

# Keys to Unlock Cancer: Targeted Therapy

Carol S. Viele, RN, MS

2005 Oncology Nursing Society/Schering-Plough Oncology/Biotech Clinical Lectureship

For decades, perhaps even centuries, researchers have searched for a cure for cancer. The effort has taken many approaches, from surgery to cytotoxic or cytostatic chemotherapy to radiation therapy to agents that alter the cellular microenvironment to preventive measures, such as nutrition, screening, and medications. The ultimate goal of each intervention has been to specifically affect the malignant cells, leaving normal cells intact. Unfortunately, this simple concept has been difficult to implement. The problem has been two-fold: first, identifying a unique property of malignant cells (target) and second, developing an agent that interacts solely with that property. Agents developed to interact with such targets are called targeted therapy. Epidermal growth factor receptors (EGFRs) and vascular endothelial growth factor (VEGF) are two such targets.

A targeted therapy approach to the treatment of disease is not exclusive to cancer and has been used successfully in other disease processes. The science of targeted therapy in cancer has taken years to evolve, beginning with the pioneering work by Folkman that elucidated the role of angiogenesis in cancer to the discovery of a molecular marker, such as the Philadelphia chromosome in chronic myelogenous leukemia, to signal transduction research, which showed the importance of the human EGFR family in the growth and proliferation of malignancies. The journey has been long and arduous and is far from complete.

This article focuses on the function of the human EGFR family and VEGF-mediated angiogenesis and their role in therapeutic options for control of tumor growth.

## Epidermal Growth Factor Receptors

The human EGFR family consists of four transmembrane receptors: EGFR (HER1/*erb* B-1), HER2 (*erb* B-2/*neu*), HER3 (*erb* B-3), and HER4 (*erb* B-4) (Yarden, 2001), as seen in Figure 1. The receptors are composed of three main structural domains: an extracellular region, a transmembrane segment, and a cytoplasmic portion (Hong & Ullrich, 2000). The extracellular domain acts to bind the different epidermal growth factor (EGF) ligands and is made up of two cysteine-rich domains (Hong & Ullrich). The transmembrane structure is a lipophilic region that anchors the receptor to the cell membrane. The intracellular portion of the receptor contains a tyrosine kinase domain and docking sites for additional kinase substrates (Hong & Ullrich). EGFs and their transmembrane receptor kinases play important cellular roles in normal and malignant cells, including cellular proliferation, survival, migration, and differentiation (Yarden). EGFR tyrosine kinase (EGFR-TK) is responsible for activating multiple downstream

signaling pathways and has been shown through clinical trials to govern several aspects of tumor growth.

Wells (1999) was one of a number of authors to identify the seven genetically distinct ligands capable of binding with the EGFR. A ligand is a molecule, such as an antibody, hormone, or drug, that binds to a receptor. The seven distinct ligands are EGF, transforming growth factor alpha, heparin-binding EGF, amphiregulin, betacellulin, epiregulin, and neuregulin G2beta. The ligands, when bound to the extracellular receptor, can trigger *erb* B receptor aggregation or the formation of receptor heterodimers or homodimers and internalization (Yarden, 2001).

EGFR signal transduction occurs in normal and abnormal cells and is the result of a receptor being bound by a ligand. In normal cells, it is a multistage process. A ligand binds to the extracellular domain, inducing the receptor to dimerize (Hong & Ullrich, 2000). Dimerization that occurs between two molecules of the same receptor is known as homodimerization; between two molecules of different EGFRs, it is referred to as heterodimerization (Hong & Ullrich). Once dimerization occurs, the "circuit" is complete and the signal relayed.

EGFRs are widely expressed by many cell types, including those of epithelial and mesenchymal origin (Wells, 1999). Their biologic effects range from mitogenesis to apoptosis and migration to differentiation to dedifferentiation, even in the same cell, depending on the signaling pathway activated (Wells).

EGFRs are overexpressed on malignant cells and can stimulate tumor growth through the promotion of proliferation, angiogenesis, invasion, metastasis, and inhibition of apoptosis. Significant variation in overexpression and downregulation (or underexpression) has been identified in a number of malignancies.

EGFR expression has been reported to be downregulated in 33%–50% of human epithelial tumors (Harari, 2004; Mendelsohn, 2001). The variation may be a result of the



*Carol S. Viele, RN, MS, is a clinical nurse specialist in hematology oncology bone marrow transplant at the University of California, San Francisco Medical Center. As the recipient of the 2005 Oncology Nursing Society (ONS)/Schering-Plough Oncology/Biotech Clinical Lectureship, Viele presented this article at the ONS 30th Annual Congress in Orlando, FL. (Mention of specific products and opinions related to those products do not indicate or imply endorsement by the Oncology Nursing Forum or the Oncology Nursing Society.)*

Digital Object Identifier: 10.1188/05.ONF.935-940