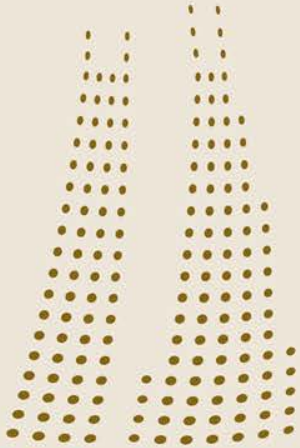


2015

ANNUAL MEETING ON WOMEN'S CANCER®

CHICAGO

Identification of Potential Therapeutic Targets by Molecular and Genomic Profiling of 628 Cases of Uterine Serous Carcinoma

Nathaniel L Jones[1], Joanne Xiu[2] , Sandeep K. Reddy[2], Ana I. Tergas[1], William M. Burke[1], Jason D. Wright[1], June Y. Hou[1]

[1]Columbia University College of Physicians and Surgeons and New York Presbyterian Hospital , [2]Caris Life Sciences

Verbal Disclosures

- No disclosures

Uterine Serous Carcinoma

- Rare cancer: 5-10% of all uterine cancers[1-2]
- Accounts for 50% of relapses[3]
- Accounts for 40% of deaths[3]
- 5-year survival: 18-27%[4]

Current Landscape of USC

Marker/Mutation	Total # tumors	Frequency
TP53	n=129	82-91% [5-6]
HER2	n=207	14-80% [5, 7-12]
EGFR	n=151	34-56% [14-15]
PIK3CA	n=174	15-42% [5-6, 15]
FBWX7	n=129	20-30% [5-6]
KRAS	n=162	2-5% [16-17]
ER	n=21	24% [18]
PR	n=21	19% [18]

Objectives

- We aim to identify patterns of molecular and genetic change in USC tumors
- Offer potential targetable pathways for future therapeutic study
- Identify patients that may benefit from the large number of biological therapeutics available

Methods

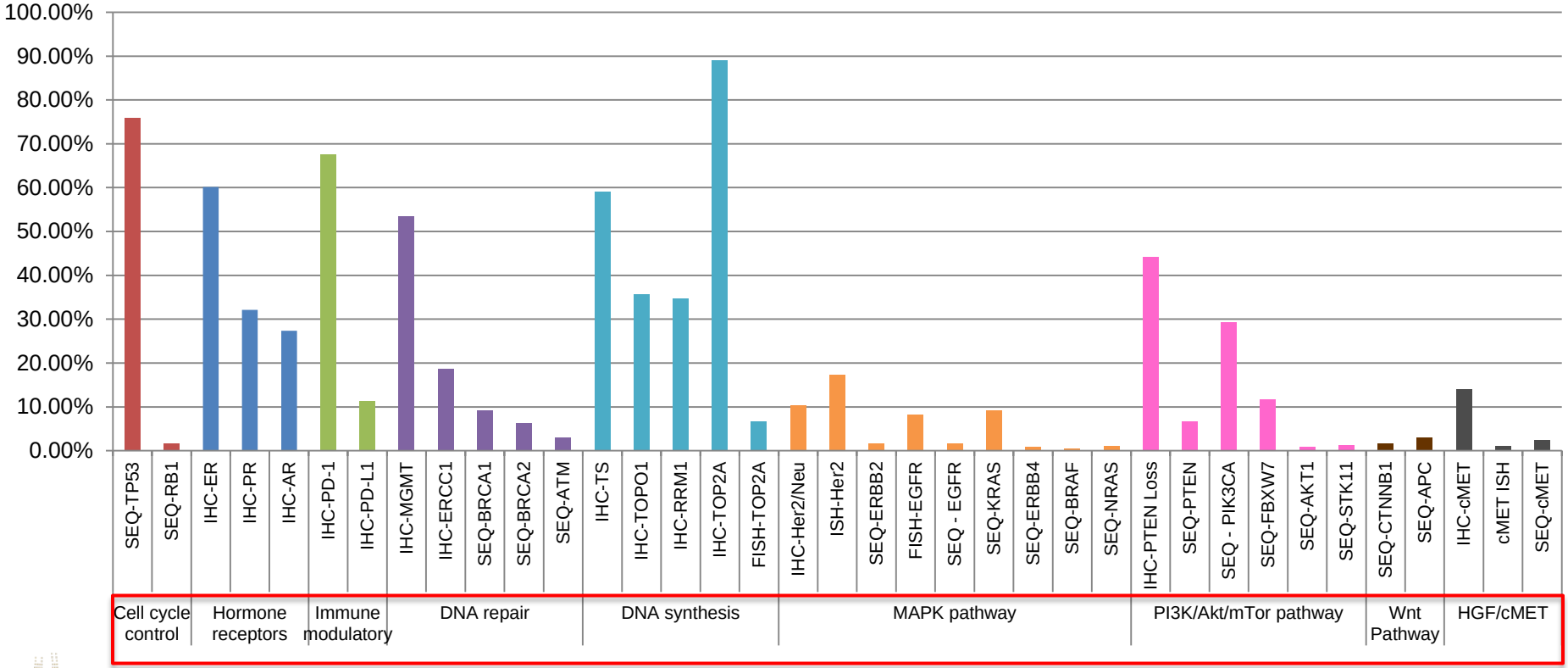
- 628 uterine serous tumors evaluated from March 2011 to July 2014
- Diagnoses confirmed by board-certified pathologists.
- Multiplatform testing included DNA sequencing, IHC, and FISH

Current Landscape of USC

Marker/Mutation	Total # tumors	Known Frequency	Our Study
TP53	n=129	82-91% [5-6]	76%
HER2	n=207	14-80% [5, 7-12]	17%
EGFR	n=151	34-56% [14-15]	8%
PIK3CA	n=174	15-42% [5-6, 15]	29%
FBWX7	n=129	20-30% [5-6]	12%
KRAS	n=162	2-5% [16-17]	9%
ER	n=21	24% [18]	60%
PR	n=21	19% [18]	32%
AR	---	?	27%

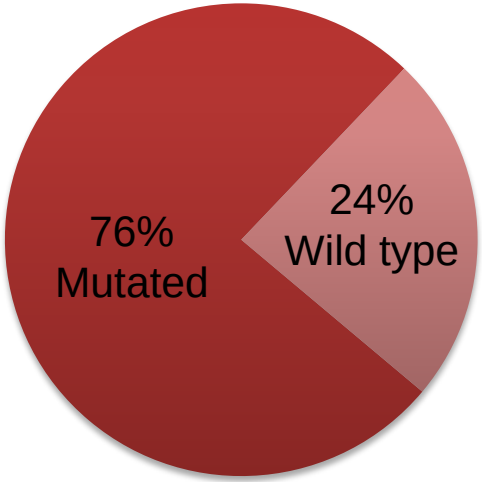
n=628

Specific Pathway Dysregulation in USC



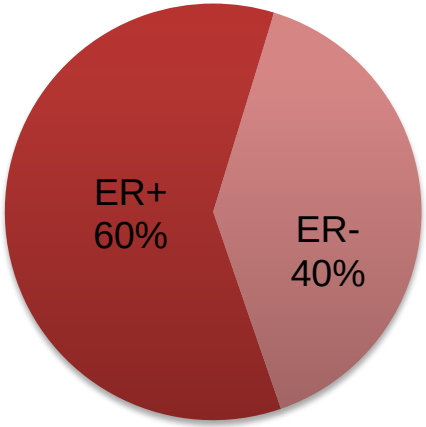
Bars indicate gene mutations or protein overexpression

TP53 wild type status associated with Wnt pathway involvement



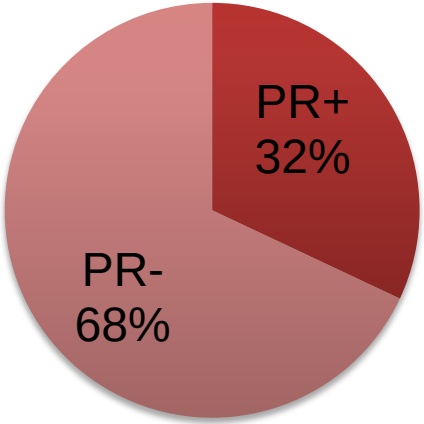
	TP53 mutated	TP53 wildtype	P-value
Greater **CTNNB1** mutation	0% 0/181	**7%** 4/58	**< 0.01**
Greater **APC** mutation	2% 3/181	**7%** 4/58	**< 0.01**

Estrogen Receptor Subanalysis



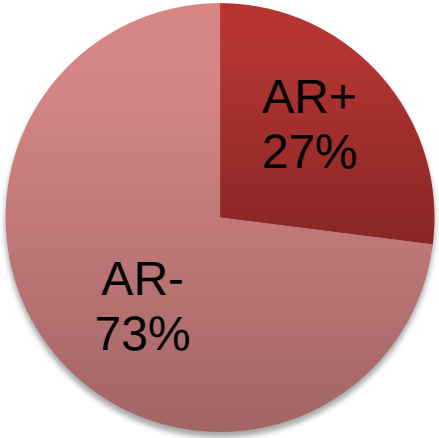
	ER-	ER+	P-value
Greater **PTEN** loss	**44%** 80/183	33% 87/266	**0.02**
Lower **MGMT** expression	**48%** 88/182	58% 154/265	**0.04**
Lower **ERCC1** expression	**6%** 4/66	24% 20/83	**<0.01**
Greater **BRCA1** mutations	**27%** 3/11	0% 0/20	**0.03**
Greater **KRAS** mutations	**14%** 24/171	7% 17/247	**0.02**
Lower **AR** expression	**10%** 19/182	42% 111/265	**<0.01**

Progesterone Receptor Subanalysis



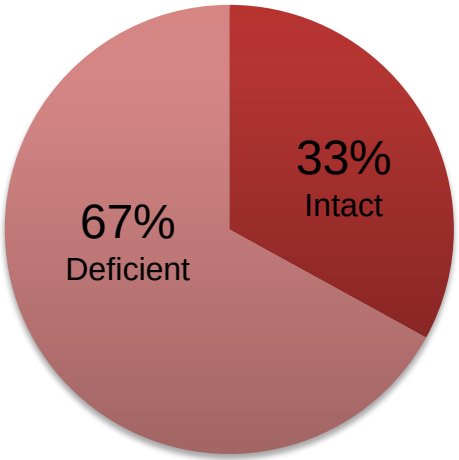
	PR-	PR+	P-value
Greater **PIK3CA** mutation	23% 55/241	**44%** 44/101	**< 0.01**
Lower **ERCC1** expression	**15%** 29/195	26% 27/103	**0.02**

Androgen Receptor Subanalysis



	AR-	AR+	P-value
Greater **TOPO1** expression	32% 123/390	**46%** 67/145	**< 0.01**
Greater **RRM1** expression	32% 125/396	**42%** 61/145	**< 0.01**
Greater **PTEN** mutation	**9%** 14/161	1% 1/73	**< 0.01**
Greater **FBXW7** mutation	**15%** 25/163	4% 3/74	**< 0.01**

DNA Repair Pathway Subanalysis



ERCC1, MGMT, BRCA1/2, ATM

	DNA Repair Deficient	DNA Repair intact	P-value
Greater **PTEN** loss	**51%** 215/420	28% 52/183	**< 0.01**
Greater **PTEN** mutation	**10%** 37/369	7% 12/163	**< 0.01**
Lower **TOPO1** expression	**27%** 99/374	58% 87/149	**< 0.01**
Lower **TS** expression	**55%** 208/379	66% 98/148	**0.02**

Additional Findings

PD-L1, HER2, KRAS, PTEN/PI3K

- PD-L1 expression in 11% and PD-1 expression in 67%
- Her2 overexpression in 17%
- KRAS mutation in 9%
- TOPO2A overexpressed in 90%
- Only 7% with PTEN mutation but 45% with PTEN loss on IHC.
- PIK3CA mutation in 29%

Conclusions

- USC is a genetically heterogeneous disease.
- Largest cohort to date of 628 uterine serous tumors
- Provides valuable information on the molecular and genetic characteristics of uterine serous cancer
- Identified possible targets for therapeutic exploration
- Hypotheses generating for future research

Acknowledgements

- June Hou
- Jason Wright
- Billy Burke
- Ana Tergas
- Joanne Xiu

References

1. Hamilton, C.A., et al., *Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers.* Br J Cancer, 2006. **94**(5): p. 642-6.
2. Boruta, D.M., 2nd, et al., *Management of women with uterine papillary serous cancer: a Society of Gynecologic Oncology (SGO) review.* Gynecol Oncol, 2009. **115**(1): p. 142-53.
3. Hendrickson M, Ross J, Eifel P, Martinez A, Kempson R. Uterine papillary serous carcinoma: a highly malignant form of endometrial adenocarcinoma. Am J Surg Pathol. 1982;6(2):93–108.
4. Acharya, S., et al., *Rare uterine cancers.* Lancet Oncol, 2005. **6**(12): p. 961-71.
5. *Integrated genomic characterization of endometrial carcinoma.* Nature, 2013. **497**(7447): p. 67-73.
6. Kuhn, E., et al., *Identification of molecular pathway aberrations in uterine serous carcinoma by genome-wide analyses.* J Natl Cancer Inst, 2012. **104**(19): p. 1503-13.
7. Santin, A.D., et al., *Overexpression of HER-2/neu in uterine serous papillary cancer.* Clin Cancer Res, 2002. **8**(5): p.1271-9.
8. Santin, A.D., et al., *Racial differences in the overexpression of epidermal growth factor type II receptor (HER2/neu): a major prognostic indicator in uterine serous papillary cancer.* Am J Obstet Gynecol, 2005. **192**(3): p. 813-8.
9. Santin, A.D., et al., *Discrimination between uterine serous papillary carcinomas and ovarian serous papillary tumours by gene expression profiling.* British journal of cancer, 2004. **90**(9): p. 1814-1824.
10. Santin, A.D., et al., *Gene expression fingerprint of uterine serous papillary carcinoma: identification of novel molecular markers for uterine serous cancer diagnosis and therapy.* Br J Cancer, 2005. **92**(8): p. 1561-73.
11. Slomovitz, B.M., et al., *Her-2/neu overexpression and amplification in uterine papillary serous carcinoma.* Journal of Clinical Oncology, 2004. **22**(15): p. 3126-3132.
12. Togami, S., et al., *Clinicopathological and prognostic impact of human epidermal growth factor receptor type 2 (HER2) and hormone receptor expression in uterine papillary serous carcinoma.* Cancer Sci, 2012. **103**(5): p. 926-32.
13. Grushko, T., et al., *An exploratory analysis of HER-2 amplification and overexpression in advanced endometrial carcinoma: a Gynecologic Oncology Group study.* Gynecologic oncology, 2008. **108**(1): p. 3-9.
14. Konecny, G.E., et al., *HER2 gene amplification and EGFR expression in a large cohort of surgically staged patients with nonendometrioid (type II) endometrial cancer.* Br J Cancer, 2008. **100**(1): p. 89-95.
15. Hayes, M.P. and L.H. Ellenson, *Molecular alterations in uterine serous carcinoma.* Gynecologic oncology, 2010. **116**(2): p. 286-289.
16. Forbes, S.A., et al., *The Catalogue of Somatic Mutations in Cancer (COSMIC).* Curr Protoc Hum Genet, 2008. **Chapter 10**: p. Unit 10.11.
17. Lax, S.F., et al., *The frequency of p53, K-ras mutations, and microsatellite instability differs in uterine endometrioid and serous carcinoma: evidence of distinct molecular genetic pathways.* Cancer, 2000. **88**(4): p. 814-24.
18. Kounelis, S., et al., *Immunohistochemical Profile of Endometrial Adenocarcinoma: A Study of 61 Cases and Review of the Literature.* Mod Pathol, 0000. **13**(4): p. 379-388.