**Systems biology approach to predict optimal therapeutic strategies for aggressive prostate cancer**

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**Background:** Recent large-scale genomic analyses of cancer have led to the identification of "actionable" driver genes that represent therapeutically accessible targets, including oncogene and non-oncogene dependencies. However, the accurate and efficient identification of drugs and drug combinations that target such drivers represents a major challenge, particularly for transcriptional regulators, which are generally considered pharmacologically inaccessible for therapeutic targeting. Here we introduce an approach that uses in vivo drug perturbation data from Genetically Engineered Mouse models of aggressive prostate cancer to predict drug efficacy in human patients.

**Methods:** We have developed a novel computational systems approach to analyze gene expression profiles of pharmacological perturbations in mouse models of aggressive prostate cancer and identified drugs and drug combinations that inhibit the transcriptional activity of the key regulatory genes that drive prostate cancer malignancy, namely FOXM1 and CENPF.

**Results:** Validation of our computational predictions in mouse and human prostate cancer experimental essays confirmed the specificity and synergy of a predicted drug combination to abrogate activity of FOXM1 and CENPF and inhibit tumorigenicity. Furthermore, computational analysis of transcriptional regulatory alterations after the drug administration identified treatment-responsive genes, which are potential biomarkers of patient response to the therapy.

**Conclusions:** This approach may allow systematic identification of drugs targeting specific tumor dependencies, and thus might potentially provide direct therapeutic benefits for prostate cancer patients with specific transcriptional dysregulations.

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