

Coupling *in vitro* drug sensitivity data with whole-transcriptome expression profiles allows for prediction of patient specific response to individual drugs.

Robert B. Den¹, **Jonathan Lehrer**², Mohammed Alshalalfa², Nicholas Erho², Elai Davicioni², Karen E. Knudsen¹, W. Kevin Kelly¹, Jean Hoffman-Censits¹, Jianqing Lin¹, Edouard Trabulsi¹, Costas Lallas¹, Leonard G. Gomella¹, Adam P. Dicker¹, Thangavel Chellapagounder¹, Alex Haber¹, R. Jeffery Karnes³, Scott Tomlins⁴, Felix Y. Feng⁵, Edward Schaeffer⁶

1. Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA, USA
2. GenomeDx Biosciences, Vancouver, BC, Canada
3. Department of Urology, Mayo Clinic, Rochester, MN, USA
4. Michigan Center for Translational Pathology, Department of Pathology, Urology, University of Michigan Medical School, Ann Arbor, MI, USA
5. Department of Radiation Oncology, University of Michigan Health System, Ann Arbor, MI, USA.
6. Department of Urology, Northwestern University, Chicago, IL, USA

Background: Multiple drugs improve overall survival in men with advanced prostate cancer, but general predictors of therapeutic sensitivity are lacking. We hypothesized that coupling *in vitro* drug sensitivity data from cell lines with whole-transcriptome expression profiles from those cell lines and from prostate cancer patients would allow for patient-specific drug response prediction.

Methods: Using *in vitro* drug sensitivity and microarray data from the NCI-60 panel, we generated gene signatures predicting patient sensitivity to 89 drugs from prostate cancer clinical trials. Drug Response Scores (DRS) were generated across a retrospective pooled cohort (n=1,135) with known treatment (post-op radiation, hormonal therapy) and outcomes as well as across a prospective cohort (n=2,116) with no long-term follow-up data. Clustering analysis was performed and DRS were further examined in two publicly available datasets with known drug response.

Results: Consensus clustering in both prospective and retrospective cohorts revealed two drug clusters (D1, D2) with 83% of drugs clustering consistently between cohorts. In both cohorts, D1 was enriched with cell cycle inhibition drugs and taxanes (56-60%, $p < 0.05$), whereas D2 was enriched with tyrosine kinase inhibitors (36-38%, $p < 0.05$). DRS predictions for dasatinib sensitivity were validated using publicly available expression data from 16 prostate cancer cell lines with known dasatinib response. Responsive cell lines were found to have significantly higher dasatinib sensitivity scores (AUC=0.89 [0.72, 1]). When DRS predictions for docetaxel sensitivity were applied to publicly available expression data from 24 breast cancer patients with known docetaxel response, the scores trended towards predictive though significance was not attained (AUC=0.71 [0.48, 0.94]), possibly due to the low number of samples available. Consistent with prior findings that Rb-loss induces docetaxel sensitivity, E2F1 (which is inhibited by Rb) expression was positively correlated with docetaxel sensitivity predictions.

Conclusions: Coupling *in vitro* drug response signatures with Decipher assay may enable its evaluation in larger scale datasets to improve decision making around use of systemic agents in high risk prostate cancer patients.

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