
Steering Committee Member, Comprehensive Cancer Center School of Medicine Strategic Plan, UAB, 2011
Biorepository Development Committee, UAB School of Medicine, 2011-14
Endowed chair in Pathology Search Committee, UAB, 2011-14
Resident Selection Committee, UAB, 2011-14
Clinical Trial Audits, UAB, 2011
Tissue Committee, UAB, 2012-14
Board of Directors, Norma Livingston Foundation, Birmingham, AL, 2012-14
OB/GYN Fund for Excellence in Education, Advisory Committee, UAB, 2012-14
Entering Mentoring Review Group, UAB, 2013-14
Institutional representative, LCME site review, UAB, 2014
Pathobiologist faculty search committee, UAB, 2014
Hematology/Oncology Division Director search committee, UAB, 2014
Protocol Review Committee, UVA Cancer Center, 2014-current
Biorepository and Tissue Research Facility (BTRF) Advisory Board, UVA, 2014-current
School of Medicine Committee on Women, Steering Committee, UVA, 2014-current

GRANT REVIEWER SERVICE

National / International

Ontario Institute for Cancer Research, Cancer Research Fund Translational Panel, Scientist Reviewer, 2009, '10, '11
External Reviewer, Ovarian Cancer Action Research Centre Quinquennial Review, 2011-12
CDMRP DOD Ovarian Cancer Research Program, Pathobiology Panel, Scientist Reviewer, 2010, '11, '12, '15
Foundation for Women's Cancer (FWC) Research Grants/Awards Committee, Grant Reviewer, 2010-2013
Ovarian Cancer Research Fund, Ann Schreiber Research Training Program of Excellence, Grant Reviewer, 2012
Target Ovarian Cancer, Grant Reviewer, 2013
NIH CBSS Study Section, Invited reviewer, 2014
NCI Special Emphasis Panel, ZCA1 RPRB – C: SPORE proposals; Invited reviewer, 2015
NIH SBIR Panel, ZRG1 OTC-B: Cancer diagnostics and Treatment; Invited reviewer, 2015
NIH CBSS Study Section, Standing member, 2015-2020

Regional / Institutional

Ovarian Cancer Pilot Grant, University of Alabama at Birmingham Comprehensive Cancer Center, 2010
AAAS Research Competitiveness Program, Connecticut Bioscience Innovation Fund, Reviewer, 2014
Tina's Wish Research Grant, The Honorable Tina Brozman Foundation for Ovarian Cancer Research, 2014
UVA Cancer Center Transdisciplinary Project Grant, 2014

JOURNAL SERVICE

Editorial Board

Gynecologic Oncology
Gynecologic Oncology Case Report

Ad-hoc Reviewer

JAMA
Journal of Clinical Oncology
Cancer Research
Clinical Cancer Research
Molecular Cancer Therapeutics
Oncogene
Cancer
PLOS One
Genes and Cancer
Journal of Clinical Investigation

Oncotarget
Molecular Carcinogenesis
American Journal of Obstetrics and Gynecology
Expert Opinion on Therapeutic Targets
Cancer Letters
Tumor Biology
Neoplasia
Journal of Obstetrics and Gynaecology Research
British Journal of Cancer

TRAINING COURSES TAKEN

Ethics Consult Service, Medical University of South Carolina, 1998-2003
AACR Molecular Biology in Clinical Oncology Workshop, Aspen, Colorado, 7/2004
Stem Cell Training Workshop, Stem cell Technologies, Inc., Vancouver, BC, Canada, 9/2007
Clinical and Translational Science Training Program, UAB CTSA, 2011

CLINICAL TRIALS

105OC201: A Phase 2 Evaluation of TRC105 in the Treatment of Recurrent Ovarian Fallopian tube, or Primary Peritoneal Carcinoma. Role: Principal Investigator. Sponsor: TRACON Pharmaceuticals, Inc. 9/14/2011-9/9/2012.
UAB 0801: Phase I of Intraperitoneal ²¹²Pb-TCMC-trastuzumab for HER-2 expressing malignancy. Role: Co-Investigator. Sponsor: Areva Med LLC 2/23/2011-7/31/2014.
UAB 1357: Phase IB/II trial of LDE225 and Weekly Paclitaxel in Recurrent Platinum Resistant Ovarian Adenocarcinoma. Role: Co-Investigator. Sponsor: Novartis. 11/2013-7/31/2014.

TEACHING/MENTORSHIP

Courses/Programs

Gross Anatomy Teacher's Assistant, UNC School of Medicine, 1994-1995

Small group preceptor, Medical Ethics course, MUSC, 2002-2003
Angiogenesis section lecturer, Cancer Biology course, UAB Graduate School, 2010-2014
Director of Resident Research, Dept of OB/GYN, UAB, 2010-2014
Small Group leader, New Student Discussion Group (NSDG), UAB School of Medicine, 2012
Course Co-Director, Translational Cancer Research, UAB Graduate School, 2012-13

Postdoctoral fellow mentorship

Adam Steg, PhD. *The role of Jagged1 and Sonic Hedgehog in ovarian cancer growth and chemoresistance*. UAB, 12/2009-7/2014.

Dae Hoon Jeong, MD, PhD. Associate Professor, Inje University, Busan, South Korea. Visiting Research Assistant, *Combined efficacy of hedgehog and proteasome targeting in ovarian cancer*. UAB, 2012-13.

Huaping Chen, PhD. *The role of microRNAs on epigenetic mediation of chemotherapy resistance in ovarian cancer*. 7/2013-7/2014.

Graduate Student Advisor Committee Member

Patrick Garcia, PhD candidate. *Development of an animal model of pancreatic cancer for therapeutic intervention*. 2010-2014.

Huaping Chen, PhD candidate. *Epigenetic targeting of ovarian cancer*. 2011-2013.

Matt Schultz, PhD candidate. *The role of STGal-I in the ovarian tumor cell phenotype*. 2012-2014.

Hugo Jiminez, PhD candidate. *Amplitude Modulated Radiofrequency Electromagnetic Fields as a Novel Treatment for Ovarian Cancer*. 2012-2014.

Monicka Wieglos, PhD candidate. *Mechanisms of PARP sensitization in HER2-positive breast cancer*. 2012-current.

Alice Weaver, MD-PhD candidate. *Targeting DNA damage repair mechanisms in HPV-driven head and neck cancers*. 2013-current.

Ashley Conoway, PhD candidate. *The role of Tdp-1 in DNA damage and repair*. 2014-current.

Kelly Kreitzburg, PhD candidate. *Targeting the sphingosine 1-phosphate pathway in drug-resistant ovarian cancer*. 2014-current.

Kiley Anderson, PhD candidate. *SAS1B as a target in cancer*. 2014-current.

Graduate Student Mentorship

Amanda Debrot, PhD candidate. *Examination of stem cells in fallopian tubes*. Lab rotation, UAB, 2010.

Katie Jo Rohn, PhD candidate. *Development of an assay for Jagged1 inhibitors*. Lab rotation, UAB, 2011.

Hugo Jiminez, PhD candidate. *Examination of Notch-independent effects of Jagged1 signaling in ovarian cancer chemoresistance*. Lab rotation, UAB, 2011-12.

Zachary Dobbin, MD/PhD candidate. *Development and validation of a primary xenograft model in ovarian cancer*. **Primary advisor**, UAB, 2011-2014. **Successful defense** 9/10/2014. **AWARDS**: Best poster presentation, UAB Medical Student Research Day, 2012. AACR Scholar-in-Training Award, AACR, 2013. Best poster presentation, UAB Medical Student Research Day, 2014.

William Jackson, PhD candidate. *Targeting SPANX in taxane-resistant ovarian cancer*. Lab rotation, 2012.

Ann Hanna, PhD candidate. *Induction of dormancy by NR2F1 in ovarian cancer*. Lab rotation, 2013.

Kelly Kreitzburg, PhD candidate. *Targeting phingosine-1-phosphate for the treatment of drug-resistant ovarian cancer*. Lab rotation and PhD mentor, 2013-2014. **AWARDS**: 3rd place, UAB CCC Research Day, 2014.

Samantha Sherwood, PhD candidate. The role of the sphingosine 1-phosphate pathway in ovarian cancer growth and chemotherapy resistance. **Primary advisor**, UVA, 2015-present. **AWARDS:** Recipient, NIH Training Grant, 2015-2016.

Gynecologic Oncology Fellow Mentorship

Kerri Bevis, MD. Fellow in Gynecologic Oncology. *Examination of Stem Cell Markers in Matched Primary and Recurrent Ovarian Cancer*. UAB, 7/2009-6/2012. **AWARDS:** UAB CCTS Scientific Symposium award, 1st place, 2010; Featured poster, SGO Annual Meeting, 2011.

Angela Ziebarth, MD. Fellow in Gynecologic Oncology. *Targeting Endoglin (CD105) improves platinum sensitivity in epithelial ovarian cancer and The ubiquitin ligase EDD as a mediator of platinum resistance target for therapy in epithelial ovarian cancer*. UAB, 7/2010-6/2013. **AWARDS:** Featured poster, SGO Annual Meeting, 2011.

Monjri Shah, MD. Fellow in Gynecologic Oncology. *Functional assessment of defects in homologous recombination as a predictor of response to PARP inhibitors*. UAB, 7/2011-6/2014.

Erickson, Britt, MD. Fellow in Gynecologic Oncology. *Detection of somatic TP53 mutations in tampons of patients with high-grade serous ovarian cancer*. UAB, 7/1/2012-2015.

Arend, Rebecca, MD. Fellow in Gynecologic Oncology. *WNT/ β -Catenin Pathway as a Target for the Treatment of Ovarian Cancer*. UAB, 1/1/2014-6/30/2015. **AWARDS:** WeRoc/OchO Ovarian Cancer Research Grant, Foundation for Women's Cancer, 2014

OBGYN Resident Mentorship

Gretchen Zsebik, MD. Resident in Obstetrics and Gynecology. *Outcomes in Ovarian Cancer Patients Managed by General Gynecologists and Management of Complex Pelvic Masses Using the OVA1 Test: A Decision Analysis*, UAB, 2010-2012. **AWARDS:** Featured poster/Oral presentation, SGO Annual Meeting, 2011.

Jovana Martin, MD. Resident in Obstetrics and Gynecology. *Detection of ovarian cancer cells in the vagina: a pilot feasibility study*. UAB, 9/2011-6/2013. **AWARDS:** Best presentation, PGY2 Resident research Day, 2011.

Blake Porter, MD. Resident in Obstetrics and Gynecology. *Physician Adherence to the US Dept of Health and Human Services Physical Activity Guidelines: A Randomized Control Trial*. UAB, 9/2011-6/2013.

Medical Student Mentorship

Nick Nolte, MS3. *The contribution of claudin-16 to taxane resistance in ovarian cancer*. UAB, 2010.

Mata Burke, MS1. 1) *Combined Hedgehog and Notch targeting in ovarian cancer*. UAB, 2011, 2012. **AWARD:** 1st Place, Oral presentation Short Term Research Category, Medical Student Research Day, 10/25/2011, invited to present at National Student Research Forum 4/2012.

2) *Proteasome Inhibition Synergizes with Hedgehog Inhibition and Reverses Taxane Resistance in Ovarian Cancer*. **AWARD:** Honorable mention, Medical Student Research Day, 10/29/2013.

John Ogorek, MS3. *Patient characteristics of ovarian cancer managed initially managed by general OB/GYN physicians*. UAB, 2012.

Tooba Anwer, MS1. *Examination of the effect of targeting the Sphingosine-1-phosphate pathway in overcoming chemoresistance in ovarian cancer*. UAB/NIH Medical Student Summer Research Project Program, 2014.

Undergraduate Student Mentorship

Lindy Pence, Sophomore, Wofford College. *Inhibition of the mTOR/PI3K Pathways to Enhance Sensitivity of Ovarian Cancer Cells to Chemotherapy Treatment*. Summer in Biomedical Science (SIBS) Undergraduate Research Program, 2012. **AWARDS:** 2nd Place, Life Sciences Division, UAB Summer Research Expo, 2012.

Jacqueline Upp, Junior, University of Alabama at Birmingham. *Racial disparities in ovarian cancer*. 2013. Summer Research Partnership, Morehouse-Tuskegee-UAB CCC Partnership.

Technician Direct Supervision

Guillermo Armaiz-Pena, PhD. *Mediators of Stress-Induced Cancer Progression*. MDACC, 2004-2005.

Blake Goodman, B.S. *Examination of Tumor Initiating Cells in Ovarian Cancer*. MDACC, 2008-2009.

Ashwini Katre, MS. *Chemoresistance mechanisms of ALDH1 in ovarian cancer*. UAB, 2010-present.

RESEARCH FUNDING

Active

Co-Investigator, *Glycosylation-dependent mechanisms regulating ovarian tumor cell survival*. R01 GM111093, NIH/NIGMS, 4/1/2014 – 3/31/2017

Principal Investigator, *Nanoparticle delivery of siRNA to target chemoresistance in ovarian cancer*. Transdisciplinary Research Grant, UVA Cancer Center, 1/1/2015-12/31/2015

Principal Investigator, *Targeting Ribosomal RNA Synthesis for Treatment of Ovarian Cancer*, RSDP Seed Grant Program. 9/1/2014 – 8/31/2015

Principal Investigator, *Characterization and Targeting of the Aldehyde Dehydrogenase Subpopulation in Ovarian Cancer*, OC093443, Department of Defense Ovarian Academy Award, 7/1/2010 – 6/30/2015.

Co-Investigator, *Using RPS25 to Target the Survival Pathway in Ovarian Cancer*, Faculty Development Award, UAB Comprehensive Cancer Center, 3/15/14 – 3/14/15

Co-Investigator, *Ribosome biogenesis, turnover and function as a therapeutic target for ovarian cancer*, Program Project Grant Pilot Fund, UAB Comprehensive Cancer Center, 8/1/2014 – 7/31/2015

Co-Investigator, *Developing ovarian cancer stem-like cell targeted therapy to prevent disease recurrence*, Ovarian Cancer Research Program Pilot Award, CDMRP Department of Defense, 9/1/2014 – 8/31/2016

Co-Investigator, *DNA repair enzyme tyrosyl-DNA phosphodiesterase I as novel therapeutic target for ovarian cancer treatment*, Ovarian Cancer Research Program Pilot Award, CDMRP Department of Defense, 9/30/2015 – 09/29/2017

Prior

Co-Investigator, U54 pilot project: *BRCA1 Deficiency and Epithelial Ovarian Cancers*. Morehouse School of Medicine/Tuskegee University/University of Alabama Cancer Center Partnership. 9/1/2011-8/31/2014

Principal Investigator. *Identifying mediators of chemoresistance in ovarian cancer*. The Norma Livingston Foundation. 5/1/2012-4/30/2014

Principal Investigator. *Development of a Personalized Therapy Model in Cervical Cancer*. Pilot Project, SPORE in Cervical Cancer. 9/1/2012 – 8/31/2014

Co-Investigator, *Chemosensitization of Ovarian Cancer by Exploiting Novel and Safe Epigenetic Compounds*. College of Arts and Sciences Interdisciplinary Innovation Team Award (PI Trygve Tollefsbol). 10/1/2012-9/30/2014

Principal Investigator. *Detection of ovarian cancer-derived mutations in tampon extracts using Safe-SeqS*. The Laura Crandall Brown Foundation. 12/5/2012-12/4/2014

Co-Principal Investigator. Predicting response of ovarian cancers to PARP Inhibitors. The ROAR Foundation. 12/14/2012 – 12/13/2014

Principal Investigator, *105OC201: A Phase 2 Evaluation of TRC105 in the Treatment of Recurrent Ovarian Fallopian tube, or Primary Peritoneal Carcinoma*. Sponsor: TRACON Pharmaceuticals, Inc. 9/14/2011-9/9/2012.

Principal Investigator, *Targeting Jagged in Ovarian Tumor Initiating Cells*, Research Scientist Development Program Phase II (through the Ovarian Cancer Research Fund), 7/1/2009-6/30/2012

Principal Investigator, *Examination of the true mediators of resistance in ovarian cancer*, Translational Research Intramural Grant, UAB CCTS and CCC, 4/1/2010 – 3/31/2011

Principal Investigator, *Targeting the Notch pathway in Ovarian Cancer Initiating Cells*, Sarah Biedenharn/Gynecologic Cancer Foundation Ovarian Cancer Research Grant, 7/1/2009-6/30/2010

Principal Investigator, *Characterization and therapeutic targeting of ovarian cancer stem cells*, 5P50 CA083639, Career Development Award, Ovarian Cancer SPORE at MDACC, 9/1/2007 – 8/31/2009

Principal Investigator, *The role of the alpha v beta 3 integrin in signaling and as a target in human ovarian cancer*, NIH #5K12 HD00849: Reproductive Scientist Development Program (RSDP) Phase I, 7/1/2007-6/30/2009

Principal Investigator, *Characterization of ovarian cancer xenografts*, HERA Foundation Investigator Award, 5/1/2008-4/31/2009

Principal Investigator, *The role of EphA2 in ovarian cancer*. Bettyann Asche-Murray Fellowship Award, M.D. Anderson Cancer Center, 7/1/2005-6/30/2007

Patents Granted and Pending

Delivery of siRNA by neutral lipid compositions, MDACC, United States, 60/671,641, 4/15/2005, Filed.

PUBLICATIONS

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* Equal contribution

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ABSTRACTS

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112. Garcia AA, Makker V, Spitz DL, Matei DE, Nick AM, **Landen CN**, Alvarez EA, Mendelson DS, Strother RM, Seon BK, Alvarez D, Adams BJ, Theuer CP, Gordon M. TRC105 (Anti-endoglin Antibody) in Combination with Bevacizumab (BEV) and as a Single Agent for Platinum Resistant Ovarian Cancer. *ESMO*. Madrid, Spain. September, 2014.
113. Dobbin ZC, Katre AA, Jeong DJ, Erickson BK, Alvarez RD, Schneider DA, **Landen Jr CN**. Post-chemotherapy tumors in the PDX model identify ribosomal synthesis as a novel targeting strategy in ovarian cancer. *Annual Meeting of the Society of Gynecologic Oncologists*. Chicago, IL. March 2015.
114. Kreitzburg KM, Dobbins Z, Katre A, Anwer T, Alvarez R, Landen CN, Yoon KJ. Developing targeted therapy for the treatment of drug-resistant ovarian cancer. *Proceedings of the American Association of Cancer Research*, 2015.

§ Selected for Meeting Award

BOOK CHAPTERS

1. **Landen CN** and Holmes MA. Dysmenorrhea, in *Conn's Current Therapy* 2002, R. Rakel and E. Bope, Editors, W.B. Saunders Company, Philadelphia, pp 1076-1078, 2002. ISBN: 072168744X
2. Gernt PR, Norcross ED. *Sleepwell: Surgery and Obstetrics/Gynecology, Vol 2* (Sleepwell Review Series). Blackwell Publishing 2002. ISBN: 0632046643.
3. **Landen CN** and Lopez-Berestein G. Therapeutic Agents and Approaches in the Age of Personalized Cancer Care, in *Targeted Therapy for Solid Tumors and Hematologic Malignancies* 2011. AQ Cardama, DL Gibbons, V Cataldo, Eds. NOVA Science Publishers, New York, NY. ISBN: 978-1-61761-854-3
4. **Landen CN**. Biologic and Targeted Therapies, in *Society of Gynecologic Oncologists Chemotherapy Handbook*, under construction.

CONFERENCES AND SYMPOSIA

Organized conferences

Chair, Program Committee, UAB Comprehensive Cancer Center Annual Research Retreat, "Personalized Cancer Care". October, 2014.

Presentations at National or International Conferences

Invited

Differing mechanisms of inhibition of calcium rises in human uterine myocytes by indomethacin and nimesulide. The Donald F. Richardson Prize Paper Award Presentation. 50th Annual Clinical Meeting of the American College of Obstetricians and Gynecologists, 5/2002.

Neuroendocrine modulation of STAT3 in ovarian cancer. Western Association of Gynecologic Oncologic Oncologists, 5/2004.

Genomic Instability is Associated with Lack of Telomerase Activation in Ovarian Cancer. 6th International Conference on Ovarian Cancer, MD Anderson Cancer Center, 12/2005.

Therapeutic silencing of EphA2 by in vivo liposomal siRNA delivery. American Association of Cancer Research Annual Meeting. Anaheim, CA, 4/2005.

Targeting the $\alpha\beta 3$ integrin with a fully humanized antibody in ovarian cancer. 37th Annual Society of Gynecologic Oncologists Meeting, Palm Springs, CA, 3/2006.

Overexpression of the centrosomal protein Aurora-A kinase is associated with poor prognosis in epithelial ovarian cancer patients. 37th Annual Society of Gynecologic Oncologists Meeting, Palm Springs, CA, 3/2006.

SiRNA Therapeutics in Ovarian Cancer. 7th Annual International Conference on Ovarian Cancer, Houston, TX, 11/2006.

Perioperative factors associated with survival after secondary cytoreduction in patients with recurrent epithelial ovarian cancer. Society of Gynecologic Oncologists Winter Meeting, Beaver Creek, CO, 2/2007.

Trial-based review of Management of Ovarian Cancer. 39th Annual Meeting of the Society of Gynecologic Oncologists, Tampa, FL, 3/2008.

Targeting the $\alpha\beta 3$ integrin in ovarian cancer. Society of Gynecologic Investigation Annual Meeting, San Diego, CA, 3/2008.

Trial-based review of Management of Ovarian Cancer. 40th Annual Meeting of the Society of Gynecologic Oncologists, San Antonio, TX, 3/2009.

"Nanoparticle Delivery Systems for siRNA Therapy." 3rd Annual Symposium on Ovarian Cancer Research, Medical University of South Carolina, 5/2009.

"Independent targeting of the Notch pathway in tumor cells and tumor stroma." Reproductive Scientist Development Program Retreat, 10/2010.

"Establishing successful collaborations in research." Southeastern Medical Scientist Symposium, Emory University, Atlanta, GA, 9/2011.

"Ovarian Cancer Stem Cells: Clinically Significant or Experimental Phenomenon." 3rd Annual International Conference, Ovarian Cancer: Prevention, Detection and Treatment of the Disease and its Recurrence, Pittsburg, PA, 5/2012.

"Promising Recent Advances in Ovarian Cancer Research". Foundation for Women's Cancer Survivor's Course, Washington, D.C., 10/2012

Patient-Derived Xenografts for discovery of *de novo* mediators of chemoresistance in ovarian cancer." Reproductive Scientist Development Program annual meeting, Boulder CO, 10/2013.

“Meet the Expert: Managing Your First Lab.” AACR / Marsha Rivkin Ovarian Cancer Research Symposium. Seattle, WA. 9/2014.

Discussant

Molecular Therapeutics of Cancer Research Conference, Princeton, NJ, 7/2010.

“KLF6-SV1 is a Novel Uterine Leiomyosarcoma Gene: From Transgenic Mouse Model to Human Disease.” 42nd Annual Meeting of the Society of Gynecologic Oncologists, Orlando, FL, 2011.

Moderator

Focused Plenary Session III, Translational and Basic Science, 42nd Annual Meeting of the Society of Gynecologic Oncologists, Orlando, FL, 2011.

Scientific Plenary V

Invited Seminars from Other Institutions

“Therapeutic targeting of EphA2 in ovarian cancer.” Dept of Obstetrics and Gynecology Grand Rounds, Washington University, St. Louis, MO, 4/2007.

“In search of: Ovarian Cancer Stem Cells.” Lineberger Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, 10/2008.

“Translating Discovery to the Patient in Ovarian Cancer.” Dept of Obstetrics and Gynecology Grand Rounds, University of North Carolina at Chapel Hill, Chapel Hill, NC, 10/2008.

“In search of: Ovarian Cancer Stem Cells.” Hellen Diller Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, 10/2008.

“Update on screening and genetic susceptibility in gynecologic cancers.” The Gynecologic and Obstetrics Society, Medical University of South Carolina, 5/2011.

“Cancer Stem Cells: Clinically significant or an experimental phenomenon?” Felix Rutledge Society, MD Anderson Cancer Center, 5/2011.

“Cancer Stem Cells: Clinically significant or an experimental phenomenon?” Hudson Alpha Lecture series, Huntsville, AL, 4/2013.

“Cancer Stem Cells: Clinically significant or an experimental phenomenon?” Southern Cell Biology Research Symposium, Tuskegee University, 6/2013.

“Development of the patient-derived xenograft model to identify de novo mediators of chemoresistance.” University of Pittsburg, 3/2014.

“IN SEARCH OF: The chemoresistant population in ovarian cancer.” Department of Obstetrics and Gynecology Grand Rounds, University of Chicago, 4/2014.

“Targeting of mediators of chemoresistance in ovarian cancer. Legyel Lab, University of Chicago, 4/2014.

“Development of the patient-derived xenograft model to identify de novo mediators of chemoresistance.” University of Virginia, 4/2014.

“Development of the patient-derived xenograft model to identify de novo mediators of chemoresistance.” Kansas University, 5/2014.

“Identification and Targeting Mediators of Chemoresistance in Ovarian Cancer.” Indiana University, 9/2015.

“Fallopian tube origin in ovarian cancer.” South Carolina Obstetrical and Gynecological Society, 9/2015.

Presentations at Local Conferences

“Patient Satisfaction with Their Physician,” Camp Bluebird Retreat for Cancer Survivors, 5/2000.

“Telomerase and Microsatellite Instability in Ovarian Cancer.” Dept of Gynecologic Oncology Grand Rounds, MD Anderson Cancer Center, 2/2004.

“Neuroendocrine modulation of STAT3 in Ovarian Cancer.” Dept of Gynecologic Oncology Grand Rounds, MD Anderson Cancer Center, 4/2004.

“Therapeutic silencing of EphA2 by in vivo liposomal siRNA delivery.” Dept of Gynecologic Oncology Grand Rounds, MD Anderson Cancer Center, 4/2005.

“Therapeutic targeting of EphA2 in ovarian cancer.” Dept of Experimental Therapeutics, MD Anderson Cancer Center, Houston, TX, 4/2005.

“Trial-based review of Management of Ovarian Cancer.” Dept of Gynecologic Oncology, MD Anderson Cancer Center, 11/2007.

“Cancer Stem Cells in Epithelial Ovarian Cancer.” Dept of Cancer Biology, MD Anderson Cancer Center, 4/2008.

“Important Aspects of Mentorship.” Dept of Gynecologic Oncology Grand Rounds, MD Anderson Cancer Center, 5/2008.

“In search of... Ovarian Cancer Stem Cells.” Program in Experimental Therapeutics, UAB, 1/2010.

“What’s New in Gynecologic Cancer Research.” Progress in OB/GYN Annual Meeting, UAB, 2/2010.

“Independent targeting of the Notch pathway in tumor cells and tumor stroma.” Cancer Cell Biology seminar series, UAB, 5/2010.

“Neoadjuvant Chemotherapy in Ovarian Cancer.” Division of Gynecologic Oncology Grand Rounds, UAB, 7/2010.

“Historical Vignettes in Obstetrics and Gynecology.” Department of Obstetrics and Gynecology Grand Rounds, UAB, 7/2010.

“Surgical Management of Gynecologic Malignancies.” Department of Radiology Grand Rounds, UAB, 7/2010.

“Ex vivo and animal models of cancer.” Graduate School in Biomedical Sciences, Translational Research Course, UAB, 10/2013.

“Development of the patient-derived xenograft model to identify de novo mediators of chemoresistance.” Grand Rounds, Department of Hematology and Oncology, UAB, 5/2014.

“Targeting Mediators of the Chemoresistance in Ovarian Cancer.” Grand Rounds, Department of Obstetrics and Gynecology, UVA, 9/2014

“Targeting Mediators of the Chemoresistance in Ovarian Cancer.” Grand Rounds, Department of Pathology, UVA, 10/2014

“Targeting Mediators of the Chemoresistance in Ovarian Cancer.” Grand Rounds, UVA Cancer Center, UVA, 10/2014