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Précis: Longitudinal gut microbiome and immune analysis from randomized microbiome modulation in melanoma patients treated with nivolumab reveal novel insights about the impact of antibiotic preconditioning on immunity.

RESEARCH ARTICLES **CD70-Targeted Allogeneic CAR T-Cell Therapy for Advanced Clear Cell Renal Cell Carcinoma.....1176**

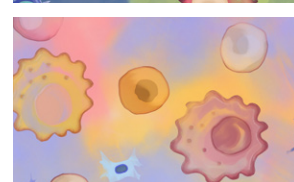
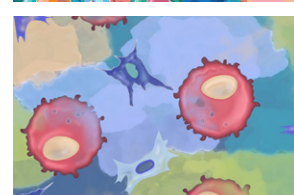
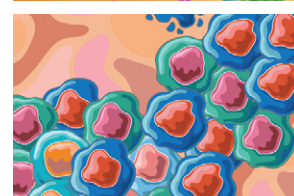
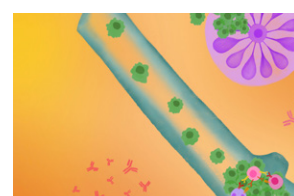
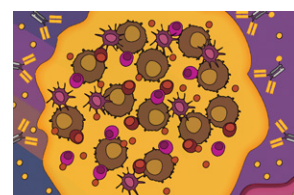
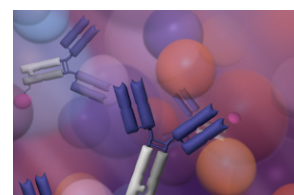
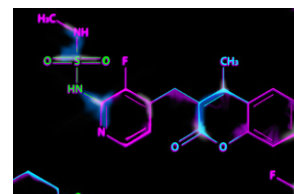
S.K. Pal, B. Tran, J.B.A.G. Haanen, M.E. Hurwitz, A. Sacher, N.M. Tannir, L.E. Budde, S.J. Harrison, S. Klobuch, S.S. Patel, L. Meza, M.L. Dequeant, A. Ma, Q.A. He, L.M. Williams, A. Keegan, E.B. Gurary, H. Dar, S. Karnik, C. Guo, H. Heath, R.R. Yuen, P.K. Morrow, N. Agarwal, and S.A. Srour

Précis: CTX130, an allogeneic CD70-targeting CAR-T cell therapy, yielded disease control in the majority of patients with clear cell renal cell carcinoma treated in a phase I clinical trial, with one patient obtaining a durable complete remission.

The Pan-RAF-MEK Nondegrading Molecular Glue NST-628 Is a Potent and Brain-Penetrant Inhibitor of the RAS-MAPK Pathway with Activity across Diverse RAS- and RAF-Driven Cancers.....1190

M.B. Ryan, B. Quade, N. Schenk, Z. Fang, M. Zingg, S.E. Cohen, B.M. Swalm, C. Li, A. Özen, C. Ye, M.S. Ritorto, X. Huang, A.C. Dar, Y. Han, K.P. Hoeflich, M. Hale, and M. Hagle

Précis: NST-628 is a potent and CNS penetrant pan-RAF-MEK molecular glue with broad efficacy in RAS- and RAF-driven models.





IL2 Targeted to CD8⁺ T Cells Promotes Robust Effector T-cell Responses and Potent Antitumor Immunity.....1206

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Précis: Cis-targeting of IL2 to CD8⁺ T cells shows improved anti-tumor activity and reduced toxicity compared to broadly acting IL2, supporting the evaluation of such a strategy in patients.

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CD8-Targeted IL2 Unleashes Tumor-Specific Immunity in Human Cancer Tissue by Reviving the Dysfunctional T-cell Pool.....1226

P. Kaptein, N. Slingerland, C. Metoikidou, F. Prinz, S. Brokamp, M. Machuca-Ostos, G. de Roo, T.N.M. Schumacher, Y.A. Yeung, K.D. Moynihan, I.M. Djuretic, and D.S. Thommen

Précis: CD8-IL2, an IL2 variant designed to selectively target CD8⁺ T cells, induced reinvigoration and cytotoxicity of dysfunctional T cells in human cancer tissues, exhibiting superior efficacy compared to PD-1 blockade.

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Combining TIGIT Blockade with MDSC Inhibition Hinders Breast Cancer Bone Metastasis by Activating Antitumor Immunity.....1252

L. Monteran, N. Ershaid, Y. Scharff, Y. Zoabi, T. Sanalla, Y. Ding, A. Pavlovsky, Y. Zait, M. Langer, T. Caller, A. Eldar-Boock, C. Avivi, A. Sonnenblick, R. Satchi-Fainaro, I. Barshack, N. Shomron, X.H.-F. Zhang, and N. Erez

Précis: Transcriptome profiling and functional assays demonstrated that MDSCs in bone metastasis impede CTL function via the TIGIT-CD155 axis and identified IL-1 β as a central driver of immunosuppression, establishing these signaling nodes as therapeutic targets for immunotherapy of bone metastasis.

Paradoxical Activation of Oncogenic Signaling as a Cancer Treatment Strategy.....1276

M.H. Dias, A. Frisques, S. Wang, J.M. Fernandes Neto, F. van Gemert, S. Mourragui, C. Papagianni, H.J. Kuiken, S. Mainardi, D. Alvarez-Villanueva, C. Liefstink, B. Morris, A. Dekker, E. van Dijk, L.H.S. Wilms, M.S. da Silva, R.A. Jansen, A. Mulero-Sánchez, E. Malzer, A. Vidal, C. Santos, R. Salazar, R.A.M. Wailemann, T.E.P. Torres, G. De Conti, J.A. Raaijmakers, P. Snaebjornsson, S. Yuan, W. Qin, J.S. Kovach, H.A. Armelin, H. te Riele, A. van Oudenaarden, H. Jin, R.L. Beijersbergen, A. Villanueva, R.H. Medema, and R. Bernards

Précis: Overactivation of oncogenic signaling, combined with perturbation of the resulting stress responses, is an efficient strategy to kill cancer cells and selects for drug resistance characterized by suppression of oncogenic capacity.

Senescent CAFs Mediate Immunosuppression and Drive Breast Cancer Progression.....1302

J. Ye, J.M. Baer, D.V. Faget, V.A. Morikis, Q. Ren, A. Melam, A.P. Delgado, X. Luo, S.M. Bagchi, J.I. Belle, E. Campos, M. Friedman, D.J. Veis, E.S. Knudsen, A.K. Witkiewicz, S. Powers, G.D. Longmore, D.G. DeNardo, and S.A. Stewart

Précis: Cellular senescence arises in a specific subset of breast cancer myfibroblastic CAFs that modulate the ECM to potentially limit NK cell function and thus could be an important therapeutic target to limit breast cancer progression.

See article, p. 1324

Senescence Defines a Distinct Subset of Myfibroblasts That Orchestrates Immunosuppression in Pancreatic Cancer.....1324

J.I. Belle, D. Sen, J.M. Baer, X. Liu, V.E. Lander, J. Ye, B.E. Sells, B.L. Knolhoff, A. Faiz, L.-I. Kang, G. Qian, R.C. Fields, L. Ding, H. Kim, P.P. Provenzano, S.A. Stewart, and D.G. DeNardo

Précis: Senescent myfibroblasts develop in the fibrotic environment of pancreatic cancer and in turn drive ECM density, promote immunosuppressive macrophage phenotypes, and limit anti-tumor T cell immunity.

See article, p. 1302

Expression of Concern

Expression of Concern: Exploiting Drug Addiction Mechanisms to Select against MAPKi-Resistant Melanoma.....1356

Expression of Concern: Durable Suppression of Acquired MEK Inhibitor Resistance in Cancer by Sequestering MEK from ERK and Promoting Antitumor T-cell Immunity.....1357

ON THE COVER

The majority of antitumor therapeutic strategies inhibit aberrant oncogenic pathways. As an alternative approach, Dias and colleagues assessed the efficacy of paradoxical hyperactivation of oncogenic signaling in disrupting cancer homeostasis and suppressing tumor growth. Inhibition of protein phosphatase 2A (PP2A) led to overactivation of several oncogenic signaling pathways and subsequent induction of stress responses in colon cancer cells. Combined inhibition of PP2A and WEE1 synergistically suppressed tumor growth in multiple models as well as patient-derived tumors. Notably, resistance to this therapeutic combination was tumor suppressive, resulting in loss of oncogenic signaling and inhibition of tumor growth *in vivo*. These findings support further clinical evaluation of deliberate hyperactivation of oncogenic signaling as a potential anticancer therapeutic strategy. For more information, see the article by Dias and colleagues on page 1276. Artwork by Bianca Dunn.

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