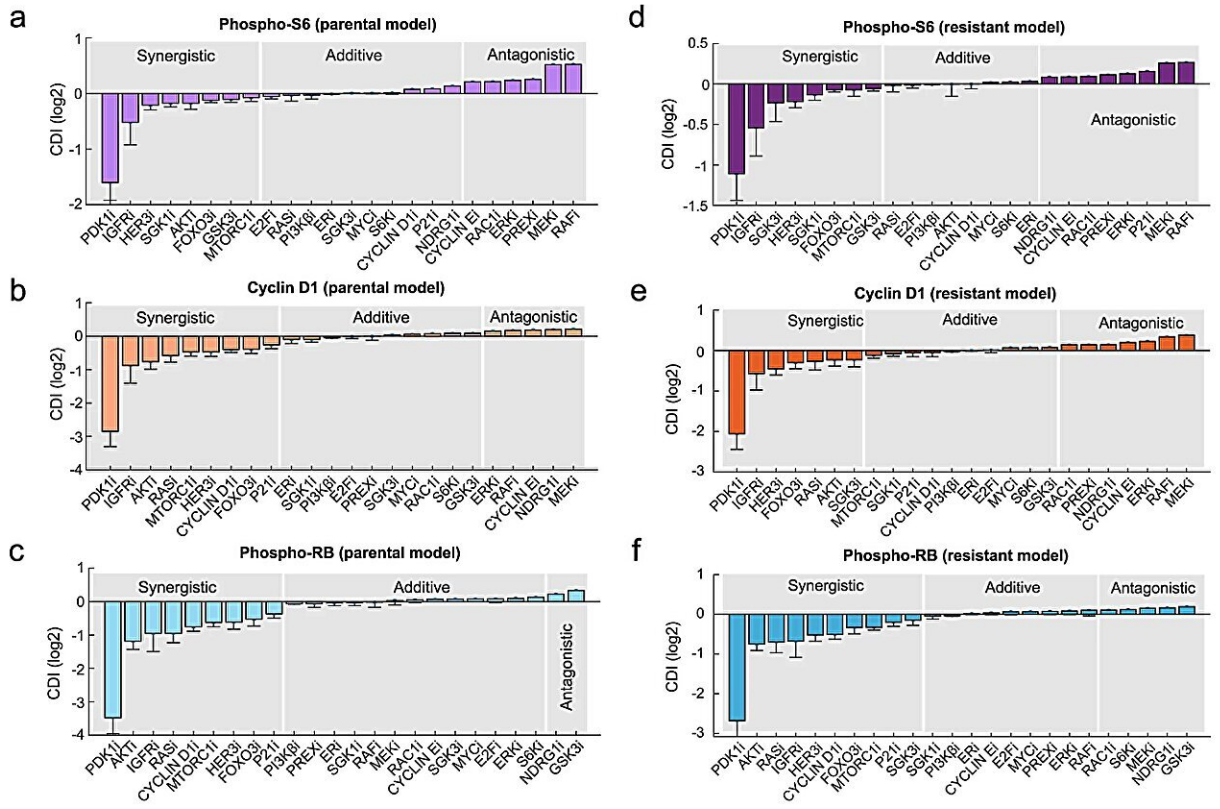
Innovative modeling may help breast cancer patients who don't respond to treatment

February 5 2024



Computational model predicts synergistic drug combinations. a–f Model prediction of drug synergism was generated using coefficient of drug interaction (CDI) index based on phospho-S6, cyclin D1 levels, or phospho-Rb. Credit: *npj Precision Oncology* (2024). DOI: 10.1038/s41698-024-00496-y

Monash University-led research is using math to predict how new

combination therapies can help patients with breast cancer who no longer respond to conventional therapies.

Published in *npj Precision Oncology*, the Monash Biomedicine Discovery Institute (BDI) study investigated breast cancer driven by a specific protein, PI3K, and how new combination therapies could effectively shut it down. The study is titled "Integrative modeling uncovers p21-driven drug resistance and prioritizes therapies for PIK3CA-mutant breast cancer."

Co-senior author Associate Professor Lan Nguyen said, "We have created new computational models that mimic the behavior of the cancer-promoting protein PI3K and its extensive downstream targets. This is critical because the PI3K pathway is mutated in about 30 percent of breast cancer patients, and contributes to resistance to primary anti-cancer treatments.

"Using this mathematical approach, we have predicted new combination therapies and confirmed through experiments in the lab that these new combination treatments are more effective at combating PI3K-mutant breast cancer cells than targeting PI3K alone."

Co-senior author Dr. Antonella Papa said the study was an important step forward in understanding and overcoming breast cancer drug resistance using innovative predictive models.

"Our study has found the way in which breast cancer cells become resistant to alpelisib, a PI3K inhibitor used in the clinic for the treatment of PI3K-mutant breast cancer," she said. "Using this knowledge, we have identified additional proteins that when inhibited, restore sensitivity to alpelisib and halt the proliferation of resistant cells."

Associate Professor Nguyen emphasized the formidable challenge of

drug resistance in cancer treatment.

"Our study not only sheds light on the complex mechanisms causing therapeutic resistance to alpelisib, but also provides a computational approach for systematically prioritizing combination therapies in an unbiased manner," he said. "This could accelerate the discovery of effective treatments, making it a valuable framework for future research in oncology and beyond.

"As drug resistance is a common reason for treatment failure, our research could lead to the testing and approval of new therapies that maintain their effectiveness longer, potentially improving survival rates and quality of life for patients. In the future, this could also mean fewer side effects and more personalized treatment options."

Associate Professor Nguyen said the next steps would entail rigorous preclinical evaluation of the identified drug combinations. "Following successful preclinical studies, initiating clinical trials will be essential to confirm the safety and efficacy of these new combination therapies in humans," he said.

Dr. Papa said, "Previous studies have demonstrated that similar treatments effectively reduce tumor growth using the mouse as a preclinical model. If preclinical validation progresses further, initial clinical trials could commence within a few years. Continuous collaboration between us researchers, clinicians, and regulatory bodies will be key to accelerating this process."

The authors acknowledged the study was a team effort between two laboratories within the Monash BDI, and the collaborative nature of the work had been instrumental in achieving these results. "It highlights the power of interdisciplinary approaches in addressing complex medical challenges like cancer," they said.

More information: Hon Yan Kelvin Yip et al, Integrative modeling uncovers p21-driven drug resistance and prioritizes therapies for PIK3CA-mutant breast cancer, *npj Precision Oncology* (2024). DOI: 10.1038/s41698-024-00496-y

Provided by Monash University