

**IN THIS ISSUE** Highlighted research articles ..... 1047

**NEWS IN BRIEF** Important news stories affecting the community ..... 1052

**RESEARCH WATCH** Selected highlights of recent articles of exceptional significance from the cancer literature ..... 1057

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**IEWS In The Spotlight**

**More T Cells versus Better T Cells in Patients with Breast Cancer** .... 1062

D.E. Speiser and G. Verdeil

*See article, p. 1098*

**Targeting the Noncoding Genome: Superenhancers Meet Their Kryptonite** ..... 1065

E. Wang and I. Aifantis

*See article, p. 1136*

**Soils and Seeds That Initiate Pancreatic Cancer Metastasis** .. 1067

C.R. Vakoc and D.A. Tuveson

*See article, p. 1184*

**REVIEW** **How Ribosomes Translate Cancer** ..... 1069

S.O. Sulima, I.J.F. Hofman, K. De Keersmaecker, and J.D. Dinman

**RESEARCH BRIEF** **TCR Repertoire Intratumor Heterogeneity in Localized Lung Adenocarcinomas: An Association with Predicted Neoantigen Heterogeneity and Postsurgical Recurrence** ..... 1088

A. Reuben, R. Gittelman, J. Gao, J. Zhang, E.C. Yusko, C.-J. Wu, R. Emerson, J. Zhang,

C. Tipton, J. Li, K. Quek, V. Gopalakrishnan, R. Chen, L.M. Vence, T. Cascone, M. Vignali, J. Fujimoto, J. Rodríguez-Canales, E.R. Parra, L.D. Little, C. Gumbs, M.-A. Forget, L. Federico, C. Haymaker, C. Behrens, S. Benzeno, C. Bernatchez, B. Sepesi, D.L. Gibbons, J.A. Wargo, W.N. William Jr, S. Swisher, J.V. Heymach, H. Robins, J.J. Lee, P. Sharma, J.P. Allison, P.A. Futreal, I.I. Wistuba, and J. Zhang

**Précis:** T-cell receptor sequencing of 45 tumor regions from 11 patients with NSCLC found T-cell repertoire intratumor heterogeneity that was associated with disease relapse and reduced disease-free survival.

**RESEARCH ARTICLES** **Immune Escape in Breast Cancer During *In Situ* to Invasive Carcinoma Transition** ..... 1098



C.R. Gil Del Alcazar, S.J. Huh, M.B. Ekram, A. Trinh, L.L. Liu, F. Beca, X. Zi, M. Kwak, H. Bergholtz, Y. Su, L. Ding, H.G. Russnes, A.L. Richardson, K. Babski, E.M.H. Kim, C.H. McDonnell III, J. Wagner, R. Rowberry, G.J. Freeman, D. Dillon, T. Sorlie, L.M. Coussens, J.E. Garber, R. Fan, K. Bobolis, D.C. Allred, J. Jeong, S.Y. Park, F. Michor, and K. Polyak

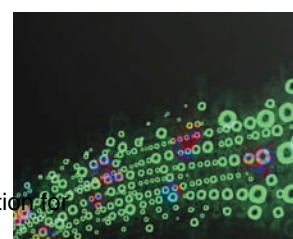
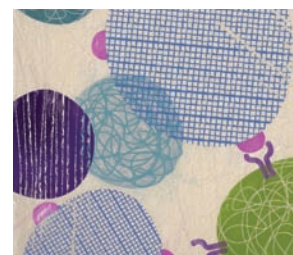
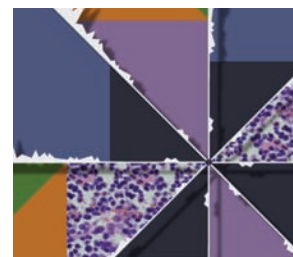
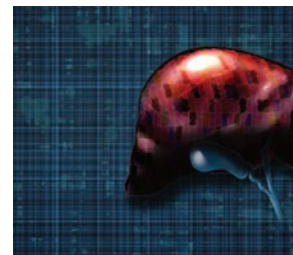
**Précis:** Progression from ductal carcinoma *in situ* to invasive ductal carcinoma is characterized by a switch to a more suppressive immune microenvironment.

*See commentary, p. 1062*

**Whole-Genome and Epigenomic Landscapes of Etiologically Distinct Subtypes of Cholangiocarcinoma** ..... 1116



A. Jusakul, I. Cutcutache, C.H. Yong, J.Q. Lim, M.N. Huang, N. Padmanabhan, V. Nellore, S. Kongpetch, A.W.T. Ng, L.M. Ng, S.P. Choo, S.S. Myint, R. Thanan, S. Nagarajan, W.K. Lim, C.C.Y. Ng, A. Boot, M. Liu, C.K. Ong, V. Rajasegaran, S. Lie, A.S.T. Lim, T.H. Lim, J. Tan, J.L. Loh, J.R. McPherson, N. Khuntikeo, V. Bhudhisawasdi, P. Yongvanit, S. Wongkham, Y. Totoki, H. Nakamura, Y. Arai, S. Yamasaki, P.K.-H. Chow, A.Y.F. Chung, L.L.P.J. Ooi, K.H. Lim, S. Dima, D.G. Duda, I. Popescu, P. Broet, S.-Y. Hsieh, M.-C. Yu, A. Scarpa, J. Lai, D.-X. Luo, A.L. Carvalho, A.L. Vettore,



H. Rhee, Y.N. Park, L.B. Alexandrov, R. Gordán, S.G. Rozen, T. Shibata, C. Pairajkul, B.T. Teh, and P. Tan

**Précis:** In-depth genetic characterization defines cholangiocarcinoma subtypes and identifies previously undescribed drivers, noncoding promoter mutations, and structural variants.

**Superenhancer Analysis Defines Novel Epigenomic Subtypes of Non-APL AML, Including an RAR $\alpha$  Dependency Targetable by SY-1425, a Potent and Selective RAR $\alpha$  Agonist** ..... 1136



M.R. McKeown, M.R. Corces, M.L. Eaton, C. Fiore, E. Lee, J.T. Lopez, M.W. Chen, D. Smith, S.M. Chan, J.L. Koenig, K. Austgen, M.G. Guenther, D.A. Orlando, J. Lovén, C.C. Fritz, and R. Majeti

**Précis:** Characterization of enhancer landscapes in patients with AML identified a subset of non-APL AML with an RARA superenhancer that confers sensitivity to treatment with the selective RAR $\alpha$  agonist SY-1425.

*See commentary, p. 1065*

**Overcoming the Immunosuppressive Tumor Microenvironment of Hodgkin Lymphoma Using Chimeric Antigen Receptor T Cells** ..... 1154

M. Ruella, M. Klichinsky, S.S. Kenderian, O. Shestova, A. Ziober, D.O. Kraft, M. Feldman, M.A. Wasik, C.H. June, and S. Gill

**Précis:** Anti-CD123 chimeric antigen receptor T cells overcome the immunosuppressive

tumor microenvironment in Hodgkin lymphoma by targeting both malignant cells and tumor-associated macrophages.

**Loss of MutL Disrupts CHK2-Dependent Cell-Cycle Control through CDK4/6 to Promote Intrinsic Endocrine Therapy Resistance in Primary Breast Cancer** ..... 1168



S. Haricharan, N. Punturi, P. Singh, K.R. Holloway, M. Anurag, J. Schmelz, C. Schmidt, J.T. Lei, V. Suman, K. Hunt, J.A. Olson Jr, J. Hoog, S. Li, S. Huang, D.P. Edwards, S.M. Kavuri, M.N. Bainbridge, C.X. Ma, and M.J. Ellis

**Précis:** Dysregulation of the mismatch repair complex MutL promotes intrinsic resistance to endocrine therapy in ER<sup>+</sup> breast cancer model systems and patients and may confer sensitivity to CDK4/6 inhibitors.

**BLIMP1 Induces Transient Metastatic Heterogeneity in Pancreatic Cancer** ..... 1184

S.-H. Chiou, V.I. Risca, G.X. Wang, D. Yang, B.M. Grüner, A.S. Kathiria, R.K. Ma, D. Vaka, P. Chu, M. Kozak, L. Castellini, E.E. Graves, G.E. Kim, P. Mourrain, A.C. Koong, A.J. Giaccia, and M.M. Winslow

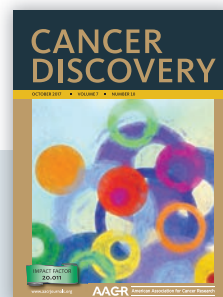
**Précis:** Pancreatic ductal adenocarcinoma metastasis is promoted by hypoxia and HIF-driven upregulation of the prometastatic transcription factor BLIMP1.

*See commentary, p. 1067*

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**ON THE COVER** To determine how intratumor heterogeneity in the T-cell landscape correlates with the genomic landscape and with patient outcome in non-small cell lung cancer (NSCLC), Reuben and colleagues characterized the T-cell repertoire in a cohort of 11 patients with NSCLC who had previously been subject to whole-exome sequencing. T-cell receptor (TCR) sequencing profiled 45 tumor regions across the 11 tumors and revealed a high level of intratumor heterogeneity, with differences in T-cell density, clonality, and repertoire. TCR intratumor heterogeneity was linked to neoantigen heterogeneity and was correlated with disease relapse and reduced disease-free survival in patients with NSCLC. These findings link T-cell repertoire heterogeneity to genomic intratumor heterogeneity and relapse in NSCLC. For details, please see the article by Reuben and colleagues on page 1088.



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7 (10)

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