

Novel mixed-cancer cell models designed to capture inter-patient tumor heterogeneity for accurate evaluation of drug combinations

Sampreeti Jena, Daniel Kim, Adam M. Lee, Weijie Zhang, Kevin Zhan, Yingming Li, Dr. Scott M. Dehm, and Dr. R. Stephanie Huang
Department of Experimental and Clinical Pharmacology, University of Minnesota, Minneapolis, MN



Introduction

Prostate cancer (PC), especially castration resistant PC (CRPC), is known to exhibit a high degree of heterogeneity. Inter-patient diversity in large clinical cohorts gives rise to large-scale variability in therapy response. Yet, preclinical drug screening is typically performed on individual cell lines or specimens derived from 1-2 patients without consideration of cohort-level heterogeneity. This lacuna has in part caused the high failure rate when preclinical drug leads are translated into the clinic.

Aims & Methods

Transcriptomic profiles of PC lines were integrated with CRPC clinical specimens to select cell-lines representing distinct patient tumor subtypes. A mixed cell model was created by co-culturing rationally selected PC cell-lines to depict the heterogenous molecular landscape of CRPC patient tumors. To demonstrate the functional accuracy of the model, drug combinations clinically validated in PC cohorts were evaluated. Additionally, novel drug combinations with docetaxel, the current Standard of Care, were computationally nominated and preclinically validated in the model.

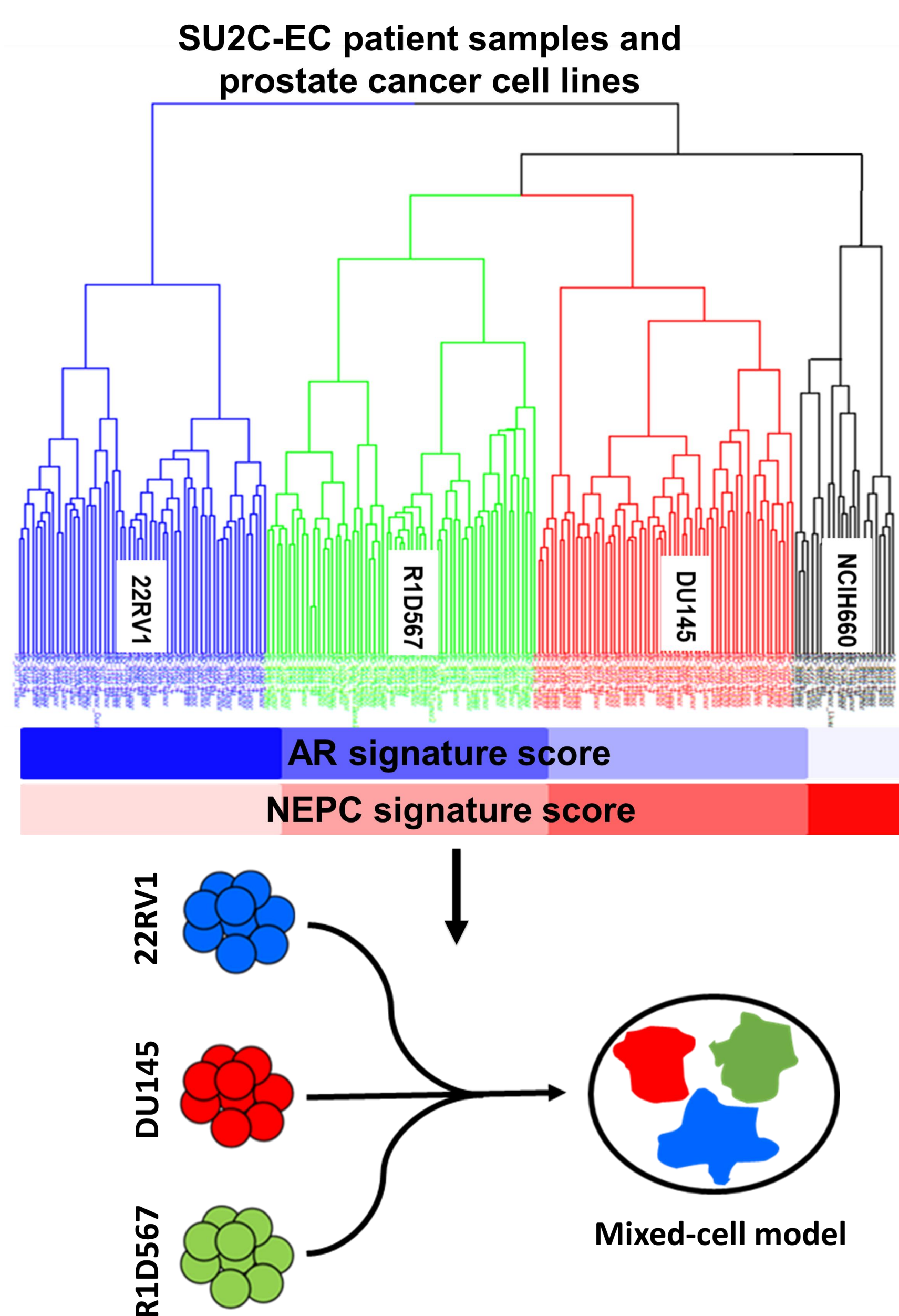


Figure 1: A set of systematically selected prostate cancer cell lines representative of distinct tumor subtypes in a large CRPC cohort, may capture the full scope of genetic and phenotypic diversity exhibited in the patient samples.

Results

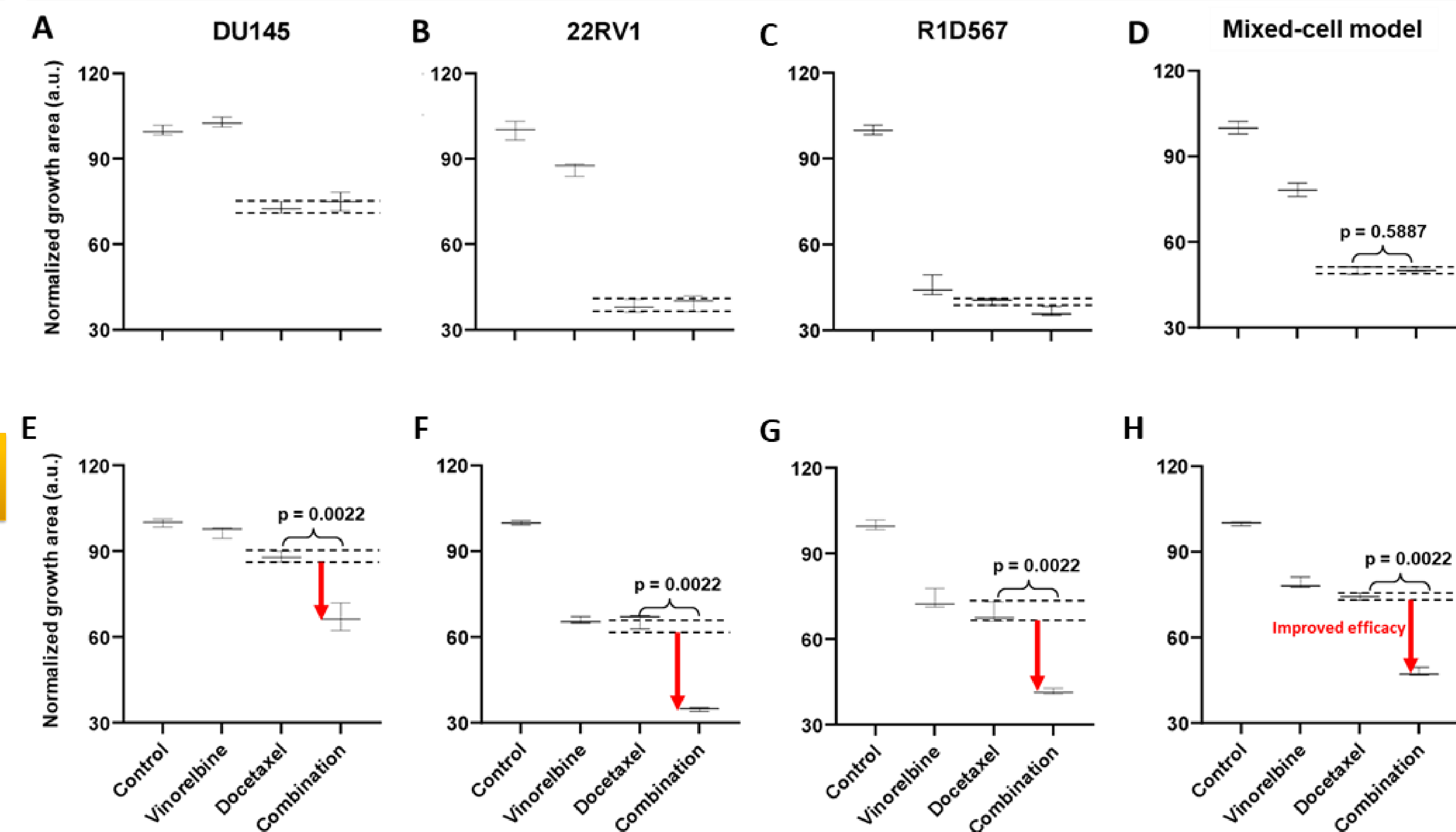


Figure 2: Functional validation of mixed-cell model depicting inter-patient heterogeneity, by testing clinically validated drug combinations. (A-D) The models were treated with dasatinib, docetaxel, their combination, or the vehicle control. (E-H) The models were treated with vinorelbine, docetaxel, their combination, or the vehicle control. Normalized growth areas of each component cell line (A-C and E-G) were measured and totaled to determine proliferation of the tumor mixture (D and H), after 5 days of drug exposure. Black dashed lines outline the effects of the most efficacious monotherapy. Significance was assessed using the Mann-Whitney U test.

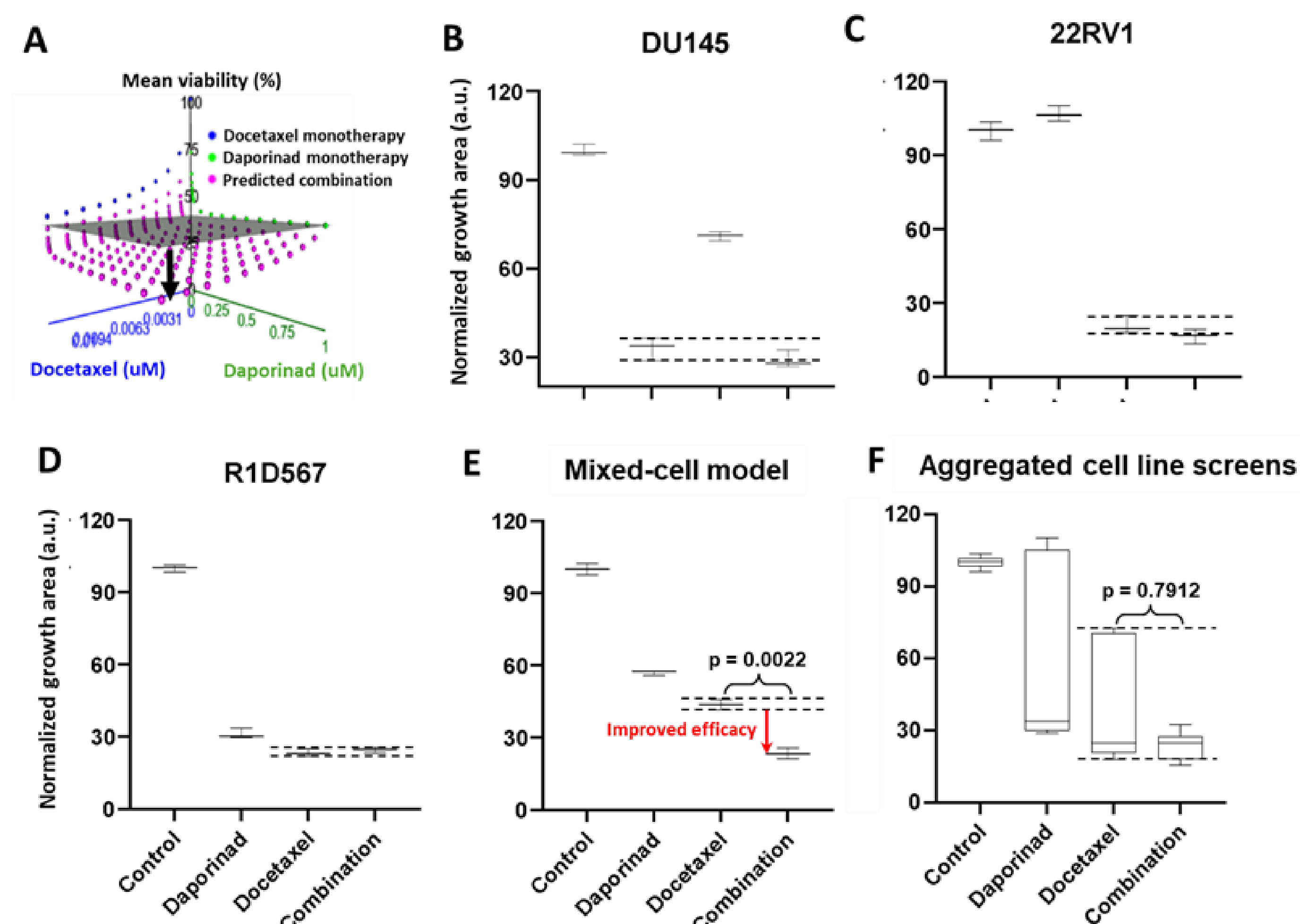


Figure 3: Computational discovery and preclinical validation of novel efficacious drug combinations. (A) IDACombo prediction of docetaxel and daporinad combination efficacy using monotherapy responses of 887 cancer cell lines from CTRPv2. Mixed-cell models depicting inter-patient heterogeneity, were treated with daporinad, docetaxel, their combination or the vehicle control. Measured proliferation values across all component cell-lines were aggregated for each treatment condition to mimic common pharmacological practice (F).

Results Continued

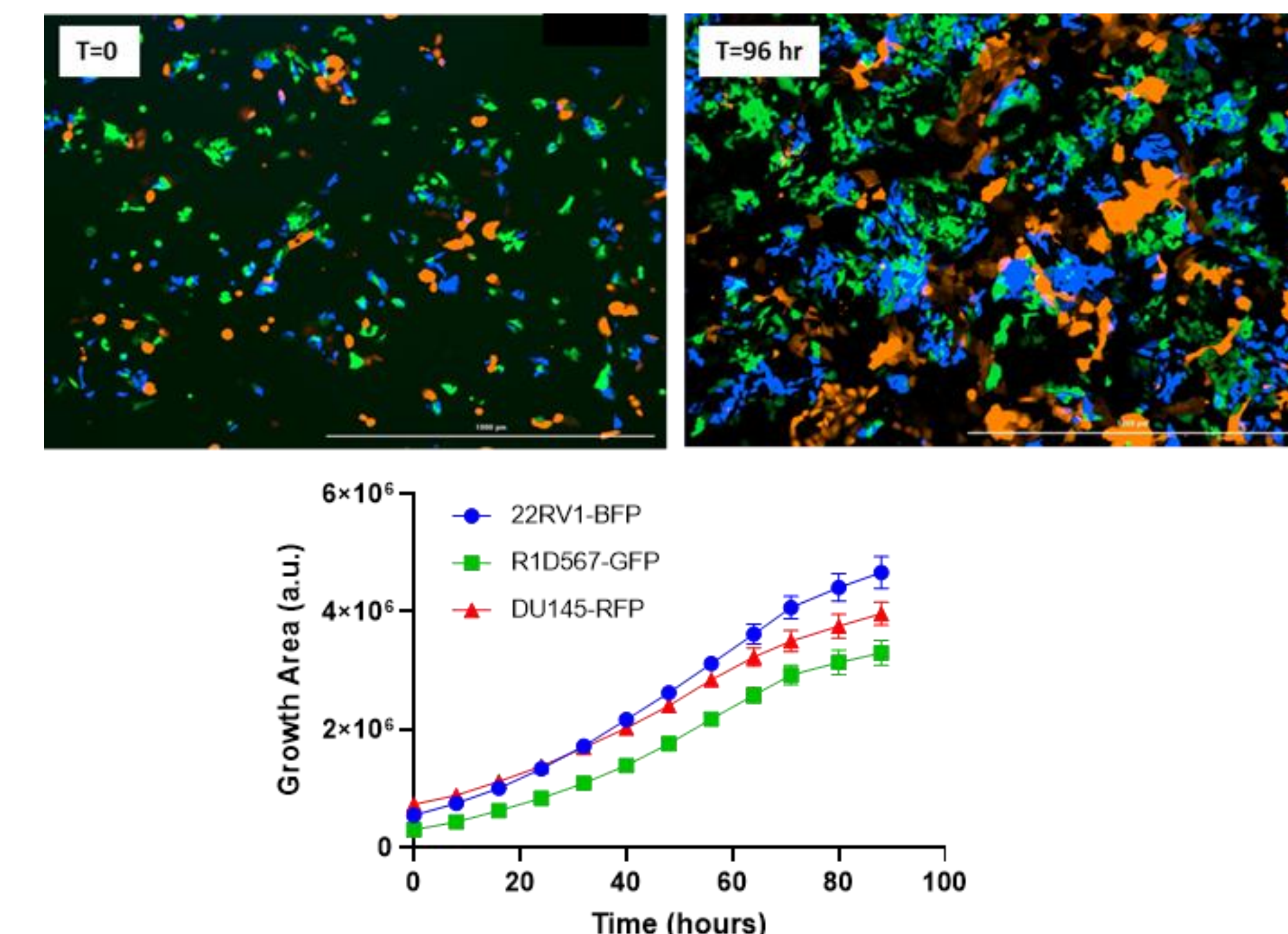


Figure 4: Labeled PC cell lines, DU145-RFP, 22RV1-BFP and R1D567-GFP mixed in a 1:2:2 proportion, proliferate exponentially in co-cultures in the absence of drug pressure.

Conclusions and Future Directions

- We developed and functionally validated mixed cancer-cell models depicting inter-patient heterogeneity in CRPC.
- We nominated novel drug combinations that are likely to be efficacious in heterogenous CRPC patient cohorts and preclinically validated them in our models.
- Work is in progress to generate CDX models by subcutaneously injecting the mixture of labeled PC lines into immunocompromised mice. Cryo-sectioned tumor slices will be imaged to quantify each cellular subpopulation under varying treatment conditions.
- Work is in progress to create a mixed cell model depicting intra-tumoral heterogeneity. Single-cell CRPC datasets will be analyzed to identify distinct subpopulations.

References

[1] A. Ling et al., "Computationally predicting clinical drug combination efficacy with cancer cell line screens and independent drug action", Nature Communications, 11, 5848 (2020).

This research was sponsored by UMN Faculty Research Developmental Grant.