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Chen-Hua Chuang, Madeleine Dorsch, Philip Dujardin, Sukrit Silas, Kristina Ueffing, Johanna M. Höken, Dian Yang, Monte M. Winslow, and Barbara M. Grünert  
This study characterizes altered mitochondria functionality of the metastatic cell state in lung cancer and opens new avenues for metastasis-specific therapeutic targeting.

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These findings show that a novel IncRNA SCIRT counteracts breast tumorigenesis by opposing transcriptional networks associated with cell cycle and self-renewal.  
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594 Gain of HIF1 Activity and Loss of miRNA let-7d Promote Breast Cancer Metastasis to the Brain via the PDGF/PDGFR Axis
Christof B. Wyss, Nathalie Duffey, Sanam Peyvandi, David Barras, Amaia Martinez Usatorre, Oriana Coquoz, Pedro Romero, Mauro Delorenzi, Girieca Lorusso, and Curzio Rüegg
These findings show that loss of miRNA let-7d and active HIF1 signaling promotes breast cancer brain metastasis via PDGF and that pharmacologic inhibition of PDGFR suppresses brain metastasis, suggesting novel therapeutic opportunities.

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606 Stromal Platelet-Derived Growth Factor Receptor-β Signaling Promotes Breast Cancer Metastasis in the Brain
This study reveals a previously unknown role for PDGFB-to-PDGFRβ paracrine signaling in the promotion of breast cancer brain metastases and support the prognostic and therapeutic clinical utility of this pathway for patients.

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Georg Hilfenhaus, Ana Mompeón, Jonathan Freshman, Divya P. Prajapati, Gloria Hernandez, Vanessa M. Freitas, Feiyang Ma, Adam D. Langenbacher, Snezana Mirkov, Dana Song, Byoung-Kyu Cho, Young Ah Goo, Matteo Pellegrini, Jau-Nian Chen, Robert Damoiseaux, and M. Luisa Iruela-Arispe
This study reveals a previously unknown role for PDGFB-to-PDGFRβ paracrine signaling in the promotion of breast cancer brain metastases and support the prognostic and therapeutic clinical utility of this pathway for patients.

634 Myeloma-Modified Adipocytes Exhibit Metabolic Dysfunction and a Senescence-Associated Secretory Phenotype
Heather Fairfield, Amel Dudakovic, Casper M. Khatib, Mariah Farrell, Samantha Costa, Carolyne Falank, Maja Hinge, Connor S. Murphy, Victoria DeMambro, Jessica A. Pettitt, Christine W. Lary, Heath E. Driscoll, Michelle M. McDonald, Moustapha Kassem, Clifford Rosen, Thomas L. Andersen, Andre J. van Wijnen, Abbas Jafari, and Michaela R. Reagan
This study changes the foundational understanding of how cancer cells hijack the bone marrow microenvironment and demonstrates that tumor cells induce senescence and metabolic changes in adipocytes, potentially driving new therapeutic directions.

See related article by Wyss and colleagues, p. 594

648 Hyal2 Expression in Tumor-Associated Myeloid Cells Mediates Cancer-Related Inflammation in Bladder Cancer
Paul R. Dominguez-Gutierrez, Elizabeth P. Kwenda, William Donelan, Padraic O’Malley, Paul L. Crispen, and Sergei Kusmartsev
This study identifies Hyal2-expressing tumor-associated myeloid cells of monocyte-macrophage lineage as contributors to hyaluronan degradation in bladder cancer tissue, leading to accumulation of inflammatory and proangiogenic low molecular weight hyaluronan fragments.

658 Myeloid-Derived Suppressor Cells Are a Major Source of Wnt5A in the Melanoma Microenvironment and Depend on Wnt5A for Full Suppressive Activity
Stephen M. Douglass, Mitchell E. Fane, Emilio Sansreviero, Brett L. Ecker, Curtis H. Kugel III, Reeti Behera, Vinit Kumar, Evgenii N. Tcyganov, Xiangfan Yin, Qin Liu, Yash Chhabra, Gretchen M. Alicea, Reiji Kuruvilla, Dmitry I. Gabrilovich, and Ashani T. Weeraratna
These findings demonstrate that myeloid cells provide a major source of Wnt5A to facilitate metastatic potential in melanoma cells and rely on Wnt5A for their immunosuppressive function.

671 Folate Receptor Beta Designates Immunosuppressive Tumor-Associated Myeloid Cells That Can Be Reprogrammed with Folate-Targeted Drugs
FRβ serves as both a means to identify and target MDSCs and TAMs within the tumor, allowing for delivery of immunomodulatory compounds to tumor myeloid cells in a variety of cancers.
Cyclophosphamide and Vinorelbine Activate Stem-Like CD8+ T Cells and Improve Anti-PD-1 Efficacy in Triple-Negative Breast Cancer

Paolo Falvo, Stefania Orecchioni, Roman Hillje, Alessandro Raveane, Patrizia Mancuso, Chiara Camisaschi, Lucilla Luzi, PierGiuseppe Pellici, and Francesco Bertolini

A combinatorial therapy in mouse models of breast cancer increases checkpoint inhibition by activating antigen-presenting cells, enhancing intratumoral Tcf1+ stem-like CD8+ T cells, and increasing progenitor exhausted CD8+ T cells.

Axl and Mertk Receptors Cooperate to Promote Breast Cancer Progression by Combined Oncogenic Signaling and Evasion of Host Antitumor Immunity

Viralkumar Davra, Sushil Kumar, Ke Geng, David Calianese, Dhriti Mehta, Varsha Gadiyar, Canan Kasikara, Kevin C. Lahey, Yun-juan Chang, Michael Quigley, Thomas E. Spires, and Raymond B. Birge

This study demonstrates how TAM receptors act both as oncogenic tyrosine kinases and as receptors that mediate immune evasion in cancer progression.

Cisplatin-Mediated Upregulation of APE2 Binding to MYH9 Provokes Mitochondrial Fragmentation and Acute Kidney Injury

Yi Hu, Chun Yang, Tania Amorim, Mohsin Maqbool, Jenny Lin, Chuanfeng Fang, Li Xue, Ariel Kwart, Hua Fang, Mei Yin, Allison J. Janocha, Daisuke Tsuchimoto, Yusaku Nakabeppu, Xiaofeng Jiang, Alex Mejia-Garcia, Faiz Anwer, Jack Khouri, Xin Qi, Qing Y. Zheng, Jennifer S. Yu, Shan Yan, Thomas LaFramboise, Kenneth C. Anderson, Leal C. Herlitz, Nikhil C. Munshi, Jianhong Lin, and Jianjun Zhao

These results reveal and highlight an unexpected role of APE2 via its interaction with MYH9 and suggest that APE2 has the potential to prevent acute kidney injury in cisplatin-treated cancer patients.

Radiomic Detection of EGFR Mutations in NSCLC

Giovanni Rossi, Emanuele Barabino, Alessandro Fedeli, Gianluca Micara, Simona Coco, Alessandro Russo, Vincenzo Adamo, Francesco Buemi, Lodovica Zullo, Mariella Dono, Giuseppe De Luca, Luca Longo, Maria Giovanna Dal Bello, Marco Tagliamento, Angela Alama, Giuseppe Cittadini, Paolo Pronzato, and Carlo Genova

These findings demonstrate that data normalization and “test-retest” methods might improve the performance of machine learning models on radiomics images and increase their reliability when used on external validation datasets.

Steroid Hormone Receptor and Infiltrating Immune Cell Status Reveals Therapeutic Vulnerabilities of ESRI-Mutant Breast Cancer


Targetable alterations in MBC, including AR, CHI3L1, and ISG, arise following estrogen-deprivation, and ER-mutant metastases may respond to immunotherapies due to elevated PD-L1+ macrophages.

See related article by Arnesen and colleagues, p. 539

Activation of Receptor Tyrosine Kinases Mediates Acquired Resistance to MEK Inhibition in Malignant Peripheral Nerve Sheath Tumors

Jiawan Wang, Kai Pollard, Ana Calizo, and Christine A. Prattillas

This study demonstrates that MEKi plus MET inhibitor may delay or prevent a novel mechanism of acquired MEKi resistance, with clinical implications for MPNST patients harboring NF1 alterations.

Optimized Doxorubicin Chemotherapy for Diffuse Large B-cell Lymphoma Exploits Nanocarrier Delivery to Transferrin Receptors

Artavaad Arunov, Piumi Y. Liyanage, Asaad Trabolsi, Evan R. Roberts, Lingxiao Li, Braulio C.L.B. Ferreira, Zhen Gao, Yuguang Ban, Austin D. Newsam, Melissa W. Taggart, Francisco Vega, Daniel Bilbao, Roger M. Leblanc, and Jonathan H. Schatz

Targeted nanoparticle delivery of doxorubicin chemotherapy via the TRF1 receptor presents a new opportunity against high-risk DLBCL tumors using potency and precision.

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Translational Science

Cisplatin-Mediated Upregulation of APE2 Binding to MYH9 Provokes Mitochondrial Fragmentation and Acute Kidney Injury

Yi Hu, Chun Yang, Tania Amorim, Mohsin Maqbool, Jenny Lin, Chuanfeng Fang, Li Xue, Ariel Kwart, Hua Fang, Mei Yin, Allison J. Janocha, Daisuke Tsuchimoto, Yusaku Nakabeppu, Xiaofeng Jiang, Alex Mejia-Garcia, Faiz Anwer, Jack Khouri, Xin Qi, Qing Y. Zheng, Jennifer S. Yu, Shan Yan, Thomas LaFramboise, Kenneth C. Anderson, Leal C. Herlitz, Nikhil C. Munshi, Jianhong Lin, and Jianjun Zhao

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Targeted nanoparticle delivery of doxorubicin chemotherapy via the TRF1 receptor presents a new opportunity against high-risk DLBCL tumors using potency and precision.
ABOUT THE COVER

Stromal specific activation of platelet-derived growth factor receptor-β (PDGFRβ) in the metastatic microenvironment promotes breast cancer metastasis to the brain. Specifically, the Fsp1-cre transgene was used to hyperactivate PDGFRβ in the mesenchymal population. A confocal image shows native tdTomato fluorescence (red) and GFAP (green) immunostaining in the brain stroma of a Fsp1-cre;Rosa26-LSL-tdTomato reporter mouse. The dual tdTomato(FSP1)/GFAP-positive cells represent a novel stromal population implicated in creating a prometastatic niche through PDGFRβ signaling. For details, see article by Thies and colleagues on page 606.
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