EGFR and HER2 in Metastatic Lung and Breast Cancer

Technical Bulletin

Targets for Personalized Cancer Therapeutics

Source: Eric Yao, MSc. Research Assistant; Allan Mah, PhD. Product Manager - SignalChem

Members of the HER/ErbB family of receptor tyrosine kinases (RTKs) play essential roles in the normal cellular functions of cell proliferation, differentiation, motility and apoptosis. This protein family consists of four members: EGFR/ErbB1, HER2/ErbB2, HER3/ErbB3 and HER4/ErbB4. When stimulated, members of HER RTK family modulate the downstream activity of several different signal transduction cascades including MAPK/ERK, AKT/PI3K and PLCγ. The dysregulation of HER function can lead to uncontrolled excitation of these (often) oncogenic signaling cascades, causing tumorigenesis and metastasis through enhancing cell survival mechanisms and the promotion of cell proliferation. Not surprisingly, HER2 and EGFR have very well defined roles in the development and progression of breast cancer as well as non-small cell lung cancer (NSCLC), making these protein kinases excellent targets for pharmacological interventions by tyrosine kinase inhibitors (TKIs).

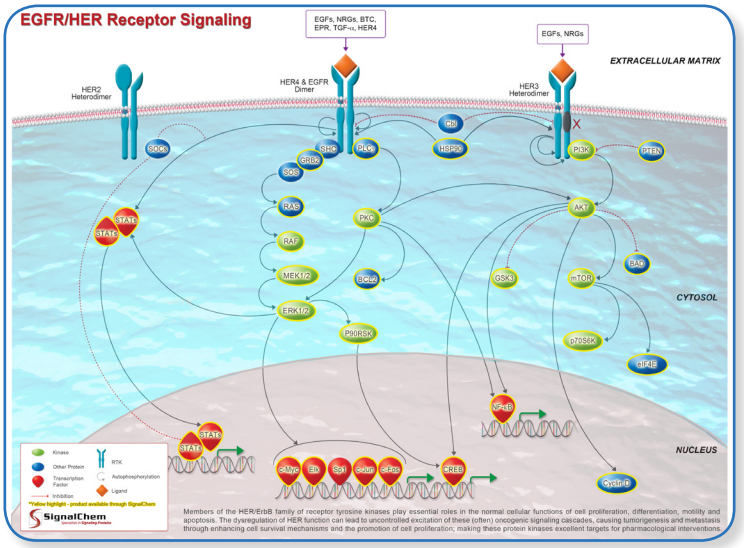


Figure 1: Overactivation of HER/EGFR Receptors Stimulate Pro-Oncogenic Pathways Including: PI3K/AKT, MAPK/ERK, and PLCγ

Breast Cancer

HER2 overexpression is a common diagnostic biomarker for identifying HER2-positive breast cancer, a condition that affects approximately 20% of metastatic breast cancer patients [1]. Unfortunately, HER2-positive breast cancer is associated with aggressive tumor growth and results in poor patient prognoses [2]. So far, drug discovery efforts have yielded a few primary treatment options that directly target the HER2 protein using humanized monoclonal antibodies (mAbs) as a way to manipulate downstream cellular processes.

Trastuzumab (Herceptin, Genentech) was the first HER2-targeted drug approved for clinical use. The mAb binds to HER2's extracellular domain IV, which initiates rapid degradation of the receptor, and consequently a reduction of downstream signaling [3,4]. Pertuzumab (Omnitarg, Abgenix) is able to attenuate downstream signaling through preventing the formation of HER2/HER3 heterodimers [5]. Despite the effectiveness of targeted mAbs for the treatment of HER2-positive breast cancer, their resulting clinical outcomes remain highly variable and patient specific. In addition to the challenges posed by patient heterogeneity, common secondary mutations in the HER2 protein can arise in tumor cells that enable them to evade targeted inhibition, rendering the drugs largely ineffective [6-8; Table 1].

Lung Cancer

NSCLC represents 80% of all lung cancer cases within the United States [9]. Because lung cancer is often diagnosed in later stages of the cancer's progression, the opportunity for surgical resection is limited, providing a need for effective molecular interventions to treat the disease.

The EGFR protein is overexpressed in nearly half of all NSCLC patients, while mutated variants of EGFR are identified in roughly one-fifth of lung adenocarcinomas [10]. Because of its key role in oncogenesis, EGFR is a widely studied target for TKI development. The TKIs gefitinib (Iressa, AstraZeneca), erlotinib (Tarceva, Genentech) and afatinib (Gilotrif, Boehringer Ingelheim) have all been established as first-in-line TKI treatments for NSCLC cases associated with EGFR mutations [11; Table 1]. Initial clinical research compared the effectiveness of each of these EGFR-targeted compounds against traditional chemotherapeutic approaches: Results from these studies indicated that these TKIs were more effective in prolonging patient lifespan than their chemotherapeutic counterparts [12]. Unfortunately, clinical challenges have arisen from the use of these TKIs after being released for widespread use. Subsequent studies on erlotinib were unable to support its initial clinical findings, prompting the FDA to withdraw the use of the drug after

being available to patients for only two years. Although afatinib is still widely used, the drug has been found to inhibit both wild type and mutant forms of EGFR; this indiscriminant RTK inhibition leads to patient side-effects when afatinib is administered in high-doses [13]. To further complicate the use of TKIs in cancer therapy, secondary mutations often arise that enable EGFR to escape targeted inhibition [14; Table 1].

There are many challenges involved in developing TKIs against the HER family of proteins, however their roles in activating multiple oncogenic signaling pathways will continue to drive the development of drugs that specifically target members of this RTK family. In addition, the ever-present problems associated with acquired drug resistance and patient specificity fuel the need for new inhibitors that selectively target mutant forms of these RTKs.

SignalChem Pharmaceuticals manufactures products to support the development of new cancer therapies through the production of high quality and consistent biological reagents. Along with proteins involved directly with the HER/EGFR pathway, our offerings include a wide range of active wild-type and mutant kinases, cell signaling proteins, enzyme inhibitors, siRNAs, antibodies, growth factors and other active enzymes.

Kinase	Mutation	Mutation Frequency	Disease Relevance
EGFR	T790M	50% of EGFR-mutated tumors with acquired resistance to erlotinib/gefitinib*	Confers acquired resistance to TKIs*
	L858R	40% of EGFR-mutated lung tumors*	Confers increased sensitivity to TKIs*
	Exon 19 Deletions	50% of EGFR-mutated lung tumors*	Confers increased sensitivity to TKIs*
	G719X (G719C, G719D and G719S)	3% of EGFR-mutated lung tumors*	Confers increased sensitivity to TKIs*
	L861Q	2% of EGFR-mutated lung tumors*	Confers increased sensitivity to TKIs*
HER2	Exon 19 Mutations	~70% of HER2-mutated breast tumors; and ~50% of HER2-mutated ovarian surface epithelial tumors[Ŧ]	Potential driver for breast and ovarian cancers[Ŧ]
	Exon 20 Mutations	~20% of HER2-mutated breast tumors; and ~90% of HER2-mutated NSCLC[Ŧ]	Potential driver for breast cancer and NSCLC[Ŧ]
Sources:	** mycancergenome.org* *[Ŧ] ERBB (HER2) Mutation Spectrum in Solid Tumors (Caris Life Sciences)*		

Table 1: Frequency and Relevance of Common EGFR and HER2 Somatic Mutations

References:

1. Kurebayashi J et al., Biological and clinical significance of HER2 overexpression in breast cancer. Breast Cancer. 2001;8(1) 45-51.

2. Jelovac D and Emens LA., HER2-directed therapy for metastatic breast cancer. Oncology (Williston Park). 2013 Mar;27(3):166-75.

3. Zelnak AB and Wisinski KB., Management of patients with HER2-positive metastatic breast cancer: is there an optimal sequence of HER2-directed approaches? Cancer. 2015 Jan 1;121(1):17-24.

4. Vu T1 and Claret FX., Trastuzumab: updated mechanisms of action and resistance in breast cancer. Front Oncol. 2012 Jun 18;2:62. doi: 10.3389/fonc.2012.00062.

5. Adams CW et al., Humanization of a recombinant monoclonal antibody to produce a therapeutic HER dimerization inhibitor, pertuzumab. Cancer Immunol Immunother. 2006 Jun;55(6):717-27.

6. Vu T et al., Personalized drug combinations to overcome trastuzumab resistance in HER2-positive breast cancer. Biochim Biophys Acta. 2014 Dec;1846(2):353-65.

7. Wang SE et al., HER2 kinase domain mutation results in constitutive phosphorylation and activation of HER2 and EGFR and resistance to EGFR tyrosine kinase inhibitors. Cancer Cell. 2006 Jul;10(1):25-38.

8. Fabi A et al., Therapeutic targeting of ERBB2 in breast cancer: understanding resistance in the laboratory and combating it in the clinic. J Mol Med (Berl). 2014 Jul;92(7):681-95. doi: 10.1007/s00109-014-1169-7.

9. Charloux A et al., The increasing incidence of lung adenocarcinoma: reality or artefact? A review of the epidemiology of lung adenocarcinoma. Int J Epidemiol. 1997 Feb;26(1):14-23.

10. Siegelin MD and Borczuk AC, Epidermal growth factor receptor mutations in lung adenocarcinoma. Lab Invest. 2014 Feb;94(2):129-37.

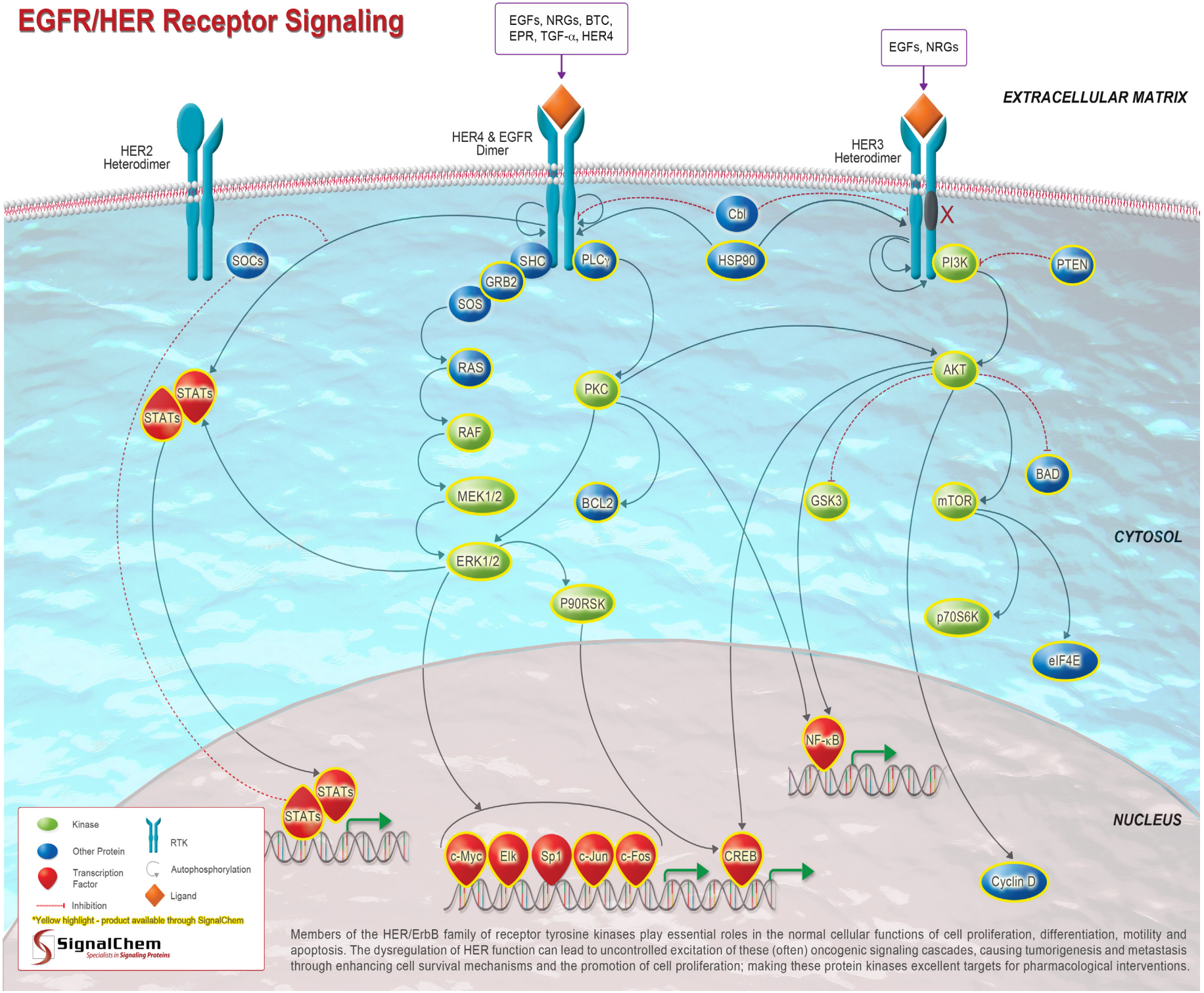
11. Jorge SE et al., Epidermal growth factor receptor (EGFR) mutations in lung cancer: preclinical and clinical data. Braz J Med Biol Res. 2014 Sep 5;0:0.

12. Lampaki S et al., Defining the role of tyrosine kinase inhibitors in early stage non-small cell lung cancer. J Cancer. 2015 May 7;6(6):568-74. doi: 10.7150/jca.11893.

13. Juchum M et al., Fighting cancer drug resistance: Opportunities and challenges for mutation-specific EGFR inhibitors. Drug Resist Updat. 2015 May 12. pii: S1368-7646(15)00023-0. doi: 10.1016/j.drup.2015.05.002.

14. Nguyen KS et al., Acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancers dependent on the epidermal growth factor receptor pathway. Clin Lung Cancer. 2009 Jul;10(4):281-9. doi: 10.3816/CLC.2009.n.039.

EGFR/HER Receptor Signaling



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