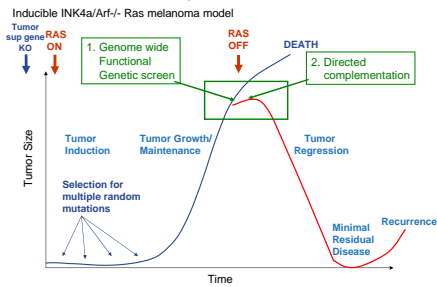


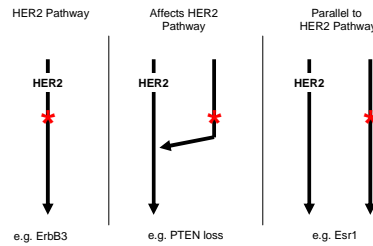
In vivo Genetic Approaches to Identify Mechanisms of Resistance to Inhibition of the HER2 Receptor Tyrosine Kinase

Shirley Markant, Alisa Bell, John Yang, Fanglei You, Jodi Zarycki, Lorena Lerner, Isabel Chiu, Ronan O'Hagan
AVEO Pharmaceuticals, Inc.

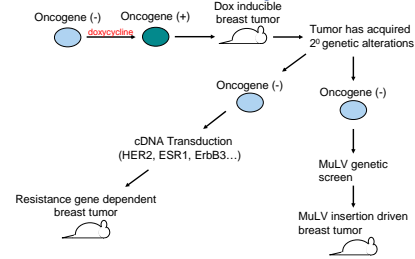
1. Inducible model enables *in vivo* functional genetic complementation



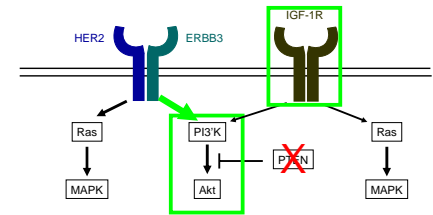
5. Mechanistic classes of HER2 complementation/resistance genes



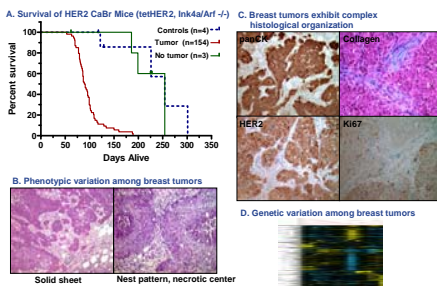
9. Directed Complementation: Genetic Model of Drug Resistance



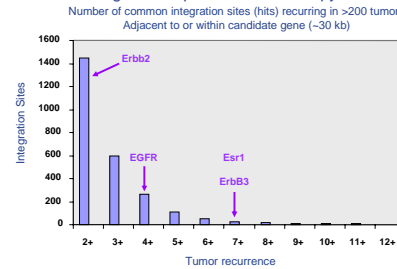
13. Proposed Mechanisms of Resistance to HER2 Inhibition



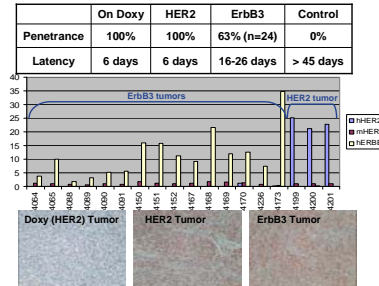
2. Characterization of HER2 Breast Cancer Model



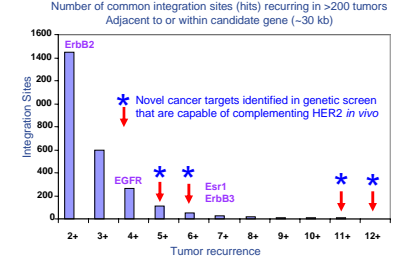
6. HER2 Complementation Screen Identifies Genes That Might Be Expected to Phenocopy HER2



10. ErbB3 Can Functionally Complement HER2 in Breast Tumorigenesis



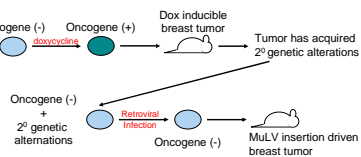
14. Novel Cancer Targets Identified in HER2 Complementation Screen



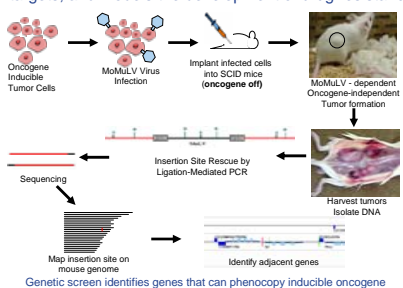
3. *In vivo* genetic screen identifies functionally relevant targets, and models the development of drug resistance

Resistance Mechanisms:
Target no longer affected by compound e.g. EGFR T790M in acquired tarceva resistance
Target no longer required due to activation of alternate pathway (Complementation)

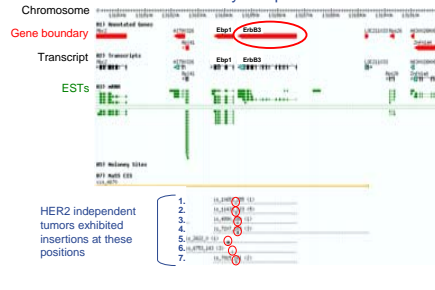
Inducible models enable identification of proteins/pathways that can complement in the genetic context in which the oncogene was originally tumorigenic



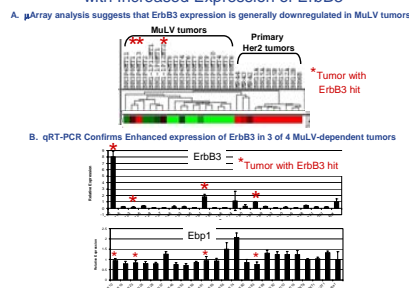
4. *In vivo* genetic screen identifies functionally relevant targets, and models the development of drug resistance



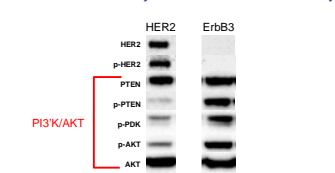
7. The screen identified recurrent insertions adjacent to ErbB3 across many complemented tumors



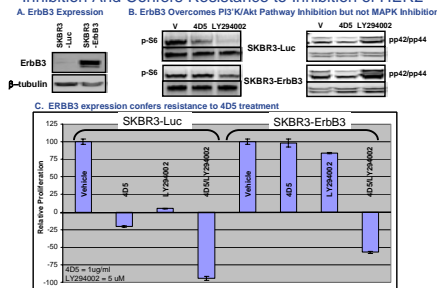
8. Proximal MuLV Integrations Correlate with Increased Expression of ErbB3



11. ErbB3 Complemented Tumors Exhibit Enhanced Activity of the PI3K/Akt Pathway



12. ErbB3 Expression Overcomes PI3K/Akt Pathway Inhibition And Confers Resistance to Inhibition of HER2



15. Summary/Conclusions

- Retroviral insertional mutagenesis screen identified numerous genes capable of complementing HER2 for *in vivo* oncogenesis & tumor maintenance
- ErbB3 - identified as a highly recurrent hit in the screen
 - complements HER2 *in vivo*
 - confers resistance to HER2 inhibition in human cancer cell lines
- Identification of ErbB3 enhanced PI3K/Akt pathway activity as a mechanism of resistance to inhibition of HER2 is consistent with clinical observations and significant supporting literature
- Hence, identification of novel cancer targets may provide novel therapeutic opportunities in HER2-independent, or HER2 inhibition resistant breast cancer
- Directed Complementation platform provides a unique opportunity to examine genetic context of drug-response *in vivo*

16. Acknowledgements

Contributions from the following groups:

- Model Development
- Genetic Screens
- Bioinformatics
- Target Validation/Biology
- Human Response Prediction
- Antibody Discovery/Development