



# Oncogene and Tissue Specific Pathway Activation in an HER2 Dependent Mouse Mammary Tumor Model

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AACR 2008 Annual Meeting, Abstract # 4573

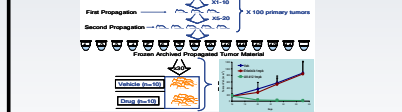
## ABSTRACT

Breast cancer is the second most prevalent cancer in females with an estimated 216,000 new cases resulting in 40,000 deaths per year. The most prominent oncogenic lesion in breast cancer is amplification of HER2 locus. To better understand and characterize breast cancer with HER2 amplification we generated a complex inducible mouse model (BH) based on our chimeric model platform which allows for fast and efficient generation of mouse models. Most prominently the chimeric mouse models provide wildtype tissue for the developing tumor thus mimicking the tumor stroma interactions seen in human tumors. We directed inducible expression of HER2 and Luciferase to the luminal epithelium in the mouse mammary gland by means of the MMTV LTR promoter expressing the rTA gene. Compromising the p53 and Rb pathway was achieved by inactivating the mouse INK4a/Arf locus by targeted recombination. Expression of activated HER2 resulted in invasive adenocarcinomas with a short latency of 2-4 months and a penetrance of 100%. Surprisingly tumors displayed high stroma content reminiscent of human ductal carcinomas. We analyzed activation status of major signal transduction pathways like PI3K, MAPK, SAPK and STAT in our primary tumors and were able to establish patterns of pathway activation specific to HER2 dependent tumors as well as patterns specific to mammary gland tumors when compared to lung adenocarcinomas derived from our chimera based HER2 NSCLC model. In addition we have characterized the breast HER2 model extensively for progression and regression of inducible tumors as well as variation in histopathological features.

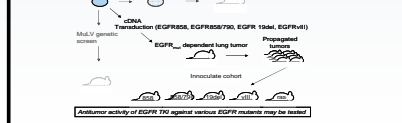
## Applications of Inducible Tumor Models



## In vivo Propagation of primary tumors creates stable "archive"



## Directed Complementation enables oncogene switching



## Features of Chimeric Inducible Tumor Models

**Expression of Luciferase allows early tumor detection and monitoring**

**Cassette approach combines speed and flexibility**

- Knock out tumor suppressor gene
- Add model gene for tissue origin (e.g. Ltr)
- Activate gene for tissue origin (e.g. rTA)
- Add inducible oncogene (rEGF driven)

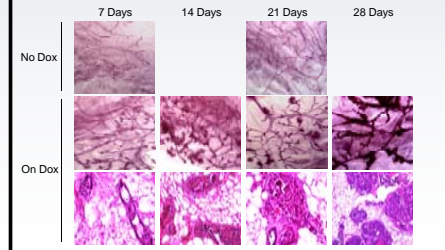
**Oncogene dependence, ratpasa and potential residual disease**

**Established Models**

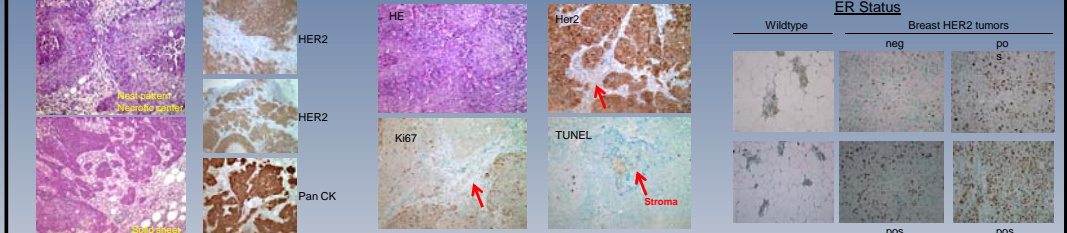
Model	Tissue	Oncogenes
BH	Breast	Her2 <sup>trac</sup>
LK	Lung	KRAS <sup>WT/WT</sup>
LW	Lung	NRAS <sup>WT/WT</sup>
LER	Lung	EGFR <sup>WT/WT</sup>
LEM	Lung	EGFR <sup>WT/WT95</sup>
CB	Colon	β-Catenin <sup>WT/WT</sup>
OP	Ovary	p110 <sup>WT</sup>

**Tumor development in the context of wild type tissue**

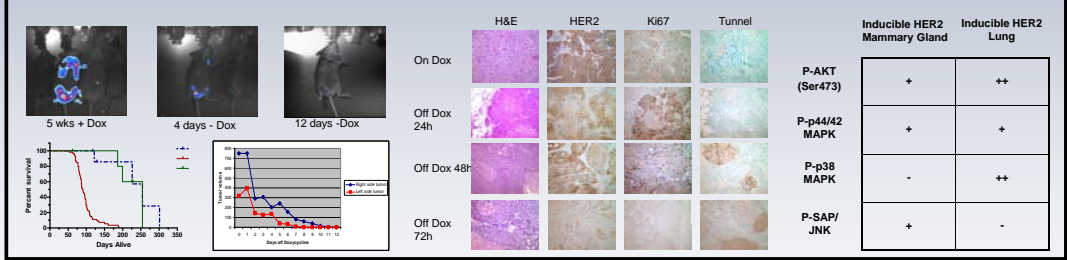
## HER2 Induced Tumors are Polyclonal



## Tumor Characterization



## Tumor Regression After Doxycycline Withdrawal



## SUMMARY

- Chimeric ES cell based tumor models represent a rapid, robust approach for generating complex inducible tumors with precise genetic alterations
- The Her2 dependent model (BH) develops multiple ductal adenocarcinomas within 2-4 month
- BH tumors are Doxycycline dependent and regress within days after Doxycycline withdrawal indicating BH tumors require continuous HER2 expression for tumor maintenance
- HER2 activation is mediated through canonical MAPK pathways unlike the activation of HER2 in the lung
- To see applications of our chimeric breast tumor models, please visit AVEO presentation at the AACR (Abstract number: 2499, 1734, 2962, 2988, 3615, LB201)