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Detailed Local Models of Signaling Pathways

The Impact of a Detailed Mechanistic Model of a Complex Signaling Pathway on Drug Discovery and Development

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Abstract:

The advent of therapy targeted at the molecular mechanisms driving tumour growth has obviated a need for a detailed understanding of cell signalling. Using genetics, genomics and biochemistry, many of the pathways involved in these processes have been studied in detail and their parts described.

These approaches have been used for target selection and validation in drug discovery with some success. Gefitinib (Iressa), is the primary example of this new class of inhibitors. This EGFR Tyrosine Kinase inhibitor has proven effective in a lung cancer setting. Even with many dramatic responses, a number of patients do not respond.

In order to understand why certain tumours do not respond to Gefitinib therapy, we partnered with Doug Lauffenburger at MIT and have developed a mathematical model of EGFR and related ErbB signalling down to two important clinical markers for outcome, ERK and AKT. In a tight collaboration with the Lauffenburger laboratory, we have trained and validated this model in a cell line setting.

Using this model, we are able to generate detailed hypotheses with regards to the role of other ErbB receptors in Gefitinib response, as well as generating understanding with regards to the mode of action of other ErbB targeted therapies. This allows us to make rational choices for co-treatment with other agents in clinical settings.