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

Sampreeti Jena

Huang lab, Experimental and clinical pharmacology

University of Minnesota

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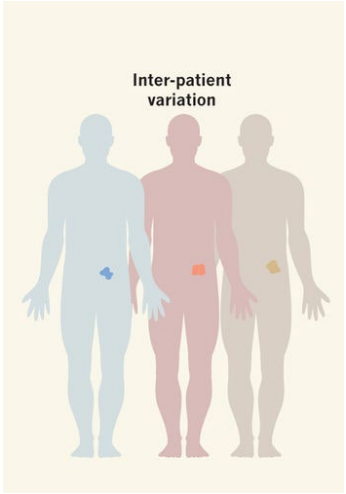
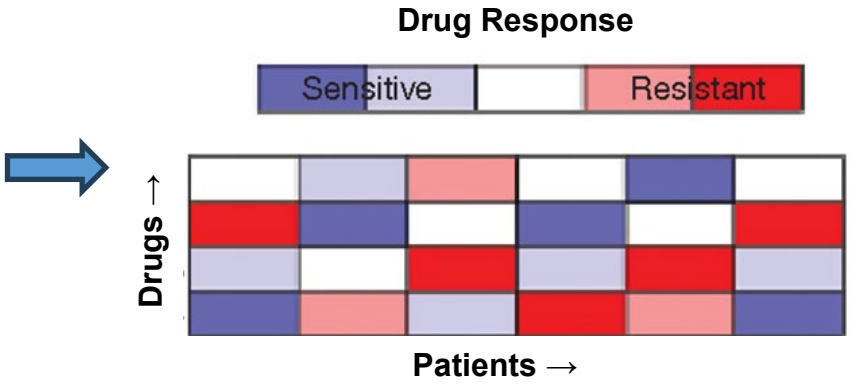
Email: jenax004@umn.edu

Lab website: https://huang-lab.umn.edu/

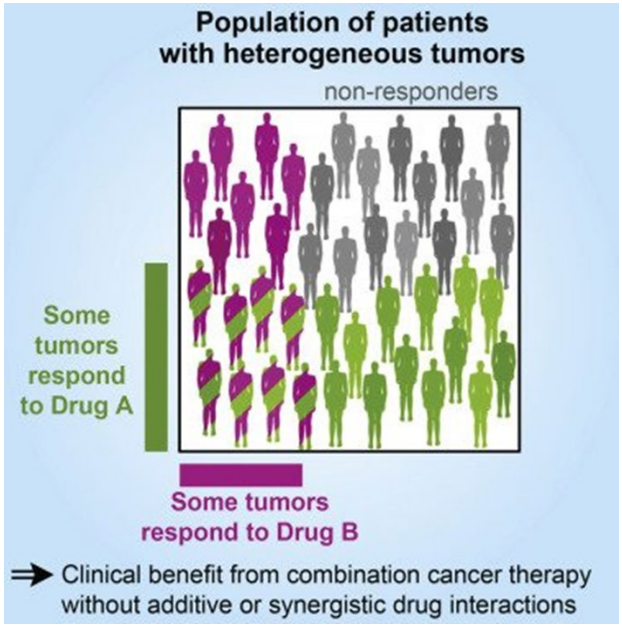
Current preclinical models cannot depict inter-patient tumor heterogeneity in cancer

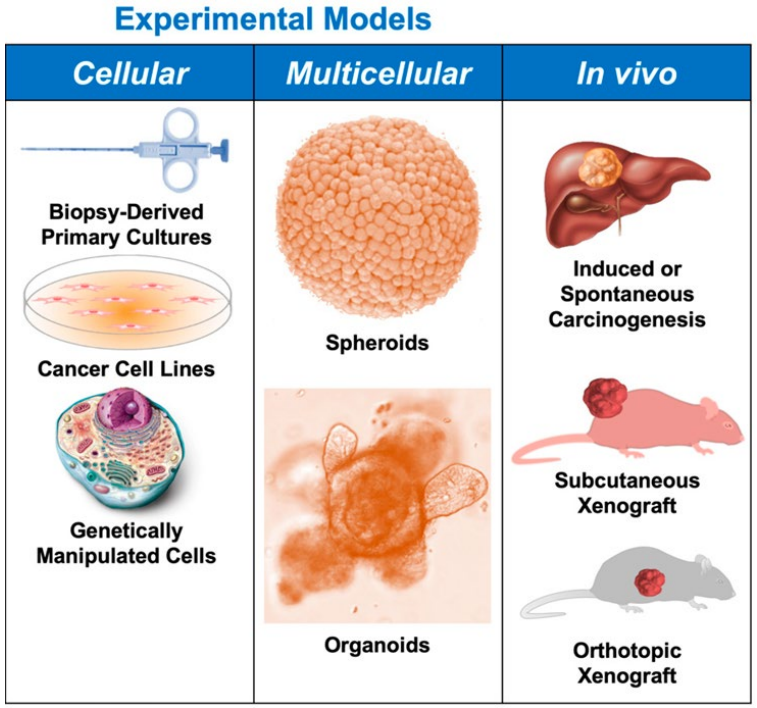




Inter-patient diversity in cancer cells hinders novel drug development and leads to translational failure!!

Clinical efficacy of drug combinations is attributable to inter-patient heterogeneity.

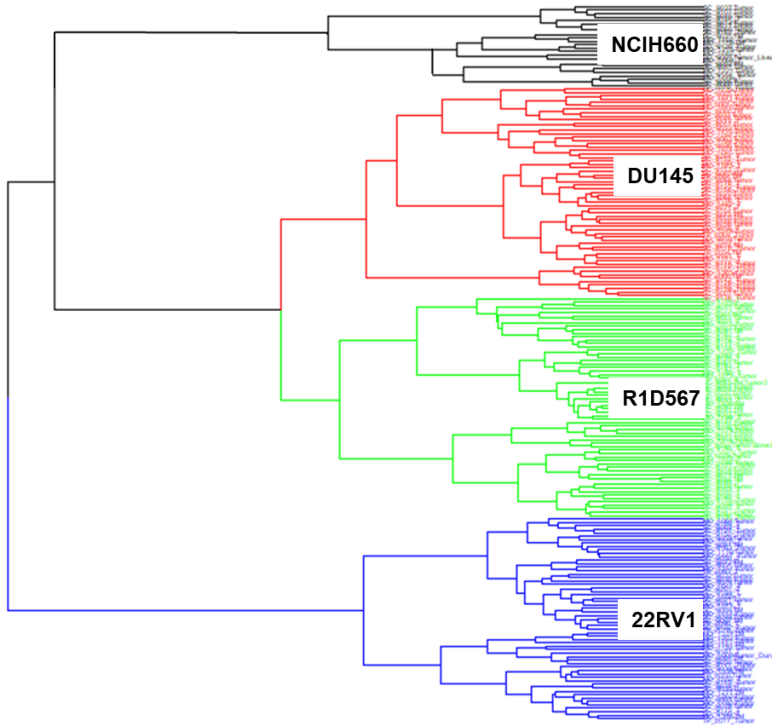


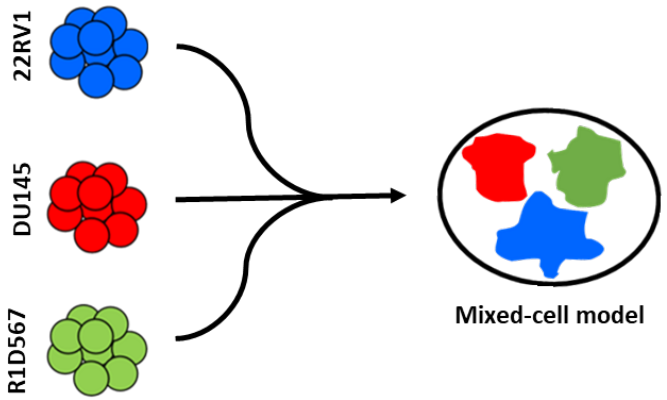


Source: Palmer, A. C. & Sorger, P. K. Combination Cancer Therapy Can Confer Benefit via Patient-to-Patient Variability without Drug Additivity or Synergy. Cell 171, 1678-1691.e13 (2017).

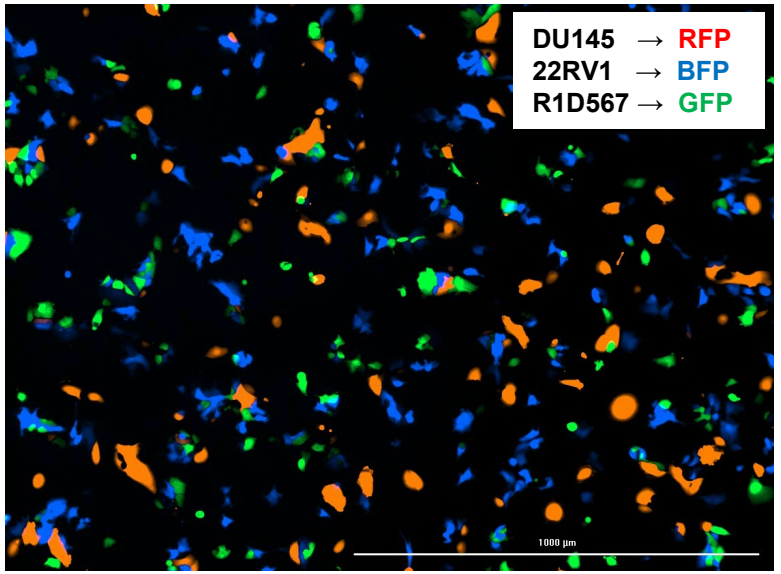
A mixture of PC lines can mimic tumor molecular diversity in CRPC patient cohorts

SU2C-EC patient samples and prostate cancer cell lines



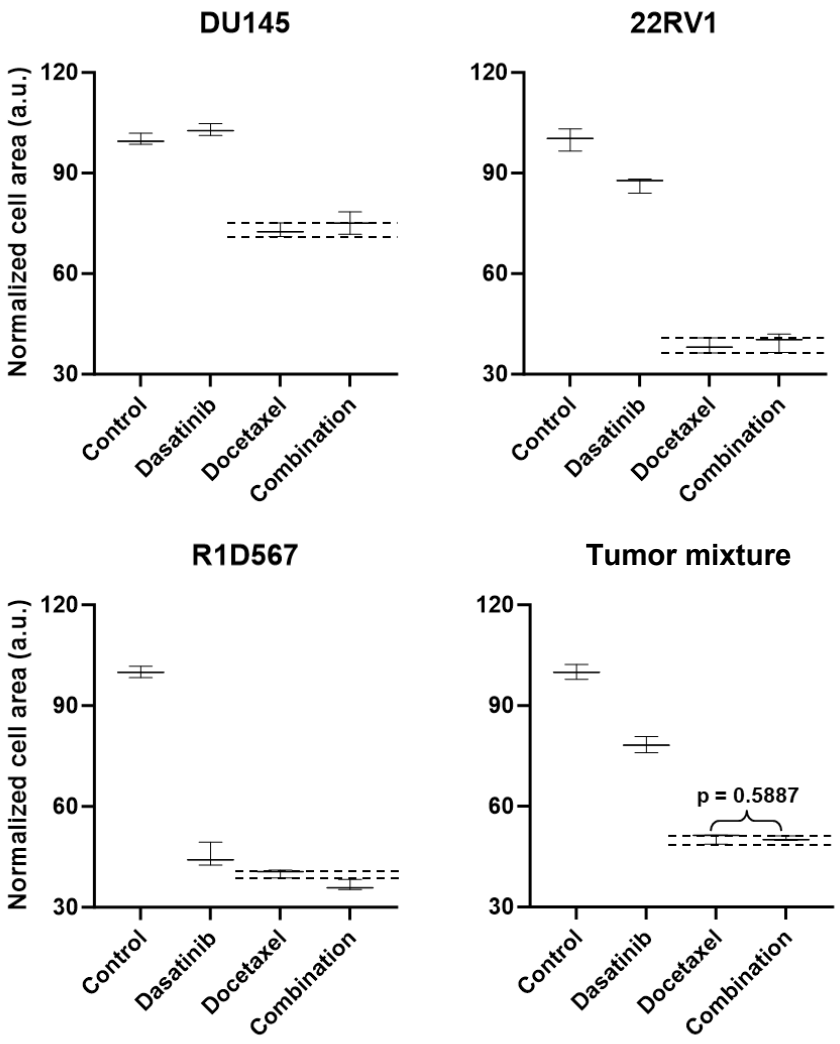


Prostate cancer cell-lines representing distinct patient tumor variants are selected and co-cultured to model a heterogenous patient cohort.

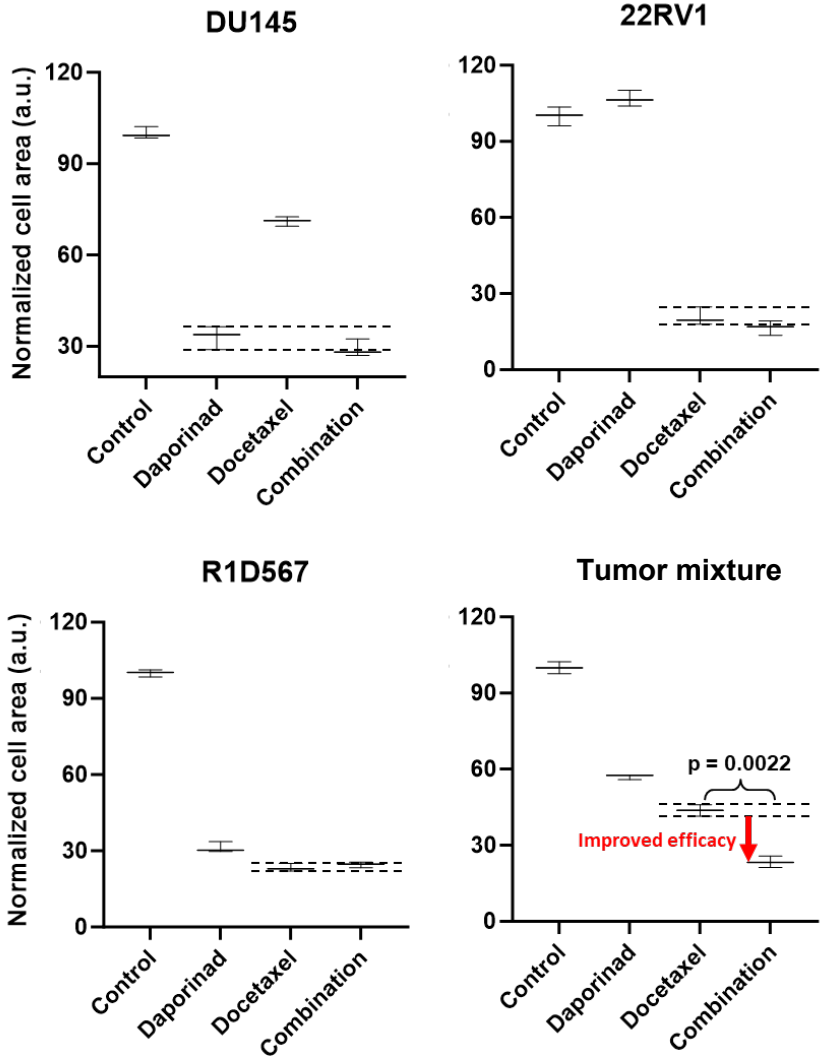


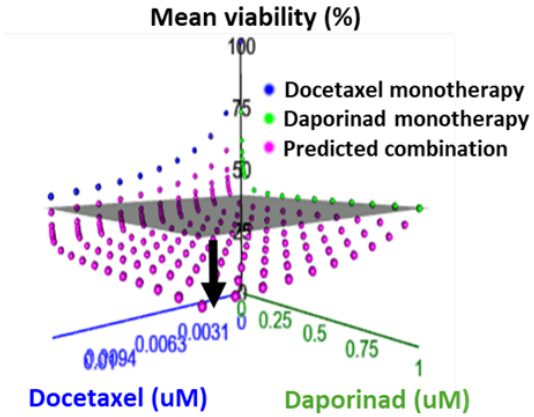
Model can accurately predict the clinical performance of drug combinations

Model validation
Docetaxel+Dasatinib: Clinically failed combination



Novel drug discovery
Docetaxel+Daporinad: Novel combination





Unpublished, DO NOT POST

Conclusions

- We developed and functionally validated a mixed cancer-cell model depicting inter-patient heterogeneity in CRPC clinical cohorts.
- We nominated novel drug combinations that are likely to be efficacious in heterogenous CRPC patient cohorts and preclinically validated them in our models.
- The model development pipeline can be applied to other cancer types to depict heterogeneity. A small number of cell lines that capture the major variability in the genetic landscape of cancer.
- We aim to incorporate the TME by generating mixed-cell mouse CDX models and in-vitro co-cultures with cancer associated fibroblasts.

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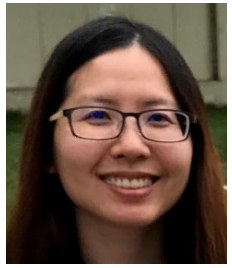
Acknowledgments

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Collaborators:

Dr. Scott Dehm, Department of Laboratory Medicine & Pathology, University of Minnesota
Dr. Adam Palmer, Department of Pharmacology, UNC Chapel Hill

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