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- 187 **The Carcinoma-Associated Fibroblast Expressing Fibroblast Activation Protein and Escape from Immune Surveillance**  
 Douglas T. Fearon



## CANCER IMMUNOLOGY AT THE CROSSROADS: EXPERIMENTAL IMMUNOTHERAPIES

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 Martin Olt

## PRIORITY BRIEF

- 200 **Transient Complement Inhibition Promotes a Tumor-Specific Immune Response through the Implication of Natural Killer Cells**  
 Valérie Janelle, Marie-Pierre Langlois, Esther Tarrab, Pascal Lapierre, Laurent Poliquin, and Alain Lamarre  
**Synopsis:** Using cobra venom factor to induce transient C3 molecule exhaustion in a mouse model of melanoma, Janelle and colleagues show that the antitumor immune response is NK dependent, uncovering a link between complement proteins and NK cells in tumor development.

## RESEARCH ARTICLES

- 207 **Disruption of CD8<sup>+</sup> Treg Activity Results in Expansion of T Follicular Helper Cells and Enhanced Antitumor Immunity**  
 Diana A. Alvarez Arias, Hye-Jung Kim, Penghui Zhou, Tobias A.W. Holderried, Xuan Wang, Glenn Dranoff, and Harvey Cantor  
**Synopsis:** Alvarez Arias, Kim, and colleagues show that disruption of CD8<sup>+</sup> Tregs binding to Qa-1<sup>+</sup> T follicular helper cells (T<sub>FH</sub>) improves tumor vaccination-elicited immunity, a robust autoimmune antitumor response driven by enhanced T<sub>FH</sub> activity and a strong antibody response.
- 217 **Establishment of Tumor-Associated Immunity Requires Interaction of Heat Shock Proteins with CD91**  
 Yu Jerry Zhou, Michelle Nicole Messmer, and Robert Julian Binder  
**Synopsis:** Zhou and colleagues identify a mechanism by which immune responses are primed against a developing tumor: Disruption of the HSP-CD91 pathway abrogates cross-presentation of tumor-derived antigenic peptides and prevents antitumor immunity that characterizes tumor immunosurveillance.

- 229 **Ex Vivo Assays of Dendritic Cell Activation and Cytokine Profiles as Predictors of In Vivo Effects in an Anti-Human CD40 Monoclonal Antibody ChiLob 7/4 Phase I Trial**  
 F. Chowdhury, P.W. Johnson, M.J. Glennie, and A.P. Williams  
**Synopsis:** Chowdhury and colleagues use whole blood samples in *ex vivo* assays to show that ChiLob 7/4 induces a pattern of DC activation and cytokine secretion matching the *in vivo* responses, providing a strategy to predict dosages and cytokine release syndromes.

- 241 **Untreated Stage IV Melanoma Patients Exhibit Abnormal Monocyte Phenotypes and Decreased Functional Capacity**  
 Rahul Chavan, Daniela Salvador, Michael P. Gustafson, Allan B. Dietz, Wendy Nevala, and Svetomir N. Markovic  
**Synopsis:** Chavan and colleagues analyzed peripheral blood monocytic cells from 18 patients with untreated stage IV melanomas; they found a decrease in the frequency of circulating myeloid dendritic cells and classical CD14<sup>+</sup>CD16<sup>-</sup> monocytes, and the latter also have decreased functional capacity.

- 249 **Gene-Modified Human  $\alpha/\beta$ -T Cells Expressing a Chimeric CD16-CD3 $\zeta$  Receptor as Adoptively Transferable Effector Cells for Anticancer Monoclonal Antibody Therapy**  
 Fumihiko Ochi, Hiroshi Fujiwara, Kazushi Tanimoto, Hiroaki Asai, Yukihiko Miyazaki, Sachiko Okamoto, Junichi Mineno, Kiyotaka Kuzushima, Hiroshi Shiku, John Barrett, Eiichi Ishii, and Masaki Yasukawa  
**Synopsis:** Ochi and colleagues engineered T cells to express chimeric CD16 V158-CD3 $\zeta$  receptors that mediate antibody-dependent tumoricidal activity; upon stimulation these T cells proliferate and differentiate into effector memory T cells, which could combine with and enhance clinical responses by anticancer monoclonal antibodies.

- 263 **Influenza Virus Infection Elicits Protective Antibodies and T Cells Specific for Host Cell Antigens Also Expressed as Tumor-Associated Antigens: A New View of Cancer Immunosurveillance**  
 Uzoma K. Iheagwara, Pamela L. Beatty, Phu T. Van, Ted M. Ross, Jonathan S. Minden, and Olivera J. Finn  
**Synopsis:** Iheagwara and colleagues used a mouse model of influenza virus infection to validate a new cancer immunosurveillance hypothesis and show that viral infections elicit immunity against antigens abnormally expressed in infected cells and cancer cells that can provide effective anticancer control.

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## 274 Polyamine-Blocking Therapy Reverses Immunosuppression in the Tumor Microenvironment

Candace S. Hayes, Allyson C. Shicora,  
Martin P. Keough, Adam E. Snook, Mark R. Burns,  
and Susan K. Gilmour

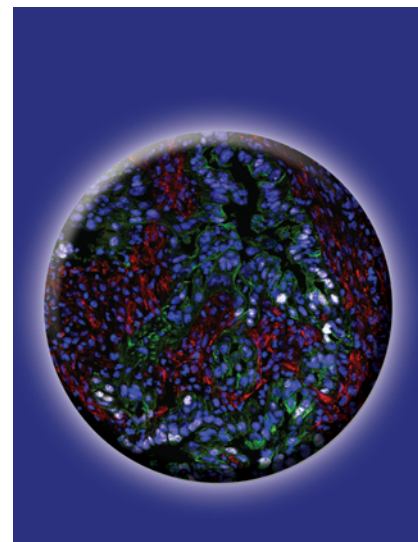
**Synopsis:** Hayes and colleagues report that polyamine elevation in cancer contributes significantly to tumor immunosuppression; they developed a novel polyamine-depletion strategy combining inhibitors of the polyamine transport system and ornithine decarboxylase to prevent tumor immune escape and promote antitumor immunity.

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### ABOUT THE COVER

The ability of T cells to accumulate among cancer cells is impaired in many cancers. T-cell exclusion from the "cancer cell nests" may account for the failure of systemic immunity to control tumor growth, and for the absence of a response to checkpoint antagonist anti-PD-L1 in the murine model of pancreatic ductal adenocarcinoma (PDA). Recent studies have shown that fibroblast-like stromal cells, termed carcinoma-associated fibroblasts (CAF), in the tumor microenvironment exert an immune-suppressive function, and the depletion of CAF permits tumor infiltration of T cells and control of PDA tumors. PDA cancer cells are p53<sup>+</sup> because they contain stable p53R172H proteins due to the loss of the wild-type p53 allele. The cover image is a confocal immunofluorescence photomicrograph of a mouse PDA containing epithelial cells (stained green for cytokeratin 19), p53<sup>+</sup> cancer cells (silver), and CAF that express fibroblast-activating protein- $\alpha$  (FAP; red). All nuclei are stained blue with DAPI. For details, see the Masters of Immunology article by Douglas T. Fearon on page 187 of this issue.



### ABOUT THE MASTER

Douglas T. Fearon, MD, FRS, is the Emeritus Sheila Joan Smith Professor of Immunology at the University of Cambridge, UK, and senior group leader at the Cancer Research UK Cambridge Institute. He received his medical degree at the Johns Hopkins University School of Medicine, followed by internship and residency in internal medicine at the Johns Hopkins Hospital (Baltimore, MD). His scientific training began in 1972 when he joined Dr. Frank Austen's laboratory at Harvard Medical School (HMS) and the Robert bent Brigham Hospital (now part of the Brigham and Women's Hospital) in Boston, MA, as a clinical research fellow in rheumatology and immunology. During this time, Dr. Fearon learned the fundamentals of basic research; he studied innate immunity, identifying and characterizing components of the complement system that enhance immune responses and support antibody functions. He became a full professor at HMS in 1984.

Dr. Fearon returned to Johns Hopkins School of Medicine in 1987, where he developed and directed the graduate program in immunology. During this period, the Fearon laboratory studied various aspects of adaptive immunity and B-cell and T-cell biology, culminating in the identification of complement C3d as a molecular adjuvant that bridges the innate and adaptive immunity. In 1993, ending his dual role as clinician and scientist, Dr. Fearon moved his laboratory to the University of Cambridge to work as a full-time researcher. The Fearon laboratory has been exploring the means by which tumors escape control by the immune system. Currently they focus on the role of the carcinoma-associated fibroblast that is identified by its expression of fibroblast activation protein in the tumor microenvironment and immune control of tumor growth.

Dr. Fearon received his BA *cum laude* with honors in English literature from Williams College (Williamstown, MA) while quarterbacking for the college's football team. After completing his medical training at Johns Hopkins in 1970, Dr. Fearon served as a major in the U.S. Army Medical Corps for two years, one of which was spent in Vietnam, and he received the Bronze Star for his efforts at helping soldiers overcome heroin addiction. He was elected a fellow of both the UK Royal Society and the Academy of Medical Sciences and a member of both the U.S. National Academy of Sciences and the American Academy of Arts and Sciences. Dr. Fearon has published over 140 peer-reviewed research papers and 78 reviews.



# Cancer Immunology Research

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