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Forum

Clinical Success of Drug Targets Prospectively Predicted by *In Silico* Study

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The selection of the right drug targets is critically important for the successful and cost-effective development and clinical testing of drugs. A 2009 paper reported an *in silico* prospective prediction of the clinical potential of 156 targets of clinical trial drugs (all of these targets were without an approved drug at the time of the paper's publication). Eight years later, the assessment of the clinical status of these targets revealed impressive capability of the *in silico* method in prospectively predicting the clinical success of drug targets.

The selection of a good target is critical for the successful discovery and clinical testing of effective drugs [1]. A 2009 paper [2] reported a prospective prediction of the clinical potential of 31, 84, and 41 targets of drugs in Phase III, II, and I clinical trials, respectively. These 156 targets were all without an approved drug at the time of that study [2]. Based on the *in silico* analysis of their sequence, structural, physicochemical, and human systems profiles, 41 targets have been predicted as clinically promising (likely to yield an approved drug) and the remaining 115 targets as nonpromising (unlikely to yield an approved drug). Eight years later, its target prediction results can be judged by the current clinical status of the 156 targets.

The current clinical status of the targets revealed an impressive performance of the *in silico* method in predicting the clinical success of the Phase III targets (see Figure 1 and Supplemental Table S1 online). Of the 16 Phase III targets predicted as promising, 10 (62.5%) targets have since yielded Food and Drug Administration (FDA)-approved drug, two (12.5%) targets remain in Phase III, and four (25%) targets have been downgraded (1 to Phase II, 1 to Phase I, and 2 discontinued clinical trial). Of the 15 Phase III targets predicted as nonpromising, 12 (80%) targets have been downgraded (3 discontinued clinical trial, 3 to Phase I, and 6 to Phase II), two (13.3%) targets remain in Phase III, and one (6.7%) target (neutral endopeptidase) paired with a pre-existing clinically successful target (angiotensin II receptor) has yielded an FDA-approved drug combination (sacubitril/valsartan) [3]. Neutral endopeptidase has yielded no other approved drug and is currently without a drug in clinical trial. Hence, it remains unclear if neutral endopeptidase can yield an individual drug.

The *in silico* method is intended for predicting the likelihood of a target to yield an approved drug. It may be premature to judge its prediction of the Phase II and Phase I targets that are expected to take longer times to reach drug approval. Nonetheless, some indication about its prediction performance may be revealed on the basis that promising targets more likely and nonpromising targets less likely advance to or remain in the higher trial phases. Of the 22 Phase II targets predicted as promising, the majority (68.2%)

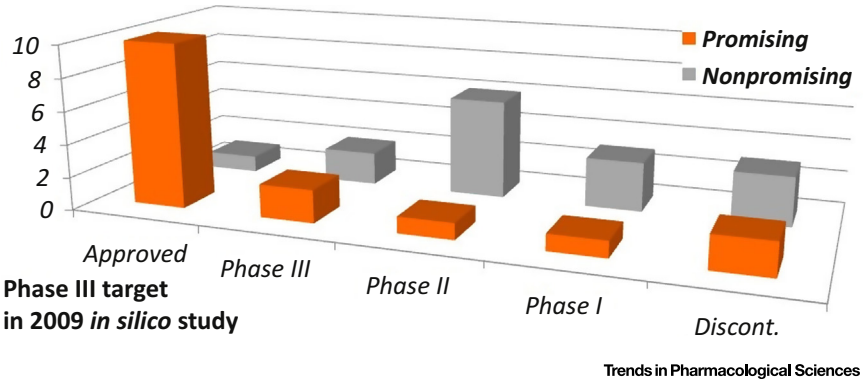

Figure 1. The Prediction Results of 31 Clinical Trial Phase III Targets Analyzed by 2009 *In Silico* Study Were Judged by Their Current Clinical Status. Discont., discontinued.

of them have advanced to a higher phase or remain in the same trial phase. Specifically, two (9.1%) targets have yielded approved drug, seven (31.8%) targets have advanced to Phase III, six targets (27.3%) remain in Phase II, and seven (31.8%) targets have been downgraded (2 to Phase I, 5 discontinued clinical trials). Of the 62 Phase II targets predicted as nonpromising, 35 targets (56.5%) have been downgraded (28 discontinued clinical trial and 7 to Phase I), 21 (33.9%) targets remain in Phase II, five (8.1%) targets have advanced to Phase III, and one (1.6%) target (interleukin-4 receptor α) has yielded an FDA-approved monoclonal antibody (mAb) drug (dupilumab) [4]. The misclassification of interleukin-4 receptor α is likely due to the inadequate representation of the mAb drug targets (15 targets) in training the *in silico* method [2].

Of the three Phase I targets predicted as promising, two (66.7%) targets have advanced to a higher phase (1 to Phase III and 1 to Phase II), and one target has discontinued clinical trial. Of the 37 Phase I targets predicted as nonpromising, 20 (54.1%) targets have discontinued clinical trial, three (8.1%) targets remain in Phase I, ten (27.0%) targets have advanced to Phase II, and four (10.8%) targets have advanced to Phase III. It is noted that a comparable majority of the predicted nonpromising Phase I and Phase II targets have been downgraded (54.1% vs. 63.2%), and a comparably small minority of the predicted nonpromising Phase I and Phase II targets have advanced to Phase III (10.8% vs. 8.1%). These quantitatively comparable levels of the majority and minority targets seem to be the result of a consistent prediction of the nonpromising targets, and the juries are still out to judge these prediction results by the future clinical trial outcomes.

The impressive capability of the *in silico* method in prospectively predicting the clinical potential of the drug targets arises from its integrated analysis of multiple druggability properties [2] reported in the literature including sequence similarity to the pre-existing targets [5], binding-site geometric and energetic features and structural similarity to the pre-existing targets [6], the physicochemical characteristics learnt by the machine learning studies of the pre-existing targets [2], and systems profiles (similarity to human proteins, pathway, and tissue distribution) derived from the analysis of the pre-existing targets [2,7]. Recent studies have indicated the importance of human protein-network topologies in target prediction and validation [7,8]. The gene expression [9] and copy number [10] profiles have been used for mAb target selection. These and other features need be included for improved prediction of the clinical success of drug targets.

Author Contributions

X.X.L. analyzed the data. F.Z. and S.Y.Y. developed the program and software. F.Z. developed the concept and supervised the work. F.Z. and Y.Z.C. prepared the manuscript.

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Disclaimer Statement

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Supplemental Information

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