The Molecular and Cellular Biology of HER2/neu Gene Amplification/Overexpression and the Clinical Development of Herceptin (Trastuzumab) Therapy for Breast Cancer

Mark D. Pegram, M.D.
Adjunct Assistant Professor of Medicine
Division of Hematology Oncology
UCLA School of Medicine

Gottfried Konecny, M.D.
Post-Graduate Research Fellow
Division of Hematology Oncology
UCLA School of Medicine

Dennis J. Slamon, M.D.
Professor and Chief
Division of Hematology Oncology
UCLA School of Medicine
INTRODUCTION

Proto oncogenes represent a family of genes which when activated have been shown to play a role in the pathogenesis of a number of malignancies in vertebrate species including humans.$^{1,2}$ In physiologic states these same genes are known to play a role in the normal cell growth control and differentiation. The HER2/neu gene is a member of the Type I receptor tyrosine kinase (RTK) group which is one of the subfamilies in the proto oncogene family and encodes a 185kD surface membrane receptor protein. This gene has been localized to chromosome 17q21,$^1$ and the encoded protein is expressed in a wide variety of tissues including the skin, oral mucosa, breast, ovary, endometrium, lung, liver, pancreas, small and large bowel, kidney, bladder and the central nervous system as well as some connective tissues.$^{4-5}$ The exact physiological role of the HER2/neu protein in these tissues is not completely understood, but like other proto oncogenes it is believed to play an important signaling role in cellular proliferation and differentiation processes. Current data suggests that it forms hetero-dimers with other members of the RTKI family (such as HER 1, HER3 and HER4 in response to various ligands known as heregulins.$^6$-8$^8$ Activation of HER2/neu results in an increase its kinase activity which in turn initiates signal transduction resulting in either cellular proliferation and/or differentiation, depending on the ligand as well as the conditions.$^9$-14$^1$ In human breast cancers, a non-inherited alteration occurs in this gene in 25-30% of cases. This alteration is gene amplification resulting in as many as 50 to 100 gene copies per cell rather than the normal two copies of the gene per cell (one on each chromosome 17).$^{15}$-17$^{17}$ This amplification event results in overexpression of p185$^{HER2/neu}$ at both the transcript and protein levels, such that there can be as many as $\sim$2,000,000 HER2/neu molecules per cell in malignant tissues, instead of the normal $\sim$20,000 - 50,000 molecules per cell. Again this alteration is the result of a somatic (non-inherited) event occurring sometime during the life of the patient for reasons that are still unclear. When the HER2/neu gene is overexpressed at these abnormally high levels, however, its kinase activity is similarly increased, possibly due to autoactivation caused by crowding of adjacent HER2/neu receptor molecules within the cell membrane.$^9$ The net result appears to be ligand-independent activation of p185$^{HER2/neu}$ resulting in an increase in mitogenic cell signaling increased cell proliferation. There is now substantial published data demonstrating that this molecular alteration is associated with a poor clinical prognosis in early stage breast cancer in terms of a shortened disease free interval, as well as shortened overall survival.$^{15,16}$ Initially this finding was controversial with many published studies failing to