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### BREAKING ADVANCES

- [3381] Highlights from Recent Cancer Literature

### OBITUARY

- [3383] Enrico Mihich, MD: In Memoriam (1928–2016) 
  Margaret Foti and Youcef M. Rustum

### MEETING REPORT

- [3386] Obstacles, Opportunities and Priorities for Advancing Metastatic Breast Cancer Research 
  Margaret Flowers, Stephanie Birkey Reffey, Shirley A. Mertz, and Marc Hurlbert; for the Metastatic Breast Cancer Alliance

### MOLECULAR AND CELLULAR PATHOBIOLOGY

- [3391] Cyclin D1 Restrains Oncogene-Induced Autophagy by Regulating the AMPK–LKB1 Signaling Axis 
  Précis: These findings suggest how AMPK activation by cyclin D1 may couple cell proliferation to energy homeostasis.

- [3406] VHL Inactivation in Precancerous Kidney Cells Induces an Inflammatory Response via ER Stress–Activated IRE1α Signaling 
  Chan-Yen Kuo, Chih-Hung Lin, and Tien Hsu
  Précis: A tumor suppressor gene mutation in normal epithelial cells can induce inflammatory response via ER stress signaling, thus providing a potential early cancer prevention strategy via modulation of metabolic stress.

### TUMOR AND STEM CELL BIOLOGY

- [3417] Novel Androgen Receptor Coregulator GRHL2 Exerts Both Oncogenic and Antimetastatic Functions in Prostate Cancer 
  Précis: These results show how a grainyhead-like transcription factor enhances androgen receptor expression and activity, driving proliferation of prostate cancer cells, but it also acts differentially to limit their metastatic capacity.

- [3431] Liver Metastasis Is Facilitated by the Adherence of Circulating Tumor Cells to Vascular Fibronectin Deposits 
  Jorge Barbazán, Lorena Alonso-Alconada, Nadia Ellihatib, Sara Geraldo, Vasily Gurchenkov, Alexandros Gentis, Guillaume van Niel, Roberta Palmulli, Beatriz Fernández, Patricia Viaño, Tomas Garcia-Caballero, Rafael López-López, Miguel Abal, and Danijela Matic Vignjevic
  Précis: Fibronectin accumulations at the luminal side of liver blood vessels act as an anchor for cancer cells, revealing an important new mechanism of extravasation with potential therapeutic implications to retard metastatic risk.

- [3442] Distinct Roles of HES1 in Normal Stem Cells and Tumor Stem-like Cells of the Intestine 
  Norihiro Goto, Taro Ueo, Akihisa Fukuda, Kenji Kawada, Yoshiharu Sakai, Hiroyuki Miyoshi, Makoto Mark Takeo, Tsutomu Chiba, and Hiroshi Seno
  Précis: These results show how a stem cell transcription factor plays a different role in cancer stem-like cells, where its disruption leads to tumor regression without perturbing normal stem cell homeostasis, thereby validating it as a cancer therapeutic target.

  Valerie N. Barton, Jessica L. Christenson, Michael A. Gordon, Lisa I. Greene, Thomas J. Rogers, Kiel Butterfield, Beatrice Babbs, Nicole S. Spoelstra, Nicholas C. D’Amato, Anthony Elias, and Jennifer K. Richer
  Précis: These mechanistic studies demonstrate that androgen receptor–targeting therapies may empower chemotherapy in triple-negative breast cancers by targeting drug-resistant cancer stem-like cells.
3467 Mismatch Repair Proteins Initiate Epigenetic Alterations during Inflammation-Driven Tumorigenesis
Ashley R. Maiuri, Michael Peng, Ram Podicheti, Shruthi Srinivaskumar, Caitlin M. Kamplain, Douglas B. Busch, Christina E. DeSefano Shields, Cynthia L. Sears, and Heather M. O’Hagan
Précis: MSH2 is required for recruitment of epigenetic proteins to damaged chromatin and for DNA hypermethylation-mediated alterations in inflammation-induced tumors.

3513 Inhibition of Mitochondrial Matrix Chaperones and Antiapoptotic Bcl-2 Family Proteins Empower Antitumor Therapeutic Responses
Georg Karpel-Massler, Chiaki Tsuge Ishida, Elena Blanchetti, Chang Shu, Rolando Perez-Lorenzo, Basil Horst, Matei Banu, Kevin A. Roth, Jeffrey N. Bruce, Peter Canoll, Dario C. Altieri, and Markus D. Siegelin
Précis: This study offers a preclinical proof of concept for the combination of BH3 mimetic drugs and mitochondrial chaperone inhibitors as an effective therapeutic strategy for better management of drug-resistant tumors.

3527 Targeting FBW7 as a Strategy to Overcome Resistance to Targeted Therapy in Non–Small Cell Lung Cancer
Mingxiang Ye, Yong Zhang, Xinxin Zhang, Jianbin Zhang, Pengyu Jing, Liang Cao, Nan Li, Xia Li, Libo Yao, Jian Zhang, and Jian Zhang
Précis: FBW7 downregulations stabilize the antiapoptotic BCL-2 family member MCL-1, unveiling a new mechanism of resistance to targeted therapeutics in the most common form of lung cancer.

3540 Immune-Related Gene Expression Profiling After PD-1 Blockade in Non–Small Cell Lung Carcinoma, Head and Neck Squamous Cell Carcinoma, and Melanoma
Alex Prat, Alejandro Navarro, Laia Paré, Noemí Reguart, Patricia Galván, Tomás Pascual, Alex Martínez, Paolo Nuciforo, Laura Conmera, Lluíca Alos, Nuria Paro, Susana Cerdà, Cheng Fan, Joel S. Parker, Lydia Gaba, Iván Victoria, Nuria Viholas, Ana Vivancos, Ana Arance, and Enriqueta Felip
Précis: These results argue that a pre-existing stable adaptive immune response is sufficient to predict a clinical outcome, regardless of the type of cancer or a PD-1 therapeutic antibody administered to patients.

3551 EGFR Mediates Responses to Small-Molecule Drugs Targeting Oncogenic Fusion Kinases
Aria Vaishnavi, Laura Schubert, Uwe Rix, Lindsay A. Marek, Anh T. Le, Stephen B. Keysar, Magdalena J. Głogowska, Matthew A. Smith, Severine Kako, Natalia I. Sumi, Kurtis D. Davies, Kathryn E. Ware, Mariileña Varella-Garcia, Eric B. Haura, Antonio Jimeno, Lynn E. Heasley, Dara L. Aisner, and Robert C. Doebele
Précis: These findings show how previously unknown EGFR signaling mechanisms confer a critical survival mechanism to enable evasion from oncogene-specific inhibitors, providing a rationale to cotarget EGFR to reduce risks of developing drug resistance.
The National Cancer Institute ALMANAC: A Comprehensive Screening Resource for the Detection of Anticancer Drug Pairs with Enhanced Therapeutic Activity


Précis: This study describes a validated web-based resource to identify promising combinations of approved drugs with anticancer activity for further mechanistic study and translation to clinical trials.

Microenvironment and Immunology

Chimeric PD-1:28 Receptor Upgrades Low-Avidity T cells and Restores Effector Function of Tumor-Infiltrating Lymphocytes for Adoptive Cell Therapy

Ramona Schlenker, Luis Felipe Olguín-Contreras, Matthias Leisegang, Julia Schnappinger, Anja Disovic, Svenja Rühlând, Peter J. Nelson, Heinrich Leonhardt, Hartmann Harz, Susanne Wilde, Dolores J. Schendel, Wolfgang Uckert, Gerald Willimsky, and Elfriede Noessner

Précis: This study illustrates a method to empower adoptive T-cell therapies by engineering higher avidities that can improve effector function without sacrificing specificity.

Epstein–Barr Virus-Induced VEGF and GM-CSF Drive Nasopharyngeal Carcinoma Metastasis via Recruitment and Activation of Macrophages

Di Huang, Shi-Jian Song, Zi-Zhao Wu, Wei Wu, Xiu-Ying Cui, Iia-Ning Chen, Mu-Sheng Zeng, and Shi-Cheng Su

Précis: These findings define a feed-forward loop between virally infected nasopharyngeal cancer cells and macrophages and show how metastatic potential can evolve concurrently with virus-induced chronic inflammation.

Tumor-Associated Macrophages Promote Malignant Progression of Breast Phyllodes Tumors by Inducing Myofibroblast Differentiation

Yan Nie, Jianing Chen, Di Huang, Yandan Yao, Jiewen Chen, Lin Ding, Jiayi Zeng, Shicheng Su, Xue Chao, Fengxi Su, Herui Yao, Hai Hu, and Erwei Song

Précis: In establishing how tumor-associated macrophages drive myofibroblast differentiation and malignant progression of a type of stromal breast tumor, this study uncovers a series of potential therapeutic targets for its treatment.

STING Activation Reverses Lymphoma-Mediated Resistance to Antibody Immunotherapy

Lekh N. Dahal, Lang Dou, Khiyam Hussain, Rena Liu, Alexander Earley, Kerry L. Cox, Salome Murinello, Ian Tracy, Francesco Foroni, Andrew J. Steele, Patrick J. Duriez, Diego Gomez-Nicola, Jessica L. Teeling, Martin J. Glennie, Mark S. Cragg, and Stephen A. Beers

Précis: These findings suggest that STING agonists can empower monoclonal antibody therapies by reprogramming tumor-associated macrophages and curbing locoregional immunosuppression in the tumor microenvironment.

Deletion of Lactate Dehydrogenase-A in Myeloid Cells Triggers Antitumor Immunity

Pankaj Seth, Eva Csizmadia, Andreas Hedblom, Marta Vuermich, Han Xie, Maillin Li, Maria Serena Longhi, and Barbara Wegiel

Précis: Lactate dehydrogenase-A in the tumor microenvironment is a key determinant of immune responses against cancer and as such may provide a therapeutic target to blunt locoregional immune escape in tumors.

Sarcoma Eradication by Doxorubicin and Targeted TNF Relies upon CD8+ T-cell Recognition of a Retroviral Antigen

Philipp Probst, Janine Kopp, Annette Oxenius, Mario P. Colombo, Danilo Ritz, Tim Fugmann, and Dario Neri

Précis: These findings offer evidence that retroviral genes contribute to tumoral immune surveillance through a process that can be improved by treatment with a TNF derivative and the chemotherapeutic drug doxorubicin.

CXCL1 Is Critical for Premetastatic Niche Formation and Metastasis in Colorectal Cancer

Dingzhi Wang, Haiyan Sun, Jie Wei, Bo Cen, and Raymond N. DuBois

Précis: These findings show how VEGFA induces production of the neutrophil chemotactant CXCL1 in primary tumor macrophages, driving myeloid-derived suppressor cells to generate a premetastatic niche that enables later metastasis.

Landscape of Combination Immunotherapy and Targeted Therapy to Improve Cancer Management

Leandro M. Colli, Mitchell J. Machiela, Han Zhang, Timothy A. Myers, Lea Jessop, Olivier Delattre, Kai Yu, and Stephen J. Chanock

Précis: A survey of genomic profiles from public databases indicate that 8.9% of solid tumor patients could benefit from combinations of immunotherapy and targeted therapy, an approach that might significantly impact overall patient survival.

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3564 The National Cancer Institute ALMANAC: A Comprehensive Screening Resource for the Detection of Anticancer Drug Pairs with Enhanced Therapeutic Activity

3577 Chimeric PD-1:28 Receptor Upgrades Low-Avidity T cells and Restores Effector Function of Tumor-Infiltrating Lymphocytes for Adoptive Cell Therapy

3591 Epstein–Barr Virus-Induced VEGF and GM-CSF Drive Nasopharyngeal Carcinoma Metastasis via Recruitment and Activation of Macrophages

3605 Tumor-Associated Macrophages Promote Malignant Progression of Breast Phyllodes Tumors by Inducing Myofibroblast Differentiation

3619 STING Activation Reverses Lymphoma-Mediated Resistance to Antibody Immunotherapy

3632 Deletion of Lactate Dehydrogenase-A in Myeloid Cells Triggers Antitumor Immunity

3644 Sarcoma Eradication by Doxorubicin and Targeted TNF Relies upon CD8+ T-cell Recognition of a Retroviral Antigen

3655 CXCL1 Is Critical for Premetastatic Niche Formation and Metastasis in Colorectal Cancer

3666 Landscape of Combination Immunotherapy and Targeted Therapy to Improve Cancer Management
Expansion of Tumor-Infiltrating CD8+ T cells Expressing PD-1 Improves the Efficacy of Adoptive T-cell Therapy

Sarita M. Fernandez-Poma, Diego Salas-Benito, Teresa Lozano, Noelia Casares, Jose-Ignacio Riezu-Boj, Uxua Mancheño, Edurne Elizalde, Diego Alignani, Natalia Zubeldia, Itziar Otxoa, Enrique Conde, Pablo Sarobe, Juan Jose Lasarte, and Sandra Hervas-Stubbs

Précis: The antitumor activity of adoptive T-cell therapy is limited by low rates of ex vivo expansion of the highly differentiated PD-1+ CD8 TIL population, which is responsible for the majority of tumor cell recognition in bulk CD8 TIL.

Persistent Immune Stimulation Exacerbates Genetically Driven Myeloproliferative Disorders via Stromal Remodeling

Claudio Tripodo, Alessia Burocchi, Pier Paolo Piccaluga, Claudia Chiodoni, Paola Portararo, Barbara Cappetti, Laura Botti, Alessandro Gulino, Alessandro Isidori, Arcangelo Liso, Giuseppe Visani, Maria Paola Martelli, Brunangelo Falini, Pier Paolo Pandolfi, Mario P. Colombo, and Sabina Sangaletti

Précis: Formation of neutrophil extracellular traps (NET) composed of DNA-protein complexes in the bone marrow tissue microenvironment stimulates the expansion of myeloid precursor cells, which support a certain class of human leukemias.

RETRACTION

Retraction: Molecular Mechanism of MART-1+ / A*0201+ Human Melanoma Resistance to Specific CTL-Killing Despite Functional Tumor–CTL Interaction

PREVENTION AND EPIDEMIOLOGY

Beta-Blocker Drug Use and Survival among Patients with Pancreatic Adenocarcinoma

Ruzan Udumyan, Scott Montgomery, Fang Fang, Henrik Almroth, Unnur Valdimarsdottir, Anders Ekborn, Karin E. Smedby, and Katja Fall

Précis: These results suggest the repositioning of beta-blocker drugs, which are used widely to control hypertension and cardiac arrhythmias, to improve the survival of pancreatic cancer patients.

Assessment of Breast Cancer Risk Factors Reveals Subtype Heterogeneity

Johanna Holm, Louise Eriksson, Alexander Ploner, Mikael Eriksson, Mattias Rantalainen, Jingmei Li, Per Hall, and Kamila Czene

Précis: Breast cancer risk factors differ by molecular subtype, supporting distinct etiologies and offering implications for prevention studies, which rely on modeling risk prediction.

RETRACTION

Retraction: Molecular Mechanism of MART-1+ / A*0201+ Human Melanoma Resistance to Specific CTL-Killing Despite Functional Tumor–CTL Interaction

CORRECTIONS

Correction: Rescue of p53 Function by Small-Molecule RITA in Cervical Carcinoma by Blocking E6-Mediated Degradation

Correction: Epigenetic Switch between SOX2 and SOX9 Regulates Cancer Cell Plasticity

Correction: Genetic Disruption of the Multifunctional CD98/LAT1 Complex Demonstrates the Key Role of Essential Amino Acid Transport in the Control of mTORC1 and Tumor Growth
ABOUT THE COVER

Immunometabolism is emerging as a critical determinant of cancer pathophysiology. A balance between tumor promotion and elimination is dependent on the state of functional polarization of macrophage populations within the tumor microenvironment. Lactic acid generated by lactate dehydrogenase-A is a key metabolite that facilitates the immunosuppressive tumor microenvironment. Deletion of lactate dehydrogenase-A in myeloid cells restores the immunocompetent tumor microenvironment by reversing macrophage phenotype and antitumor immunity. Immunofluorescence staining revealed an increased number of infiltrating inducible nitric oxide synthase-positive (red) and M1-skewed F4.80-positive (green) macrophages in K-Ras tumors after deletion of lactate dehydrogenase-A. For details, see article by Seth and colleagues on page 3632.