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BMS

Judging Dept.

**Cheryl Eifert**

Student

BMS

2

Doug Conklin

Dept or Program Years in program

Mentor

## **A Genomic Analysis of Tyrosine Kinases in Breast Cell Tumorigenesis**

Author (s)

**Cheryl Eifert, Doug Conklin**

Tyrosine kinases are considered to be highly promising potential drug targets. Receptor protein tyrosine kinases (RPTKs) transmit extracellular signals across the plasma membrane to cytosolic proteins, stimulating the formation of complexes that regulate key cellular functions. The 90 known tyrosine kinases catalyze the transfer of a phosphate group from a molecule of ATP to tyrosine residues on polypeptides. Over half have been implicated in human cancers. The promise of targeted tyrosine kinase cancer therapies was first realized with the success of treating chronic myeloid leukemia (CML), caused by the BCR-ABL TK fusion protein, with imatinib mesylate. Herceptin, an antibody specifically targeting the Erb-B2 protein in Erb-B2 positive, metastatic breast cancers was soon seen as another, at least partial, success. The necessity for understanding the molecular pathways responsible for individual cancers was highlighted, however, by the disappointments of other targeted tyrosine kinase therapies, including using imatinib mesylate to treat gastrointestinal stromal tumors (GISTS), and using either gefitinib or erlotinib to treat non-small-cell lung cancers caused by EGFR mutations. We have begun a large-scale loss-of-function analysis of the tyrosine kinases, using RNA interference, in the clinically relevant Erb-B2 positive, breast cancer cell line (BT474) in order to gain insight into the tyrosine kinases that contribute to breast cancer related cellular mechanisms. Preliminary data suggests that the cytosolic non-receptor tyrosine kinase Bruton's tyrosine kinase (BTK) participates in the maintenance of BT474 breast cancer cells. In future studies we intend to further explore several aspects of BTK-related cancer cell phenotypes.