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A Genomic Analysis of Tyrosine Kinases in Breast Cell Tumorigenesis

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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. Over half of the 90 tyrosine kinases 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. 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) may participate in the maintenance of BT474 breast cancer cells. Results of a rapid amplification of cDNA ends (RACE) experiment indicate that an N-terminally elongated form of the BTK protein may be expressed in BT474 breast cancer cells. In future studies we intend to examine the effect of this protein on normal, epithelial breast cells as well as to document its presence or absence in both normal and carcinogenic breast cancer cells.