Personalized Medicine and Drug Discovery in Urological Cancer

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Previous studies have used gene expression models (GEMs) to predict therapeutic response in cancer patients. Such conventionally derived models are developed from a priori knowledge of outcomes and are then validated on independent clinical cohorts. While promising, deriving models this way is expensive, lengthy and available only for a limited number of cancer types and drug combinations. Furthermore, such approaches are unable to use the same biomarkers when new agents are incorporated into established combinations.

We overcome this limitation by developing GEMs based on in vitro drug sensitivities and microarray analyses of the commonly used "NCI-60" cancer cell line panel. The U.S. National Cancer Institute has used this panel of 60 diverse human cancer cell lines to screen >150,000 chemical compounds for anticancer activity. However, not all important cancer types are included on the panel nor are drug responses on the panel predictive of clinical efficacy in patients. We asked, therefore, whether it would be possible to extrapolate from that rich database (or analogous ones from other drug screens) to predict activity in cell types not included or, for that matter, clinical responses in patients with tumors. Recently we have addressed this challenge by developing and applying a novel algorithm we term "Co-eXpression ExtrapolationN" (COXEN). COXEN uses expression microarray data as a "Rosetta Stone" for translating between drug activities in the NCI-60 to drug activities in any other cell panel or set of clinical tumors. In addition, we have adapted this approach to the prediction of radiation response.

We will show that evaluating the COXEN GEM ("score") can accurately predict drug sensitivity of bladder cancer cell lines and clinical responses of bladder cancer patients treated with commonly used chemotherapeutic combinations. Gene expression models for breast, ovarian and colon cancer patients were also well predicted, the latter tumor to EGFR targeted agents. In addition, we developed and validated a radiation response predictor in lung, head and neck and bladder cancer and show that several of the genes in the pathway are druggable and when blocked, results in cancer radiosensitization. Importantly, GEMs effectively stratified tumor response to drug and radiotherapy independently of established clinical and pathologic tumor variables. In total, the COXEN GEM approach was evaluated in >800 patients, of which, 433 patients were in prospectively enrolled in clinical trials.

Finally, we used COXEN for in silico screening of 45,545 compounds and identify C1311 an agent with excellent activity against human bladder cancer and using yeast chemical genetics demonstrate which established bladder cancer chemotherapeutics would form rational drug combinations with C1311 in bladder cancer.

In conclusion, we demonstrate a novel, facile yet powerful approach to GEM derivation that identifies patients most likely to benefit from selected multi-agent therapy. Use of such GEMs, provides a robust and generalizable approach to personalized cancer therapy with far reaching applications in drug discovery, drug salvage and forecasting of novel single and combination drug effectiveness in cancer patients including use of radiotherapy.