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Inhibition of HSP90 with AUY922 Induces Synergy in HER2-Amplified Trastuzumab-Resistant Breast and Gastric Cancer

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Use of Molecular Biomarkers to Quantify the Spatial Distribution of Effects of Anticancer Drugs in Solid Tumors
Jasdeep K. Saggar, Andrea S. Fung, Krupa J. Patel, and Ian F. Tannock
ABOUT THE COVER

The yeast Rad6 human homologues HHR6A and HHR6B (or Rad6A and Rad6B) encode ubiquitin-conjugating enzymes (or E2) that play a central role in substrate ubiquitination and E3 ligase selection. The ubiquitin-conjugating activity of Rad6 is essential for its function in postreplication DNA repair, damage-induced mutagenesis, and proteolysis. Using virtual screening of ZINC database against a pharmacophore model for consensus, E2-ubiquitin binding sites followed by biological evaluation of virtual hits, two small molecule compounds with a triazine core structure, and possessing Rad6 ubiquitin conjugation inhibitory activity were identified. These small molecules inhibit breast cancer cell proliferation, migration, and colony formation by blocking G2–M progression. For details, see article by Sanders and colleagues on page 373.