Effective In Vitro/In Vivo Translation of Synergistic Combination Cancer Therapy Using a Systemic Modeling Approach
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Purpose
Failure of identifying optimal dosing regimens is often responsible for failed or inconclusive clinical evaluation of combination cancer therapy, and selecting synergistic combination doses remains a great challenge. Well-designed preclinical drug combination studies can significantly contribute to successful clinical trials. This study aims to develop a systemic approach for effective in vitro-in vivo translation by the combined efforts of experimental data and computational modeling.

Methods
Erlotinib and drug B against erlotinib-resistant NSCLC (H441) was used as a proof-of-concept drug combination for this study. We developed an in vitro-in vivo preclinical PK/PD model for combination therapy that delineated the response surface and nature of combined-drug effects through an interaction parameter ($\psi$), pharmacokinetics, and tumor progression to predict optimal in vivo combination doses.

Results
In vitro anti-proliferative effects of the drugs were fitted to 3-dimensional response surface model and suggested to be synergistic ($\psi < 1$). Erlotinib PK in tumor-bearing mice was described using a two-compartment model and drug B PK was simulated. Plasma-to-tumor distribution ratio was 0.60 for erlotinib and 0.36 for drug B and tumor drug concentrations were used as a driving force for the observed inhibitory effects on tumor growth in vivo. The tumor progression in non-treated mice was depicted by early-exponential and late-linear growth. In treated mice, the combined inhibitory effect was described as a function of the tumor drug concentrations and the interaction parameter $\psi$.

Conclusion
The present study lays out the strategy and tactics for translating in vitro into in vivo synergy. The developed approach can be used to better design preclinical experiments in xenograft model after in vitro combination studies, and to select the most advantageous in vivo combination doses and schedules for maximal synergy, thereby facilitating early anti-cancer drug development.