# Identification of Targets for Delayed Mammary Tumor Onset and Aggressiveness Using Diversity Outbred Mice Expressing the Delta 16 Variant of HER2/neu

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Our research aims to identify genetic regulators of breast cancer oncogenes using diversity outbred (DO) mice. We previously established a filtering process to identify genes driving aggressive, early-onset tumors in HER2/neu-expressing NeuT mice (Jacob et al., 2023). This process includes identifying founding strain-specific gene variants, survival analysis in human breast cancer patients, and identifying actionable targets using single-cell RNA sequencing (scRNA-Seq) and cellular expression.

In our current study, DO mice were crossed with FVB d16HER2 mice, which carry the human HER2 Delta 16 mutation and develop spontaneous mammary tumors with 100% penetrance, beginning at ~20 weeks. NeuT mice on the DO background (BALBxDO) F1 NeuT developed earlier, more aggressive tumors, while (FVBxDO) F1 d16HER2 mice showed delayed onset. We monitored tumor onset, days to reach 500mm³, and growth rate. Through r/qtl2 analysis, we identified quantitative trait loci (QTL) in four regions associated with tumor onset, twelve with tumor growth, and four with growth rate.

We are now using the EMBL Strain Table and the Jackson Founder Variant Database to identify candidate genes contributing to the reduced aggressiveness of tumors in (FVBxDO) F1 d16HER2 mice. scRNA-Seq data from d16HER2 tumors and adjacent tissues are helping us correlate candidate gene expression with cells in the microenvironment and identify actionable targets for tumor inhibition. One promising target is NKG7, a gene essential for cytotoxic degranulation and expressed on NK cells and activated CD8+ cytotoxic T cells. NKG7-expressing cells are found in both mammary tumors and adjacent mammary tissue in FVB d16HER2 mice.