Computational modeling and simulation lead to the development of MM-121, a human monoclonal antibody ErbB3 antagonist

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***Short Abstract* — Merrimack Pharmaceuticals is using quantitative biochemical network models to guide the development of oncology therapeutics. By analyzing an ErbB receptor network signaling model, we found ErbB3 to be an ultra-sensitive point for network inhibition. This insight led to the development of MM-121, a monoclonal antibody antagonist of ErbB3. An *in silico* version of MM-121 was used to predict inhibition of signaling in response to MM-121 in multiple cell lines; these predictions were further validated using multiple xenograft models.**

***Keywords* — ErbB network, ErbB3, sensitivity analysis, drug discovery, monoclonal antibody, betacellulin, heregulin**

I. Purpose

THE epidermal growth factor receptor and ErbB2 have been heavily targeted by therapeutic agents, with some success. Understanding the relative importance of the ErbB receptors for inducing activation of downstream signaling cascades is complicated for a number of reasons: the ErbB receptors homo and heterodimerize to become activated, are expressed to differing degrees in different cancer types, and undergo ligand-specific trafficking. Hence, we have taken a systems approach to the problem and developed a computational model of the ErbB signaling network for the purpose of developing more efficacious ErbB targeted therapeutics.

II. Methods

Sensitivity analysis was performed on the system to determine the key proteins in the network for activating pAkt over a diverse range of heterogeneous ErbB receptor profiles. ErbB3 was found to be an ultra-sensitive inhibition point in response to either Betacellulin or Heregulin. This prediction was verified by developing and testing a novel anti-ErbB3 antibody, MM121, in cell based assays. MM-121 was also found to be more effective at inhibiting Heregulin-induced pErbB3 and pAkt than other therapeutic agents targeting the ErbB pathway, further supporting the findings.

The kinetic parameters of MM-121 were also used to build an *in silico* version of the inhibitor. The model was then used to predict the IC50 values of pAkt and pErbB3 in response to MM121 in a number of cell lines stimulated with Heregulin or Betacellulin, and the predictions experimentally verified. These in vitro findings were further validated in vivo using multiple xenograft models.

III. Conclusions

In summary, we describe (1) how a systems approach to drug discovery has suggested a potentially better mechanism of inhibiting the ErbB pathway, and (2) the ability of our computational model to accurately simulate the effect of an anti-ErbB3 monoclonal antibody on signaling in a variety of cancer cell types.

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