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**VIEWES In The Spotlight**

**Improving the Armamentarium of PI3K Inhibitors with Isoform-Selective Agents: A New Light in the Darkness** ..... 666

J. Rodon and J. Tabernero

*See article, p. 704*

**Novel Mitochondrial Mechanisms of Cytarabine Resistance in Primary AML Cells** ..... 670

A.D. Schimmer

*See article, p. 716*

**The Path of Most Resistance: Transdifferentiation Underlies Exceptional Nonresponses to Androgen Receptor Pathway Inhibition in Prostate Cancer** ... 673

S. Sinha and P.S. Nelson

*See article, p. 736*

**REVIEW DNA Damage and Repair Biomarkers of Immunotherapy Response** ..... 675

K.W. Mouw, M.S. Goldberg, P.A. Konstantinopoulos, and A.D. D'Andrea

**RESEARCH BRIEF A Combined PD-1/C5a Blockade Synergistically Protects against Lung Cancer Growth and Metastasis** ... 694

D. Ajona, S. Ortiz-Espinosa, H. Moreno, T. Lozano, M.J. Pajares, J. Agorreta, C. Bértolo, J.J. Lasarte, S. Vicent, K. Hoehlig, A. Vater, F. Lecanda, L.M. Montuenga, and R. Pio

**Précis:** Inhibition of C5a relieved MDSC-mediated immunosuppression to enhance the efficacy of PD-1 blockade, thereby extending survival in mouse models of lung cancer and reducing primary and metastatic tumor growth.

**RESEARCH ARTICLES Phase I Dose-Escalation Study of Taselisib, an Oral PI3K Inhibitor, in Patients with Advanced Solid Tumors** ..... 704

D. Juric, I. Krop, R.K. Ramanathan, T.R. Wilson, J.A. Ware, S.M. Sanabria Bohorquez, H.M. Savage, D. Sampath, L. Salphati, R.S. Lin, H. Jin, H. Parmar, J.Y. Hsu, D.D. Von Hoff, and J. Baselga

**Précis:** In a phase I dose-escalation study the PI3K inhibitor taselisib was well tolerated and achieved partial responses in 36% of patients with locally advanced or metastatic solid tumors harboring *PIK3CA* mutations.

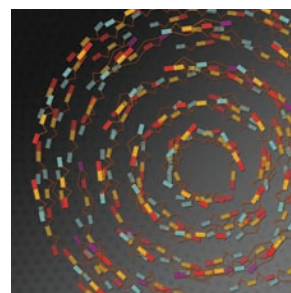
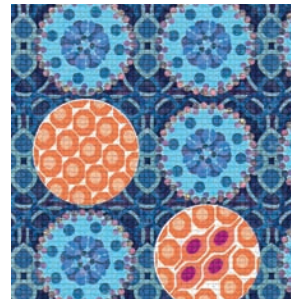
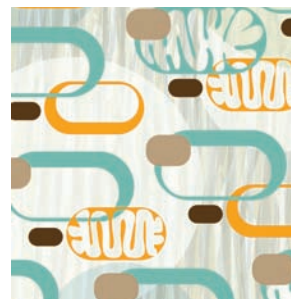
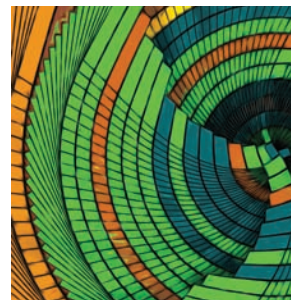
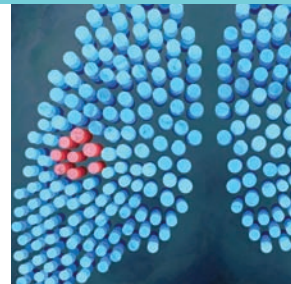
*See commentary, p. 666*

**Chemotherapy-Resistant Human Acute Myeloid Leukemia Cells Are Not Enriched for Leukemic Stem Cells but Require Oxidative Metabolism** ... 716

T. Farge, E. Saland, F. de Toni, N. Aroua, M. Hosseini, R. Perry, C. Bosc, M. Sugita, L. Stuani, M. Fraise, S. Scotland, C. Larrue, H. Boutzen, V. Féliu, M.-L. Nicolau-Travers, S. Cassant-Sourdy, N. Broin, M. David, N. Serhan, A. Sarry, S. Tavitian, T. Kaoma, L. Vallar, J. Iacovoni, L.K. Linares, C. Montersino, R. Castellano, E. Griessinger, Y. Collette, O. Duchamp, Y. Barreira, P. Hirsch, T. Palama, L. Gales, F. Delhommeau, B.H. Garmy-Susini, J.-C. Portais, F. Vergez, M. Selak, G. Danet-Desnoyers, M. Carroll, C. Récher, and J.-E. Sarry

**Précis:** In AML patient-derived xenografts, treatment with the chemotherapeutic cytarabine selected for a resistant population exhibiting enhanced oxidative phosphorylation, but did not select for quiescent leukemic stem cells.

*See commentary, p. 670*



**Transdifferentiation as a Mechanism of Treatment Resistance in a Mouse Model of Castration-Resistant Prostate Cancer** ..... 736

M. Zou, R. Toivanen, A. Mitrofanova, N. Floch, S. Hayati, Y. Sun, C. Le Magnen, D. Chester, E.A. Mostaghel, A. Califano, M.A. Rubin, M.M. Shen, and C. Abate-Shen

**Précis:** In a mouse model of *Trp53/Pten*-mutant castration-resistant prostate cancer (CRPC), abiraterone promotes transdifferentiation of luminal adenocarcinoma to neuroendocrine CRPC to promote drug resistance.

See commentary, p. 673

**Cabozantinib Eradicates Advanced Murine Prostate Cancer by Activating Antitumor Innate Immunity** ..... 750

**AC** A. Patnaik, K.D. Swanson, E. Csizmadia, A. Solanki, N. Landon-Brace, M.P. Gehring, K. Helenius, B.M. Olson, A.R. Pyzer, L.C. Wang, O. Elemento, J. Novak, T.B. Thornley, J.M. Asara, L. Montaser, J.J. Timmons, T.M. Morgan, Y. Wang, E. Levantini, J.G. Clohessy, K. Kelly, P.P. Pandolfi, J.M. Rosenblatt, D.E. Avigan, H. Ye, J.M. Karp, S. Signoretti, S.P. Balk, and L.C. Cantley

**Précis:** The tyrosine kinase inhibitor cabozantinib triggers tumor cell secretion of chemokines, resulting in an induction of neutrophil infiltration to promote tumor clearance in a treatment-refractory mouse model of prostate cancer.

**AC** AC icon indicates AuthorChoice

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**Identification of a DNA Damage-Induced Alternative Splicing Pathway That Regulates p53 and Cellular Senescence Markers** ..... 766

J. Chen, J. Crutchley, D. Zhang, K. Owzar, and M.B. Kastan

**Précis:** A DNA damage-induced alternative splicing pathway that includes induction of the  $\beta$  isoform of *TP53* as a mediator of damage-induced cellular senescence.

**Correction**

**Adaptive Reprogramming of De Novo Pyrimidine Synthesis Is a Metabolic Vulnerability in Triple-Negative Breast Cancer** ..... 782

**ON THE COVER**

Using acute myeloid leukemia (AML) patient-derived xenografts, Farge and colleagues investigated the molecular mechanisms underlying resistance to the chemotherapeutic cytarabine (AraC) *in vivo*. Previous reports suggested that a refractory quiescent leukemic stem cell (LSC) population underlies AraC resistance, but AraC treatment unexpectedly reduced the number of LSCs as well as mature AML cells, indicating that AraC resistance is not mediated by LSCs. Instead, AraC induced chemoresistance by selecting for a preexisting population of resistant cells that exhibited enhanced oxidative phosphorylation (OXPHOS). AraC-resistant cells showed elevated mitochondrial respiration, and blocking OXPHOS increased AraC sensitivity. Together, these findings demonstrate that high OXPHOS activity is associated with chemoresistance in AML and suggest the possibility that therapeutic targeting of mitochondrial metabolism may enhance chemosensitivity. For details, please see the article by Farge and colleagues on page 716.

