

MASTERS OF IMMUNOLOGY

- 823** **NF- κ B, an Active Player in Human Cancers**
 Yifeng Xia, Shen Shen, and Inder M. Verma


CANCER IMMUNOLOGY AT THE CROSSROADS: COMPLEMENTARY THERAPEUTIC MODALITIES


- 831** **Combining Radiation and Immunotherapy: A New Systemic Therapy for Solid Tumors?**
 Chad Tang, Xiaohong Wang, Hendrick Soh, Steven Seyedin, Maria Angelica Cortez, Sunil Krishnan, Erminia Massarelli, David Hong, Aung Naing, Adi Diab, Daniel Gomez, Huiping Ye, John Heymach, Ristuko Komaki, James P. Allison, Padmanee Sharma, and James W. Welsh

PRIORITY BRIEF

- 839** **Antigen-Specific Culture of Memory-like CD8 T Cells for Adoptive Immunotherapy**
 Adam J. Litterman, David M. Zellmer, Rebecca S. LaRue, Stephen C. Jameson, and David A. Largaespada
Synopsis: Litterman and colleagues created a cocktail of cytokines and small molecules for ex vivo expansion of naïve or antigen-specific T cells into polyclonal cytotoxic T cells with memory phenotype, and greater proliferative and antitumor activity in vivo.

RESEARCH ARTICLES

- 846** ***In Vitro* Characterization of the Anti-PD-1 Antibody Nivolumab, BMS-936558, and *In Vivo* Toxicology in Non-Human Primates**
 Changyu Wang, Kent B. Thudium, Minhua Han, Xi-Tao Wang, Haichun Huang, Diane Feingersh, Candy Garcia, Yi Wu, Michelle Kuhne, Mohan Srinivasan, Sujata Singh, Susan Wong, Neysa Garner, Heidi Leblanc, R. Todd Bunch, Diann Blanset, Mark J. Selby, and Alan J. Korman
Synopsis: Wang and colleagues describe the development and comprehensive preclinical characterization of nivolumab, a fully human IgG4 (S228P) anti-PD-1 receptor blocking mAb, the antitumor activity and safety profile of which has been demonstrated in human clinical trials in various solid tumors.

- 857** **Mechanisms That Can Promote Peripheral B-cell Lymphoma in ATM-Deficient Mice**
 Suprawee Tepsuporn, Jiazhi Hu, Monica Gostissa, and Frederick W. Alt
Synopsis: Tepsuporn, Hu, and colleagues generated the first mouse models for B-cell lymphoma in the context of ATM deficiency, and they provide a detailed characterization of the mature B-cell lymphomas that arise, revealing an unanticipated mechanism for the developmental propagation of V(D)J recombination-initiated DNA double-strand breaks.

- 857** **Targeting 4-1BB Costimulation to the Tumor Stroma with Bispecific Aptamer Conjugates Enhances the Therapeutic Index of Tumor Immunotherapy**
 Brett Schrand, Alexey Berezhnoy, Randall Brenneman, Anthony Williams, Agata Levay, Ling-Yuan Kong, Ganesh Rao, Shouhao Zhou, Amy B. Heimberger, and Eli Gilboa
Synopsis: Schrand and colleagues report the efficacy in five murine tumor models of an immunotherapeutic approach whereby systemic administration of tumor stroma-targeted 4-1BB aptamer conjugates, which target disseminated tumor lesions, elicits potent antitumor immunity with minimal dose-limiting toxicity.

- 878** **CALGB 150905 (Alliance): Rituximab Broadens the Antilymphoma Response by Activating Unlicensed NK Cells**
 Juan Du, Sandra Lopez-Verges, Brandelyn N. Pitcher, Jeffrey Johnson, Sin-Ho Jung, Lili Zhou, Katharine Hsu, Myron S. Czuczman, Bruce Cheson, Lawrence Kaplan, Lewis L. Lanier, and Jeffrey M. Venstrom
Synopsis: Du and colleagues report that a "missing ligand" genotype predictive of unlicensed NK cells was associated with higher progression-free survival in 101 follicular lymphoma patients treated with rituximab-containing mAb combinations, and that rituximab triggered responses in vitro from healthy-donor unlicensed NK cells.

- 890** **IL32 Is Progressively Expressed in Mycosis Fungoides Independent of Helper T-cell 2 and Helper T-cell 9 Polarization**
 Hanako Ohmatsu, Daniel Humme, Nicholas Gulati, Juana Gonzalez, Markus Möbs, Mayte Suárez-Fariñas, Irma Cardinale, Hiroshi Mitsui, Emma Guttman-Yassky, Wolfram Sterry, and James G. Krueger
Synopsis: Ohmatsu and colleagues report the consistently high and increasing expression of IL32 in cutaneous T-cell lymphoma mycosis fungoides (MF) compared with benign inflammatory skin diseases, and these findings correlate with increases in IFN γ mRNA, suggesting that IL32 may be an autocrine cytokine in MF progression.

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901 STING Ligand c-di-GMP Improves Cancer Vaccination against Metastatic Breast Cancer

Dinesh Chandra, Wilber Quispe-Tintaya, Arthee Jahangir, Denise Asafu-Adjei, Ilyssa Ramos, Herman O. Sintim, Jie Zhou, Yoshihiro Hayakawa, David K.R. Karaolis, and Claudia Gravekamp

Synopsis: Chandra, Quispe-Tintaya, and colleagues show that stimulator of IFN genes (STING) ligand c-di-GMP activated caspase-3, stimulated T cells, and nearly completely eliminated all metastases in mouse breast cancer model 4T1, when combined with Listeria monocytogenes-based Mage-b vaccine in a therapeutic setting.

911 Episomal Expression of Truncated Listeriolysin O in Lmdda-LLO-E7 Vaccine Enhances Antitumor Efficacy by Preferentially Inducing Expansions of CD4⁺FoxP3⁻ and CD8⁺ T Cells



Zhisong Chen, Laurent Ozbun, Namju Chong, Anu Wallecha, Jay A. Berzofsky, and Samir N. Khleif

Synopsis: Chen and colleagues developed an improved, attenuated L. monocytogenes-based vaccine that induced the regression of established mouse TC-1 tumors; they show that listeriolysin O serves as a vaccine adjuvant that decreases Treg frequency by inducing the expansion of non-Treg T cells.

CORRECTION

923 Correction: Bevacizumab plus Ipilimumab in Patients with Metastatic Melanoma

 AC icon indicates Author Choice

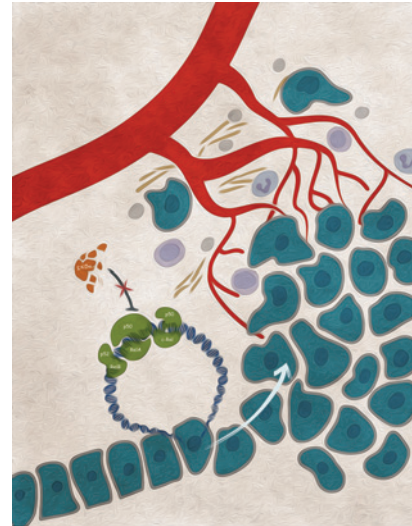
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ABOUT THE COVER

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) comprises a family of five transcription factors (NF- κ B1/p105/p50, NF- κ B2/p100/p52, RelA/p65, RelB, and c-Rel) that form distinct heterodimer or homodimer protein complexes, which bind to consensus DNA sequences at promoter regions of responsive genes. Members of the NF- κ B family are involved in signaling pathways controlling vital biologic processes, and stringent regulation of NF- κ B activity is indispensable for the integrity of cellular functions. Oncogenic mutations can lead to constitutive and/or elevated NF- κ B activity. NF- κ B is also activated by cytokines, growth factors, cellular and environmental stresses, and DNA damage. In premalignant lesions with elevated NF- κ B activity, the accumulation of proinflammatory cytokines contributes to the protumorigenic microenvironment. NF- κ B is the master regulator mediating a cross-talk between inflammation and cancer at multiple levels. NF- κ B activity promotes proliferation and angiogenesis, suppresses apoptosis, and induces epithelial–mesenchymal transition, which can lead to distant metastasis. At tumor sites, NF- κ B activation may remodel local metabolism and anergize the immune system to favor tumor growth. Suppression of NF- κ B in myeloid cells or tumor cells could lead to tumor regression, making the NF- κ B pathway a promising therapeutic target. For more details of NF- κ B activities in human cancers, see the Masters of Immunology primer by Inder M. Verma and colleagues starting on page 823 of this issue.

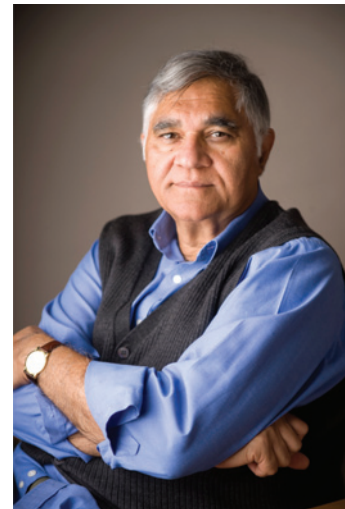


ABOUT THE MASTER

Inder Mohan Verma, PhD, is the Irwin and Joan Jacobs Chair Professor in Exemplary Life Science, Professor and Director of the Laboratory of Genetics at The Salk Institute for Biological Sciences (La Jolla, CA), and an American Cancer Society Professor of Molecular Biology. He is also an adjunct professor in the department of biology at the University of California, San Diego, and a distinguished adjunct professor in the Biotechnology Research Group at the King Abdulaziz University (Jeddah, Saudi Arabia). Dr. Verma was educated at the Lucknow University in India, and received his PhD in Biochemistry from the Weizmann Institute of Science (Rehovot, Israel), characterizing mitochondrial ribosomal RNA from the fungus *Aspergillus nidulans*, under the mentorship of Professor Uri Littauer. In 1971 he joined the laboratory of Nobel laureate David Baltimore at the Massachusetts Institute of Technology (Cambridge, MA), where he studied reverse transcriptase from RNA tumor viruses, including avian myeloblastosis virus, mouse leukemia virus, and hamster leukemia virus. Dr. Verma established his independent laboratory at The Salk Institute in 1974, and at the age of 26, he was one of the youngest faculty members.

Dr. Verma's work on RNA tumor viruses and reverse transcriptase led to his identification and/or characterization of several oncogenes, including c-fos, c-rel, and the breast cancer genes (BRCA1, BRCA2). The Verma laboratory has contributed significantly to the delineation of the regulation and expression of c-fos during prenatal and postnatal development, growth, and differentiation. These investigators have characterized the mechanism of BRCA1 tumor suppression. C-rel is a member of the nuclear factor- κ B (NF- κ B) family of master transcription factors, the subject of this Masters primer. With expertise in molecular biology and retrovirology, Dr. Verma developed viral expression vectors for gene transfer to replace missing or defective cellular proteins, and this work has become the foundation for cell and gene therapy. The Verma laboratory has used the gene therapy technology to generate a mouse model of glioblastoma, from which they have identified neural cancer stem cells, as few as ten of which can induce tumors in immunodeficient mice. They are using the same technique to investigate the initiation and treatment of lung and prostate cancers.

Dr. Verma was born in Sangrur, Punjab, India. He has received many honors, including an Outstanding Investigator Award from the NIH (1988), and he was elected as a member of the Third World Academy of Sciences (1995), the National Academy of Sciences, India (1997), the U.S. National Academy of Sciences (NAS; 1997), the U.S. NAS Institute of Medicine (1999), the American Academy of Arts and Sciences (2000), the European Molecular Biology Organization (1998), and the American Philosophical Society (2006). Dr. Verma was elected as a Foreign Fellow of the Indian National Science Academy (2005). He was awarded the Vilcek Foundation Prize (2008), the ASGT Outstanding Achievement Award (2009), the Spector Prize (2010), and the Pasarow Award in Cancer Research (2010). Dr. Verma now serves as the Editor-in-Chief of the *Proceedings of the National Academy of Science of the United States*.



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