

Highlights of This Issue 1973

REVIEW

- 1975** Durability of Kinase-Directed Therapies—A Network Perspective on Response and Resistance
Brion W. Murray and Nichol Miller

SMALL MOLECULE THERAPEUTICS

- 1985** Heat Shock Protein 90 Is a Potential Therapeutic Target in Cholangiocarcinoma
Tomoki Shirota, Hidenori Ojima, Nobuyoshi Hiraoka, Kazuaki Shimada, Hirofumi Rokutan, Yasuhito Arai, Yae Kanai, Shinichi Miyagawa, and Tatsuhiro Shibata
- 1994** Small Molecule Inhibition of MDM2–p53 Interaction Augments Radiation Response in Human Tumors
Lauryn R. Werner, Shyhmin Huang, David M. Francis, Eric A. Armstrong, Fang Ma, Chunrong Li, Gopal Iyer, Jude Canon, and Paul M. Harari
- 2004** LY2606368 Causes Replication Catastrophe and Antitumor Effects through CHK1-Dependent Mechanisms
Constance King, H. Bruce Diaz, Samuel McNeely, Darlene Barnard, Jack Dempsey, Wayne Blosser, Richard Beckmann, David Barda, and Mark S. Marshall
- 2014** Small Molecule Inhibition of MERTK Is Efficacious in Non–Small Cell Lung Cancer Models Independent of Driver Oncogene Status
Christopher T. Cummings, Weihe Zhang, Kurtis D. Davies, Gregory D. Kirkpatrick, Dehui Zhang, Deborah DeRyckere, Xiaodong Wang, Stephen V. Frye, H. Shelton Earp, and Douglas K. Graham
- 2023** Altiratinib Inhibits Tumor Growth, Invasion, Angiogenesis, and Microenvironment-Mediated Drug Resistance via Balanced Inhibition of MET, TIE2, and VEGFR2
Bryan D. Smith, Michael D. Kaufman, Cynthia B. Leary, Benjamin A. Turner, Scott C. Wise, Yu Mi Ahn, R. John Booth, Timothy M. Caldwell, Carol L. Ensinger, Molly M. Hood, Wei-Ping Lu, Tristan W. Patt, William C. Patt, Thomas J. Rutkoski, Thiwanka Samarakoon, Hanumaiah Telikepalli, Lakshminarayana Vogeti, Subha Vogeti, Karen M. Yates, Lawrence Chun, Lance J. Stewart, Michael Clare, and Daniel L. Flynn

- 2035** AKT Antagonist AZD5363 Influences Estrogen Receptor Function in Endocrine-Resistant Breast Cancer and Synergizes with Fulvestrant (ICI182780) *In Vivo*
Ricardo Ribas, Sunil Pancholi, Stephanie K. Guest, Elisabetta Marangoni, Qiong Gao, Aurélie Thuleau, Nikiana Simigdala, Urszula M. Polanska, Hayley Campbell, Aradhana Rani, Gianmaria Liccardi, Stephen Johnston, Bary R. Davies, Mitch Dowsett, and Lesley-Ann Martin

LARGE MOLECULE THERAPEUTICS

- 2049** Antitumor Effects of MEHD7945A, a Dual-Specific Antibody against EGFR and HER3, in Combination with Radiation in Lung and Head and Neck Cancers
Chunrong Li, Shyhmin Huang, Eric A. Armstrong, David M. Francis, Lauryn R. Werner, Mark X. Sliwkowski, Albert van der Kogel, and Paul M. Harari
- 2060** Cyclophosphamide-Mediated Tumor Priming for Enhanced Delivery and Antitumor Activity of HER2-Targeted Liposomal Doxorubicin (MM-302)
Elena Geretti, Shannon Curtis Leonard, Nancy Dumont, Helen Lee, Jinzi Zheng, Raquel De Souza, Daniel F. Gaddy, Christopher W. Espelin, David A. Jaffray, Victor Moyo, Ulrik B. Nielsen, Thomas J. Wickham, and Bart S. Hendriks
- 2072** Heregulin–ErbB3-Driven Tumor Growth Persists in PI3 Kinase Mutant Cancer Cells
Defne Yazar, Johanna Lahdenranta, William Kubasek, Ulrik B. Nielsen, and Gavin MacBeath
- 2081** Anti-Endosialin Antibody–Drug Conjugate: Potential in Sarcoma and Other Malignancies
Cecile Rouleau, Diego A. Gianolio, Robert Smale, Stephanie D. Roth, Roy Krumbholz, Jay Harper, Kenneth J. Munroe, Tessa L. Green, Bruce C. Horten, Steven M. Schmid, and Beverly A. Teicher

CANCER BIOLOGY AND SIGNAL TRANSDUCTION

- 2090** CDK1-Mediated SIRT3 Activation Enhances Mitochondrial Function and Tumor Radioresistance
Rui Liu, Ming Fan, Demet Candas, Lili Qin, Xiaodi Zhang, Angela Eldridge, June X. Zou, Tieqiao Zhang, Shuaib Juma, Cuihong Jin, Robert F. Li, Julian Perks, Lun-Quan Sun, Andrew T.M. Vaughan, Chun-Xu Hai, David R. Gius, and Jian Jian Li

Table of Contents

2103 STAT1 Activation Is Enhanced by Cisplatin and Variably Affected by EGFR Inhibition in HNSCC Cells
Nicole C. Schmitt, Sumita Trivedi, and Robert L. Ferris


2112 Nicotine Induces Tumor Growth and Chemoresistance through Activation of the PI3K/Akt/mTOR Pathway in Bladder Cancer
Kazuyuki Yuge, Eiji Kikuchi, Masayuki Hagiwara, Yota Yasumizu, Nobuyuki Tanaka, Takeo Kosaka, Akira Miyajima, and Mototsugu Oya

2121 USP44⁺ Cancer Stem Cell Subclones Contribute to Breast Cancer Aggressiveness by Promoting Vasculogenic Mimicry
Tiejun Liu, Baocun Sun, Xiulan Zhao, Yanlei Li, Xueming Zhao, Ying Liu, Zhi Yao, Qiang Gu, Xueyi Dong, Bing Shao, Xian Lin, Fang Liu, and Jindan An

2132 Ingenol Mebutate Signals via PKC/MEK/ERK in Keratinocytes and Induces Interleukin Decoy Receptors IL1R2 and IL13RA2
Sandra N. Freiberger, Phil F. Cheng, Guergana Iotzova-Weiss, Johannes Neu, Qinxiu Liu, Piotr Dziunycz, John R. Zibert, Reinhard Dummer, Kresten Skak, Mitchell P. Levesque, and Günther F.L. Hofbauer

2143 Histone Deacetylase Inhibitors Inhibit Rhabdomyosarcoma by Reactive Oxygen Species–Dependent Targeting of Specificity Protein Transcription Factors
Erik Hedrick, Lisa Crose, Corinne M. Linardic, and Stephen Safe

MODELS AND TECHNOLOGIES

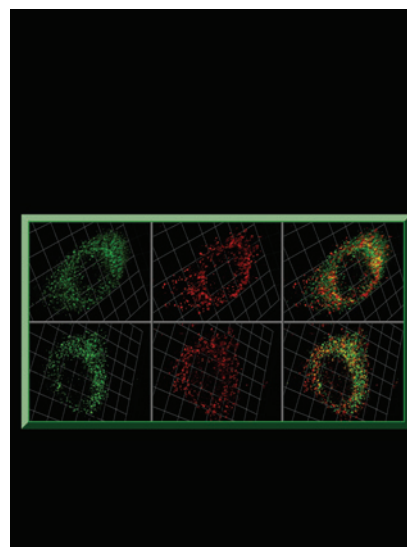
2154 Identification of Circadian Determinants of Cancer Chronotherapy through *In Vitro* Chronopharmacology and Mathematical Modeling
 Sandrine Dulong, Annabelle Ballesta, Alper Okyar, and Francis Lévi

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ABOUT THE COVER

SIRT3, a member of the sirtuin family of protein deacetylases, prevents cell aging by enhancing metabolic homeostasis through regulation of mitochondrial protein deacetylation. How it functions in tumor response to anticancer therapy is unknown. Liu and colleagues discovered that *SIRT3* was transcriptionally regulated by NF- κ B upon radiation, and its enzymatic activity was further enhanced via phosphorylation also by mitochondria-localized Cyclin B1/CDK1 complex. The phosphorylation of SIRT3 by CDK1 was required for mitochondrial functions as well as for cell survival tested by *in vitro* and *in vivo* radiation. Thus, targeting CDK1-SIRT3 phosphorylation-mediated mitochondrial metabolism provides an alternative approach to enhance tumor response to radiotherapy. For details, see the article by Liu and colleagues on page 2090.



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