# Understanding IGF signaling dynamics through computational modeling

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***Short Abstract* — By developing an experimentally-validated, mechanistic model of the IGF signaling pathway (including the PI3K and MAPK cascades) we show that understanding subtle differences in network dynamics is crucial for predicting the unintended or counter-productive effects of targeted inhibitors.**

***Keywords* — IGF pathway, computational modeling, drug discovery**

## I. Introduction

Intuition based on static protein interactions is limited when signaling networks contain multiple feedback and crosstalk loops [1-5], as in the Insulin-like growth factor-1 (IGF-1) receptor pathway. Mechanistic modeling enables for examination of the role and importance of dynamic protein interactions and provides a foundation for developing targeted therapeutics [6].

The IGF-1 receptor pathway is known to play an important role in breast cancer. Stimulation of the IGF-1 receptor results in activation of multiple pathways that generate survival and proliferation cues, such as the ERK and AKT pathways. Given the known role of IGF-1 in cancer, we have taken a quantitative approach to understanding the receptor signaling pathways at the molecular level.

## II. Experimental Design

An ordinary differential equation based model of the signaling events post IGF-1 stimulation was built using quantitative experimental data obtained from IGF-1 stimulated MCF-7 cells. To challenge the model we generated experimental and simulated dose-response and time-dependent behavior of p-ERK and p-AKT in the presence of inhibitors targeting different positions within the IGF pathway, including inhibitors that disrupt feedback and crosstalk mechanisms.

Using this model, we confirm through experiments the prediction that inhibiting AKT has a counter-productive effect on ERK activity. The model also correctly predicts enhanced AKT activity in the presence of an mTOR inhibitor as demonstrated experimentally by O'Reilly et al. [7].

## III. Conclusions

In summary, we show that understanding subtle differences in network dynamics is crucial for predicting the unintended or counter-productive effects of targeted inhibitors. In addition, target optimization can be performed *in silico* to examine these effects prior to inhibitor design.

## IV. References

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