

Researchers first linked the epidermal growth factor receptor (EGFR) to cancer in the 1980s. The signal transduction pathways through which this receptor tyrosine kinase activates cancer are understood well enough that targeted therapies are in use to thwart it, including antibodies such as cetuximab and kinase inhibitors such as erlotinib and gefitinib. But despite this long and steady accumulation of knowledge, many aspects of EGFR remain enigmatic.

One of the protein's most tenacious explorers is Kathryn M. Ferguson, PhD, Associate Professor of Pharmacology and a faculty member of Yale's Cancer Biology Institute. She has unlocked many of EGFR's doors only to find more locked gates behind them.

"What has sustained our interest in this protein over the years," she says, "is that we fundamentally want to understand how it works – how it transfers messages across the cell membrane – and we still don't. Even with all the studies that have been done, we still have a lot to learn about how it's activated by its different ligands, how the signal is turned on and off, and how the receptor is aberrantly activated in cancer. And since EGFR is implicated in a large number of cancers—breast cancer, lung cancer, head and neck cancer, colorectal cancer, glioblastoma—it's clearly very important from a clinical perspective."

About a decade ago, Dr. Ferguson and Mark Lemmon, PhD, FRS, David A. Sackler Professor of Pharmacology and Co-Director of the Cancer Biology Institute, solved the

X-ray crystal structure of the extracellular region of EGFR. That breakthrough revealed that EGFR does not simply sit down and wait for the ligand to activate it, but rather is constantly altered by conformational changes. EGFR is a shape-shifter, flexible and adjustable, and far more complex than previously realized.

"That has really colored the way we think about the receptor," explains Dr. Ferguson. "The molecule's flexibility changes the way we need to think about how it is activated and what we need to do to inhibit it in cancer patients." Dr. Ferguson intends to investigate this in glioblastoma, in which poorly understood activating mutations in the EGFR extracellular domain have been described. Her hypothesis is that these mutations alter the protein's conformational flexibility, and that this is responsible for activation. To test this hypothesis she needs to move beyond the extracellular region where most of her research has been focused and find a way to open another locked door.

"We are now generating the whole receptor for structural studies," she says, "not just the extracellular region but also the parts that go across the membrane and act inside the cell – so that we can begin to understand how conformational changes and mutations in the extracellular region influence the receptor's activity inside the cell." Truly deciphering the mechanism of transmembrane communication would open possibilities for approaches, and new kinds of antibodies that might limit the ability of the receptor to switch to an activated conformation.

EGFR's frequent conformational changes might also explain why some cancers become resistant to the effects of cetuximab, a widely used antibody that blocks EGFR function in head and neck, colorectal, and other cancers. Alterations in EGFR emerge in cetuximab-treated cancers that appear to hinder the ability of the antibody drug to bind EGFR, rendering the treatment ineffective. The mechanism behind this resistance is another door that Dr. Ferguson hopes to pry open.

"We think that fully understanding EGFR will lead to more information that can be applied rationally in the clinic," she says, "both for better uses of the treatments that already exist and for developing better ways of 'silencing' cancer-causing mutations."

She is also studying other receptor tyrosine kinases related to EGFR, in particular one called TIE2. Like EGFR, it is proving far more complex than previously expected.

Since coming to Yale a year ago from the University of Pennsylvania, Dr. Ferguson has established a new lab in the Advanced Biosciences Center on Yale's West Campus. "One of the most exciting things about being here is the Cancer Center's strength in signal transduction," she says, "and also the feeling that basic science done at Yale really impacts clinical work and approaches to patient treatment. This unique strength of Yale opens up opportunities for collaborations with other basic and clinical scientists doing clinical trials right here on the molecules we're interested in."



Kathryn Ferguson, PhD

Unlocking the Secrets of EGFR