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From the editor

The epidermal growth factor receptor (EGFR) has been viewed as a target for anticancer therapy since its discovery in 1980. The first monoclonal antibody capable of blocking EGFR activity was reported by John Mendelsohn in 1983. Twenty-one years later, the FDA approved the G225 antibody, cetuximab, for use in clinical oncology, specifically, colorectal cancer.

For some, this was a long-awaited development. For those viewing progress in cancer therapy as incremental, this marked the addition of yet another agent to the anticancer armamentarium. For those who had expected a major impact from inhibiting the often-overexpressed receptor, however, the results were disappointing. The FDA noted a tumor growth delay of 1.5 months. Similarly disappointing results were being observed as EGFR tyrosine kinase inhibitors were brought to the market. Erlotinib extended survival in lung cancer by 2 months.

This might have been the scope of clinical benefit had translational research not caught up with clinical oncology. Mutations were observed in the ATP-binding domains of the EGFR in the lung cancers of a subset of patients who had experienced dramatic responses to the tyrosine kinase inhibitors. Soon, there was a new paradigm: EGFR inhibition was successful only in cancers in which an activating mutation, presumed etiologic in the malignancy itself, was observed. Substantial amounts of ink and paper have now been expended in articles about the characteristic EGFR mutations in lung cancer.

This issue of *CCR Focus* "EGFR Activation: Mutations, Misregulation, and More" examines that seminal observation in the Focus overview, written by Rosell et al., and in an update by Riely et al., as a starting point before exploring EGFR as a target in cancers where ATP-binding domain mutations have not been found. Drs. Ono and Kuwano examine molecular mechanisms of EGFR activation, including the impact of dimerization partners and downstream mediators. Brandt et al., explain a novel mechanism of EGFR overexpression that may confer physiologic sensitivity to EGFR inhibitors. Nicholas et al., explore mutations that are outside the ATP-binding domain and frequently observed in glioblastoma. A greater understanding of these alternative mechanisms is now needed to develop therapies that will be effective against cancers exploiting them. *CCR Focus* offers these reviews to educate the interested non-expert and stimulate interest and encouragement and inspiration for those laboring in the field.

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Clinical Cancer Research

From the Editor

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