



A Novel Model of Ovarian Cancer Driven by Inducible Expression of the PI3K Catalytic Subunit (p110a)

Yinghui Zhou, Shailaja Reddypalli, Tong Zi, Angela Bressel, Qiurong Xiao, William Rideout, Adrian Cooper, Joelle Brodeur, Steven Clark, Murray Robinson & Joerg Heyer

AVEO Pharmaceuticals Inc., 75 Sidney Street, 4th Floor, Cambridge, MA 02139

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ABSTRACT

Ovarian cancer is one of the most deadly diseases among women. The unmet medical need is very high due to the lack of treatment options. One key feature of ovarian cancer is the frequent alteration of genes involved in PI3 kinase signaling. The tumor suppressor PTEN is frequently mutated or lost and conversely, activating mutations have been identified in p110a, the catalytic subunit of PI3K. It has been shown that knock out of PTEN in conjunction with KRAS activation resulted in adenocarcinomas derived from the ovary surface epithelium. It is not clear, however, whether activation of p110a is equally sufficient for tumorigenesis. To address that question, we made a complex inducible ovary tumor model using our unique chimeric model technology. This model features homozygous knock out of the Ink4a/Arf tumor suppressor gene, ovary specific expression of rTA and luciferase driven by AMHR1 promoter, and doxycycline inducible expression of myristylated p110a. The chimeric mice developed tumors with a latency of 4-7 months. Histo-pathological analysis revealed two types of malignant cells, endometrioid adenocarcinomas and tumors originated from granulosa cells. Immunohistochemistry confirmed the expression of p110 in these tumor cells. These tumors are suitable for propagation and potential pathway relevant drug studies.

Features of Chimeric Inducible Tumor Models

Expression of Luciferase allows early tumor detection and monitoring

Cassette approach combines speed and flexibility

- 1) Knock out tumor suppressor gene
- 2) Add inducible gene for luciferase (e.g. Luc)
- 3) Add inducible gene for oncogene (e.g. KRAS, EGFR, HER2)
- 4) Add inducible oncogene (rta driven)

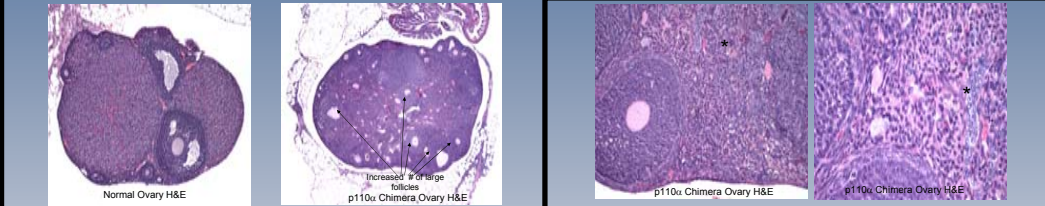
Oncogene dependence, relapse and minimal residual disease

Established Models

Model	Tissue	Oncogene
BH	Breast	Her2 ^{WT/WT}
LK	Lung	KRAS ^{G12S}
LH	Lung	Her2 ^{WT/WT}
LER	Lung	EGFR ^{L858R}
LEM	Lung	EGFR ^{L858R/T790M}
CB	Colon	β -Catenin ^{MDM11}
OP	Ovary	p110 ^{WT}

Tumor development in the context of wild type tissue

Abnormal Architecture of Chimera Ovaries



Chimera Ovaries had a significant increase in the number of large follicles and abnormal, collapsed follicles

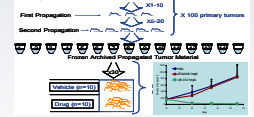
Chimera Ovaries contain cellular infiltrate with some features of granulosa cells

Applications of Inducible Tumor Models

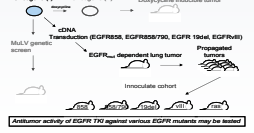
Virus Insertional mutagenesis screen in solid tumors identifies novel cancer targets



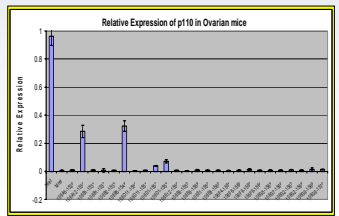
In vivo Propagation of primary tumors creates stable "archive"



Directed Complementation enables oncogene switching

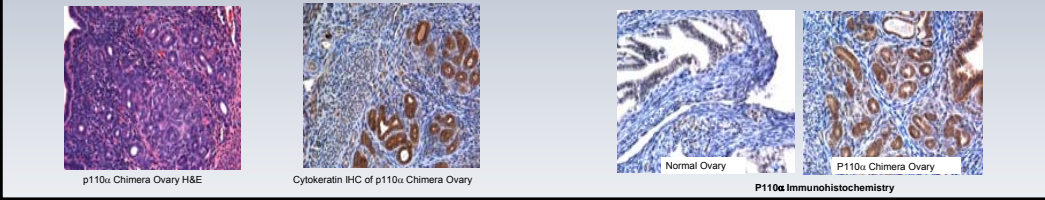


Model ES cell line selection



- Chimeras from 25 different ES cell lines were screened for p110a expression
- Lines 106B5 and 106D1 were chosen to generate chimeras

Epithelial Adenoma in p110a Ovarian Model



SUMMARY

1. Chimeric ES cell based tumor models represent a rapid, robust approach for generating complex inducible tumors with precise genetic alterations
2. The p110a model exhibited gross abnormal ovarian morphology
 - Increased number of large follicles and collapsed follicles
 - Interspersed cellularity with cytologic features of granulosa cells
3. Cytokeratin positive cells dispersed throughout the chimera ovaries expressed high levels of PI3K
4. Ovarian chimeric animals developed Adenomas with a latency of 4-7 months
5. To see our chimeric lung models, please go to Joerg Heyer's presentation at the Minisymposium Mouse Models of Cancer 6 (Wednesday, Apr 18, 10:25 AM - 10:40 AM in Room 406 A-B)