CANCER DISCOVERY

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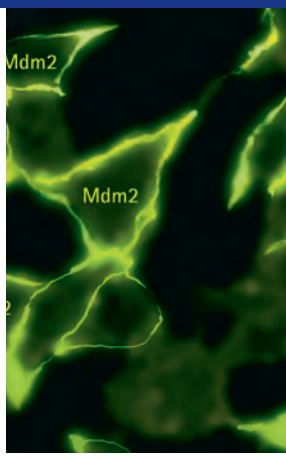
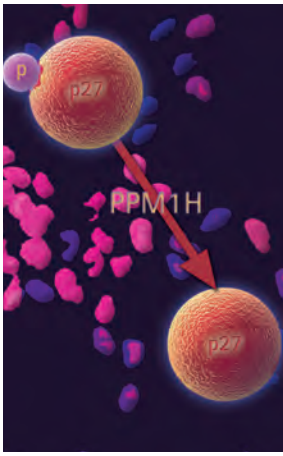
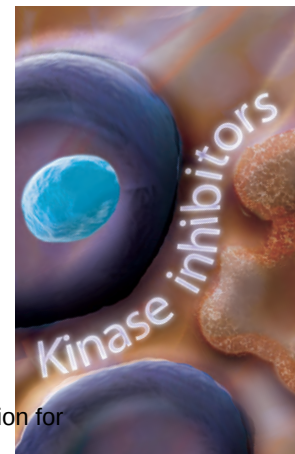
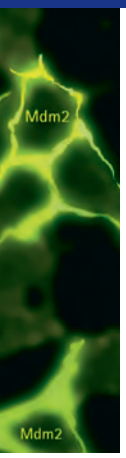
A.G. Herman, M. Hayano, M.V. Poyurovsky, K. Shimada, R. Skouta, C. Prives, and B.R. Stockwell

Précis: A novel class of small-molecule inhibitors of the Mdm2-MdmX E3 ligase heterocomplex is identified using a high-throughput cell-based Mdm2 auto-ubiquitination assay.









PPM1H Is a p27 Phosphatase Implicated in Trastuzumab Resistance 326

S.T. Lee-Hoeflich, T.Q. Pham, D. Dowbenko, X. Munroe, J. Lee, L. Li, W. Zhou, P.M. Haverty, K. Pujara, J. Stinson, S.M. Chan, J. Eastham-Anderson, A. Pandita, S. Seshagiri, K.P. Hoeflich, G. Turashvili, K.A. Gelmon, S.A. Aparicio, D.P. Davis, M.X. Sliwkowski, and H. M. Stern

Précis: PPM1H is a p27 phosphatase required for trastuzumab sensitivity *in vitro* that may be useful for predicting which HER2$^+$ breast cancers are more likely to respond to trastuzumab therapy.

ERα-Dependent E2F Transcription Can Mediate Resistance to Estrogen Deprivation in Human Breast Cancer 338

T.W. Miller, J.M. Balko, E.M. Fox, Z. Ghazoui, A. Dunbier, H. Anderson, M. Dowsett, A. Jiang, R.A. Smith, S-M. Maira, H.C. Manning, A.M. González-Angulo, G.B. Mills, C. Higham, S. Chanthaphaychith, M.G. Kuba, W.R. Miller, Y. Shyr, and C.L. Arteaga

Précis: ER drives CDK4/E2F-mediated cell cycle progression and cooperates with PI3K hyperactivation in estrogen-deprived ER$^+$ breast cancer cells.

BIM Expression in Treatment-Naïve Cancers Predicts Responsiveness to Kinase Inhibitors 352

A.C. Faber, R.B. Corcoran, H. Ebi, L.V. Sequist, B.A. Waltman, E. Chung, J. Incio, S.R. Digumarthy, S.F. Pollack, Y. Song, A. Muzikansky, E. Lifshits, S. Roberge, E.J. Coffman, C.H. Benes, H.L. Gómez, J. Baselga, C.L. Arteaga, M.N. Rivera, D. Dias-Santagata, R.K. Jain, and J.A. Engelman

Précis: Quantitation of pretreatment RNA levels of the pro-apoptotic factor BIM can predict the efficacy of tyrosine kinase inhibitor therapy in oncogene-addicted cancers.

ON THE COVER Faber and colleagues demonstrate that expression of the pro-apoptotic Bcl-2 family member BIM predicts the capacity of selective kinase inhibitors to induce apoptosis in cancers addicted to EGFR, HER2, PI3K, or BRAF signaling. Evaluating BIM levels in tumor biopsies prior to chemotherapy therefore has the potential to predict which patients are most likely to respond to single-agent kinase inhibitor therapy. For details, please see the article by Faber and colleagues on page 352.

AACR American Association for Cancer Research

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