

IN THIS ISSUE Highlighted research articlesvi

NEWS IN BRIEF Important news stories affecting the community..... 458

NEWS IN DEPTH Q&A: Michael Stratton on What's Next in Sequence 460

Broadening Trial Recruitment for Minorities, the Elderly 461

Placing Bets on Biotech 462

RESEARCH WATCH Selected highlights of recent articles of exceptional significance from the cancer literature..... 463

ONLINE For more News and Research Watch, visit *Cancer Discovery* online at www.AACR.org/CDnews.

VIEWS In The Spotlight

Understanding the Lethal Variant of Prostate Cancer: Power of Examining Extremes..... 466

A. Aparicio, C. J. Logothetis, and S.N. Maity

Commentary on Beltran et al., p. 487

NF-κB in Cancer: A Matter of Life and Death 469

B.B. Aggarwal and B. Sung

Commentary on Enzler et al., p. 496

HER2 Signaling and Resistance to the Anti-EGFR Monoclonal Antibody Cetuximab: A Further Step toward Personalized Medicine for Patients with Colorectal Cancer 472

F. Ciardiello and N. Normanno

Commentary on Bertotti et al., p. 508

mTORC 2:1 for Chemotherapy Sensitization in Glioblastoma 475

W. Wick, J. Blaes, and M. Weiler

Commentary on Tanaka et al., p. 524

Prospective

Curing “Incurable” Cancer 477

J.D. Watson

REVIEW **PI3K and STAT3: A New Alliance 481**

P.K. Vogt and J.R. Hart

RESEARCH BRIEF **Molecular Characterization of Neuroendocrine Prostate Cancer and Identification of New Drug Targets..... 487**

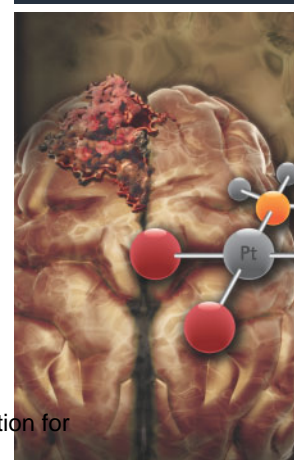
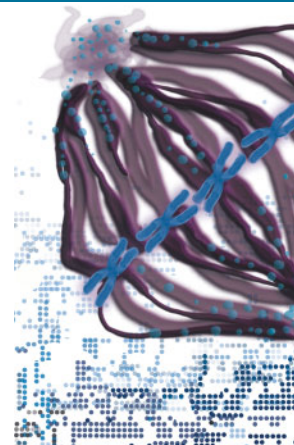
H. Beltran, D.S. Rickman, K. Park, S.S. Chae, A. Sboner, T.Y. MacDonald, Y. Wang, K.L. Sheikh, S. Terry, S.T. Tagawa, R. Dhir, J.B. Nelson, A. de la Taille, Y. Allory, M.B. Gerstein, S. Perner, K.J. Pienta, A.M. Chinnaiyan, Y. Wang, C.C. Collins, M.E. Gleave, F. Demichelis, D.M. Nanus, and M.A. Rubin

Précis: Frequent *AURKA* and *MYCN* amplification is identified in an aggressive prostate cancer subtype.

RESEARCH ARTICLES **Cell-Selective Inhibition of NF-κB Signaling Improves Therapeutic Index in a Melanoma Chemotherapy Model..... 496**

T. Enzler, Y. Sano, M-K. Choo, H.B. Cottam, M. Karin, H. Tsao, and J.M. Park

Précis: Host- and tumor-specific cellular responses, respectively, underlie the adverse and therapeutic effects of NF-κB blocking agents.





A Molecularly Annotated Platform of Patient-Derived Xenografts (“Xenopatients”) Identifies HER2 as an Effective Therapeutic Target in Cetuximab-Resistant Colorectal Cancer 508

A. Bertotti, G. Migliardi, F. Galimi, F. Sassi, D. Torti, C. Isella, D. Corà, F. Di Nicolantonio, M. Buscarino, C. Petti, D. Ribero, N. Russolillo, A. Muratore, P. Massucco, A. Pisacane, L. Molinaro, E. Valtorta, A. Sartore-Bianchi, M. Riso, L. Capussotti, M. Gambacorta, S. Siena, E. Medico, A. Sapino, S. Marsoni, P.M. Comoglio, A. Bardelli, and L. Trusolino

Précis: Population-based preclinical testing identifies HER2 amplification as a novel biomarker of cetuximab resistance in metastatic colon cancer and indicates dual targeting of HER2 and EGFR may be a more effective therapeutic approach.

Oncogenic EGFR Signaling Activates an mTORC2-NF-κB Pathway That Promotes Chemotherapy Resistance 524

K. Tanaka, I. Babic, D. Nathanson, D. Akhavan, D. Guo, B. Gini, J. Dang, S. Zhu, H. Yang, J. De Jesus, A.N. Amzajerdi, Y. Zhang, C.C. Dibble, H. Dan, A. Rinkenbaugh, W.H. Yong, H.V. Vinters, J.F. Gera, W.K. Cavenee, T.F. Cloughesy, B.D. Manning, A.S. Baldwin, and P.S. Mischel

Précis: mTORC2 is identified as a novel mediator of drug resistance and regulator of NF-κB signaling in glioblastoma.

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- Optical Tomography May Aid 3D Diagnostics
- Chemotherapy May Target Mitochondria on the Edge

ON THE COVER

Tanaka and colleagues demonstrate that mTORC2 is activated in the majority of glioblastomas and mediates chemoresistance in an AKT-independent manner via NF-κB pathway activation. Surprisingly, they show increased activity of this mTORC2-NF-κB signaling pathway in GBM cells in response to rapamycin, which may provide an explanation for the failure of rapamycin to demonstrate efficacy in GBM clinical trials. Instead, dual mTOR kinase inhibitors that block the activity of both mTORC1 and mTORC2 may improve clinical outcome, particularly when combined with other chemotherapeutic agents. For details, please see the article by Tanaka and colleagues on page 524.



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1 (6)

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