

CANCER DISCOVERY CONTENTS

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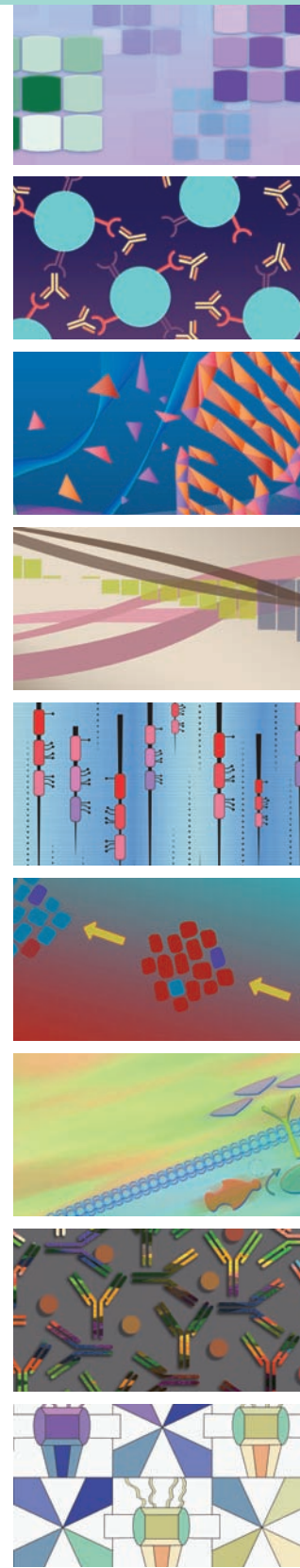
Précis: To enable rapid interpretation of radiology reports and obtain usable real-world evidence, a deep learning-based model was trained to employ natural language processing to determine best response and progression data from radiology reports.

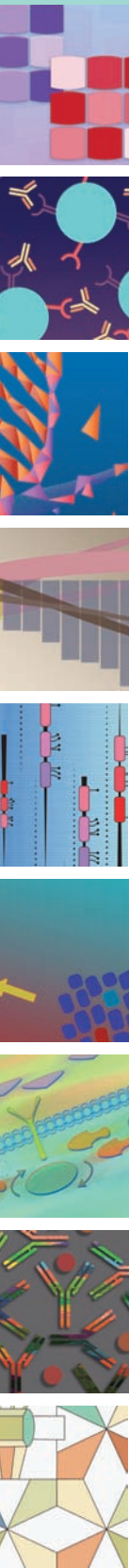
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Précis: The BCL2 inhibitor venetoclax enhanced efficacy of immune checkpoint blockade in syngeneic mouse tumor models despite reducing numbers of total lymphocytes, possibly because effector T-cell function was not affected.

RESEARCH ARTICLES	First-in-Human Trial of the Oral Ataxia Telangiectasia and RAD3-Related (ATR) Inhibitor BAY 1895344 in Patients with Advanced Solid Tumors 80 AC T.A. Yap, D.S.P. Tan, A. Terbuch, R. Caldwell, C. Guo, B.C. Goh, V. Heong, N.R.Md. Haris,
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S. Bashir, Y. Drew, D.S. Hong, F. Meric-Bernstam, G. Wilkinson, J. Hreiki, A.M. Wengner, F. Bladt, A. Schlicker, M. Ludwig, Y. Zhou, L. Liu, S. Bordia, R. Plummer, E. Lagkadinou, and J.S. de Bono

Précis: In a phase I trial, the ATR inhibitor BAY 1895344 showed preliminary evidence of efficacy against advanced solid tumors, particularly those with low ATM protein levels and/or ATM mutations.

See commentary, p. 14

Triplet Therapy with Palbociclib, Taselisib, and Fulvestrant in PIK3CA-Mutant Breast Cancer and Doublet Palbociclib and Taselisib in Pathway-Mutant Solid Cancers 92

AC J. Pascual, J.S.J. Lim, I.R. Macpherson, A.C. Armstrong, A. Ring, A.F.C. Okines, R.J. Cutts, M.T. Herrera-Abreu, I. Garcia-Murillas, A. Pearson, S. Hrebien, H. Gevensleben, P.Z. Proszek, M. Hubank, M. Hills, J. King, M. Parmar, T. Prout, L. Finneran, J. Malia, K.E. Swales, R. Ruddle, F.I. Raynaud, A. Turner, E. Hall, T.A. Yap, J.S. Lopez, and N.C. Turner

Précis: Supporting preclinical data that showed synergy between CDK4/6 inhibitors and PI3K inhibitors in PI3KCA-mutant, estrogen receptor-positive, HER2-negative breast cancer, a phase Ib trial found corresponding results in patients with advanced disease.

Resistance to Avapritinib in PDGFRA-Driven GIST Is Caused by Secondary Mutations in the PDGFRA Kinase Domain 108

S. Grunewald, L.R. Klug, T. Mühlenberg, J. Lategahn, J. Falkenhorst, A. Town, C. Ehrt, E. Wardelmann, W. Hartmann, H.-U. Schildhaus, J. Treckmann, J.A. Fletcher, S. Jung, P. Czodrowski, S. Miller, O. Schmidt-Kittler, D. Rauh, M.C. Heinrich, and S. Bauer

Précis: PDGFRA-mutant gastrointestinal stromal tumors that develop resistance to PDGFRA inhibition harbored secondary mutations in the PDGFRA kinase domain, and these tumors were still dependent on oncogenic PDGFRA signaling.

TRK xDFG Mutations Trigger a Sensitivity Switch from Type I to II Kinase Inhibitors 126

E. Cocco, J.E. Lee, S. Kannan, A.M. Schram, H.H. Won, S. Shifman, A. Kulick, L. Baldino, E. Toska, A. Arruabarrena-Aristorena, S. Kittane, F. Wu, Y. Cai, S. Arena, B. Mussolin, R. Kannan, N. Vasani, A.N. Gorelick, M.F. Berger, O. Novoplansky, S. Jagadeeshan, Y. Liao, U. Rix, S. Misale, B.S. Taylor, A. Bardelli, J.F. Hechtman, D.M. Hyman, M. Elkabets, E. de Stanchina, C.S. Verma, A. Ventura, A. Drilon, and M. Scaltriti

Précis: Mutations that cause resistance to type I tyrosine kinase inhibitors (TKI) in TRK fusion-positive cancer caused sensitivity to type II TKIs because these mutations stabilized the inactive “DFG-out” conformation of TRK, which is bound by type II TKIs.

BI-3406, a Potent and Selective SOS1-KRAS Interaction Inhibitor, Is Effective in KRAS-Driven Cancers through Combined MEK Inhibition 142

AC M.H. Hofmann, M. Gmachl, J. Ramharter, F. Savarese, D. Gerlach, J.R. Marszalek, M.P. Sanderson, D. Kessler, F. Trapani, H. Arnhof, K. Rumpel, D.-A. Botesteanu, P. Ettmayer, T. Gerstberger, C. Kofink, T. Wunberg, A. Zoephel, S.-C. Fu, J.L. Teh, J. Böttcher, N. Pototschnig, F. Schachinger, K. Schipany, S. Lieb, C.P. Vellano, J.C. O’Connell, R.L. Mendes, J. Moll, M. Petronczki, T.P. Heffernan, M. Pearson, D.B. McConnell, and N. Kraut

Précis: A novel small-molecule drug, BI-3406, was used to block interactions between KRAS and the guanine exchange factor SOS1, hindering GTP binding by KRAS and thus reducing its activity to prevent tumor cell growth *in vitro* and *in vivo*.

See commentary, p. 17

Antibody to CD137 Activated by Extracellular Adenosine Triphosphate Is Tumor Selective and Broadly Effective *In Vivo* without Systemic Immune Activation 158

AC M. Kamata-Sakurai, Y. Narita, Y. Hori, T. Nemoto, R. Uchikawa, M. Honda, N. Hironiwa, K. Taniguchi, M. Shida-Kawazoe, S. Metsugi, T. Miyazaki, N.A. Wada, Y. Ohte, S. Shimizu, H. Mikami, T. Tachibana, N. Ono, K. Adachi, T. Sakiyama, T. Matsushita, S. Kadono, S.-i. Komatsu, A. Sakamoto, S. Horikawa, A. Hirako, K. Hamada, S. Naoi, N. Savory, Y. Satoh, M. Sato, Y. Noguchi, J. Shinozuka, H. Kuroi, A. Ito, T. Wakabayashi, M. Kamimura, F. Isomura, Y. Tomii, N. Sawada, A. Kato, O. Ueda, Y. Nakanishi, M. Endo, K.-i. Jishage, Y. Kawabe, T. Kitazawa, and T. Igawa

Précis: An extracellular ATP-activated agonistic antibody to CD137, which promotes T-cell survival and proliferation, showed antitumor efficacy in multiple *in vivo* models, causing T-cell activation within tumors without off-target toxicity.

See commentary, p. 20

Inhibition of Nuclear Pore Complex Formation Selectively Induces Cancer Cell Death 176

S. Sakuma, M. Raices, J. Borlido, V. Guglielmi, E.Y.S. Zhu, and M.A. D'Angelo

Précis: *In vitro* and *in vivo*, depletion of components of the nuclear pore complex (NPC) preferentially killed cancer cells, sparing normal cells, by causing nuclear transport aberrations, gene expression changes, and DNA damage.

An Epigenetic Mechanism Underlying Chromosome 17p Deletion-Driven Tumorigenesis 194

M. Chen, X. Chen, S. Li, X. Pan, Y. Gong, J. Zheng, J. Xu, C. Zhao, Q. Zhang, S. Zhang, L. Qi, Z. Wang, K. Shi, B.-S. Ding, Z. Xue, L. Chen, S. Yang, Y. Wang, T. Niu, L. Dai, S.W. Lowe, C. Chen, and Y. Liu

Précis: Loss of the gene encoding the putative epigenetic reader PHF23, which formed a complex with the SIN3-HDAC histone deacetylase complex and reduced its activity, was a major driver of chromosome 17p loss-driven tumorigenesis.

Acknowledgment to Reviewers 208

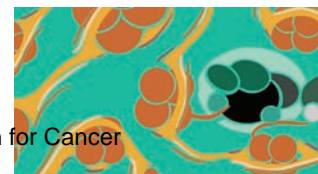
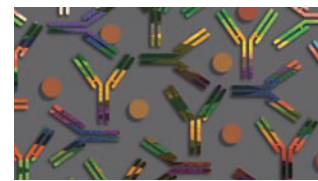
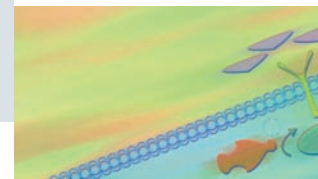
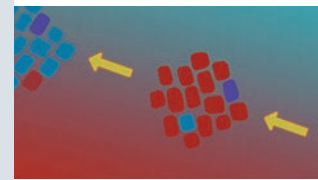
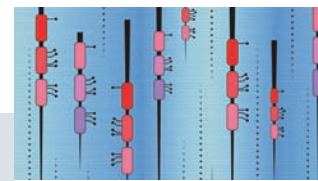
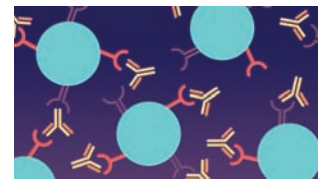
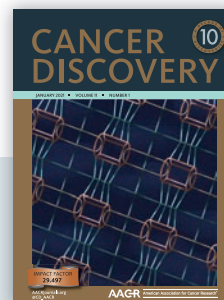


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ON THE COVER

Cancer cells require heightened numbers of nuclear pore complexes (NPC) and increased NPC synthesis relative to normal cells, but targeting this essential cellular component has not generally been considered feasible. Sakuma and colleagues showed that depletion of NPC components preferentially kills cancer cells by causing nuclear transport failure, aberrant gene expression, and DNA-damage accumulation, whereas normal cells exhibited only a reversible state of cell-cycle arrest. *In vivo*, this corresponded with regression of melanoma and colorectal cancer xenograft tumors along with inhibition of leukemia cell proliferation. This work suggests that, contrary to the common assumption, targeting the NPC may be a viable strategy for anticancer therapies. For more information, see the article by Sakuma and colleagues on page 176.



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