Modeling of Drug Synergies in AR-Resistant Prostate Cancer Using a Digital Twin

James Lo, Alex Bermudez, Liam Edwards, Yunqi Hong, Cho-Jui Hsieh, Tanya Stoyanova, Andrew Goldstein, Neil Lin

Affiliations: University of California, Los Angeles

Background
While androgen receptor (AR)-targeted therapies such as enzalutamide and abiraterone extend survival in advanced disease, resistance inevitably emerges. This occurs through AR splice variants, activation of compensatory pathways including PI3K/AKT, NF-κB, and MAPK that bypass AR dependence. Combination strategies can overcome these mechanisms, but identifying rational pairs is difficult given the vast number of possibilities and the context-specific biology of tumors. To address this, we developed a biologically informed AI digital twin that integrates pathway reasoning, drug-response modeling, and experimental validation to systematically prioritize effective combinations and re-sensitization strategies.

Methods
A large-language-model-based framework was trained to reason over curated pathway interactions and generate ranked predictions of drug synergies. Predictions were benchmarked against the DrugComb dataset and validated in 3D 22Rv1 spheroids. A natural product subset was examined for capacity to restore AR inhibitor sensitivity. To enable personalization, we implemented Automatic Context Fitting (ACF), which profiles cells with a 200-drug panel across 12 pathways, adjusts pathway-activity hypotheses until predicted and observed responses converge, and generates a context-specific digital twin. ACF was tested in parental and PTEN-deficient (shPTEN) 22Rv1 cells.

Results
Digital twin predictions showed strong concordance with the large-scale DrugComb dataset (Pearson $r = 0.67$), providing evidence that the framework can capture biologically meaningful drug interactions. Building on this, we tested predictions experimentally in 3D 22Rv1 spheroids, a model of AR-resistant disease. Nearly 20% of predicted drug pairs (28 of 150) demonstrated significant synergy (Bliss > 0.1), representing ~300-fold enrichment compared with unguided discovery rates. Among these validated synergies, a finding was the identification of a natural compound ("Compound A"), which restored enzalutamide sensitivity across three prostate cancer cell lines (22Rv1, VCaP, and MDVR). Mechanistic hypotheses generated by the digital twin suggested that Compound A acts by suppressing NF-κB signaling, disrupting energy homeostasis, and impairing AR nuclear trafficking, providing a rationale for its ability to reverse resistance.
Personalization through ACF further improved the performance and interpretability of the digital twin. Using response fingerprints from a 200-drug panel, ACF increased predictive accuracy from $r = 0.48$ to $r = 0.76$ after three iterations of tuning, with performance maintained at $r \approx 0.7$ on an independent holdout set. In AR-resistant 22Rv1 cells, ACF correctly prioritized NF-κB inhibitors as the most effective re-sensitizing agents while deprioritizing inhibitors of MAPK and angiogenesis pathways, which were predicted to have little impact. In contrast, in PTEN-deficient 22Rv1 cells, the tuned model shifted its prioritization toward PI3K-AKT-mTOR inhibitors.

Conclusions
We demonstrate that a biologically grounded digital twin framework can (i) reproduce synergy signals from large-scale datasets, (ii) enrich for experimentally validated AR re-sensitizing combinations, and (iii) generate mechanistic hypotheses explaining resistance reversal. ACF enables personalization, uncovering both tumor-specific and lesion-specific vulnerabilities.

Funding Acknowledgements
PCF Young Investigator Awards 2022, NIH NIGMS 5R35GM146735

Conflicts of Interest Disclosure Statement
The authors declare no conflicts of interest