

## DEPARTMENTS

### 284 Reflections

The Flu in Retrospect  
*Stanley Scheindlin*

### 291 Nascent Transcripts

*Emerging concepts from the literature*

### 292 Therapeutic Windows

*Visions of Drug Discovery*

### 324 Beyond the Bench

A Storied Recipe for Success, Infused with Basil  
*John W. Nelson*

### 326 Net Results

*Sites of Interest on the World Wide Web*

### 327 On Deck

*Upcoming meetings*

### 329 Professional Opportunities

*Position openings*

### 332 Outliers

mi cartoon

## EDITOR

Harry B. Smith

## ASSOCIATE EDITOR

John W. Nelson

## DESIGN & LAYOUT

Vizuál, Inc.

## EDITORIAL ADVISORY BOARD

John S. Lazo, Chair, *U Pittsburgh*  
Darrell R. Abernethy, *FDA*  
Susan Amara, *U Pittsburgh*  
Leslie Z. Benet, *UCSF*  
Joan Heller Brown, *UCSD*  
Bryan Cox, *Abbott*  
Raymond Dingleline, *Emory U*  
Sue Duckles, *UC Irvine*  
Christopher Flores, *J&J*  
Randy Hall, *Emory U*  
Ken Harden, *U North Carolina*  
John Hickman, *Servier*  
Robert S. Kass, *Columbia U*  
Serrine S. Lau, *U Arizona*  
Benedict Lucchesi, *U Michigan*  
Kenneth P. Minneman, *Emory U*  
Perry Molinoff, *U Pennsylvania*  
Richard R. Neubig, *U Michigan*  
Stefan Offermanns, *U Heidelberg*  
Carlo Patrono, *U Rome*  
Dan Roden, *Vanderbilt*  
David Roman, *U Iowa*  
Alan Sartorelli, *Yale U*  
Darryle D. Schoepp, *Merck*  
Boris Tabakoff, *U Colorado*  
Palmer Taylor, *UCSD*  
Ted Torphy, *Johnson&Johnson*  
Roger Tsien, *UCSD*  
Michael R. Vasko, *U Indiana*  
Mary Vore, *U Kentucky*  
Richard M. Weinsilboum, *Mayo*

## BOARD OF PUBLICATIONS TRUSTEES

James E. Barrett, Chair  
P. Jeffrey Conn  
Ross Feldman  
Lorraine Gudas  
Eric F. Johnson  
John S. Lazo  
Edward T. Morgan  
Richard R. Neubig  
Rick G. Schnellmann  
Darryle D. Schoepp  
Mary Vore

## EXECUTIVE OFFICER

Christine K. Carrico

## JOURNALS DIRECTOR

Richard Dodenhoff

*Molecular Interventions* (ISSN 1534-0384) is published by the American Society for Pharmacology and Experimental Therapeutics, 9650 Rockville Pike, Bethesda, MD 20814-3995. Published bimonthly in February, April, June, August, October, and December. Annual subscription rates: U.S.: \$240 for institutions; and \$78 for individuals. Outside the U.S.: \$261 for institutions and \$99 for individuals. The subscription price to ASPET members (\$30) is included in membership dues. Single issue: \$44. Subscriptions include access to the online version of *MI* at molinterv.org (ISSN 1543-2548). Indexed or abstracted by Biochemistry & Biophysics Citation Index, EMBASE/Excerpta Medica, Index to Scientific Reviews, ISI Alerting Services, ISI Web of Science, PubMed/Medline, and Science Citation Index-Expanded.

**Advertising** (FASEB AdNet): 301-634-7103; adnet@faseb.org.  
**Editorial:** 301-634-7790; mi@aspet.org. **Subscriptions:** 301-634-7099; staff@dues.faseb.org. **ASPET:** 301-634-7099; info@aspet.org.

Statements and opinions contained in the articles of *Molecular Interventions* are solely those of the individual authors and contributors and not of the American Society for Pharmacology and Experimental Therapeutics. The appearance of advertisements in *Molecular Interventions* is not a warranty, endorsement, or approval of the products or their safety. The American Society for Pharmacology and Experimental Therapeutics disclaims responsibility for any injury to persons or property resulting from any ideas or products referred to in the articles or advertisements.

*Molecular Interventions* is copyrighted by the American Society for Pharmacology and Experimental Therapeutics. Photocopying of articles beyond that permitted by Sections 107 or 108 of the U.S. Copyright Law is allowed, provided that the \$20.00 per-copy fee is paid through the Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923. Classroom photocopying is permitted at no fee, provided that students are not charged more than the cost of duplication. This consent does not extend to other kinds of copying. Reproduction of any portion of an article for subsequent republication requires permission of the copyright owner. Write to ASPET Copyright Dept., 9650 Rockville Pike, Bethesda, MD 20814-3995.

**Postmaster:** Send address changes to *Molecular Interventions*, ASPET, 9650 Rockville Pike, Bethesda, MD 20814-3995.



# molecular interventions

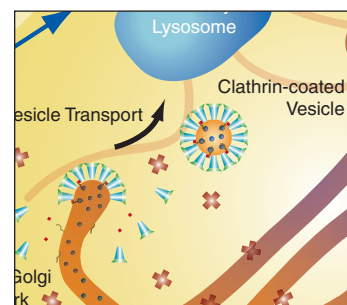
pharmacological perspectives from biology, chemistry and genomics

## VIEWPOINTS

### 294 **EBAG9: Boosting Secretory Function to Bolster Cancer Cell Cytolysis**

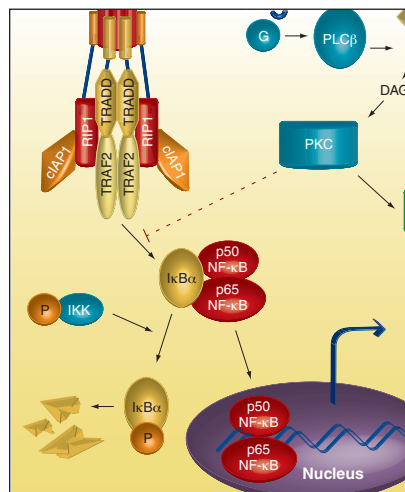
Cytotoxic-T-lymphocyte- and natural-killer-cell-mediated immune surveillance is crucial for preventing development and growth of malignancies. A recent intriguing study by Rüder et al. demonstrates that the estrogen receptor-binding fragment-associated gene 9 (EBAG9) protein acts as a novel inhibitor of cytotoxic immune responses, potentially influencing growth and spread of malignancies. EBAG9 does this by suppressing production of secretory lysosomes through negative regulation of adaptor proteins involved in intracellular vesicle transfer. Secretory lysosomes contain cell lysis effector molecules released into the immune synapse formed between cytotoxic immune cells and their target tumor cells. Thus, in addition to their direct ER-mediated suppressive effect on estrogen-dependent tumor growth, anti-estrogens may “switch off” EBAG9, thereby bolstering immune cytotoxicity against these cancer cells.

*Tomoshige Kino and George P. Chrousos*



page 294  
*Enhanced secretory trafficking might lead to better immune responses*

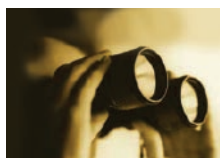
### 299 **Serotonin in the Periphery: Attenuating TNF-Mediated Inflammation**



page 299  
*5-HT influences immune response and inflammation*

Although the influence of neural activity on immune and inflammatory pathways is undisputed, details of how neurotransmitters modulate signaling by cytokine and antigen receptors remain sketchy. New findings on the influence of the serotonin receptor subtype 2A (5-HT<sub>2A</sub>) and receptors for Tumor Necrosis Factor (TNF) suggest that in some cases there may be direct interactions between neurotransmitter and cytokine receptor signaling. These findings have implications for the many psychiatric patients on medications that modulate serotonin signaling and suggest that neurotransmitter receptors should not be ignored as candidate targets for immunoregulation.

*Martin Pelletier and Richard M. Siegel*

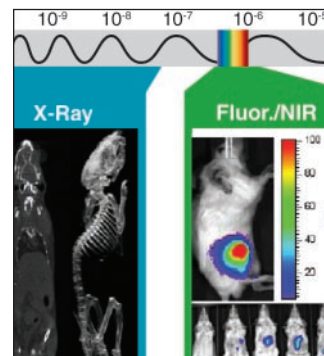


## REVIEWS

### 302 Looking within: Bioimaging of Brain Function in Drug Development

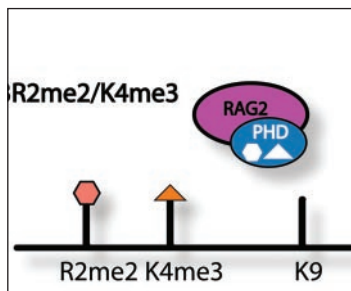
Recent advances in high-resolution and high-sensitivity equipment, along with the development of selective biological probes and biomarkers, are rapidly providing new opportunities to investigate drug efficacy and safety. Depending on the modality used, imaging has applications throughout the entire drug lifecycle, and can provide data for target validation, defining mechanism of action, demonstrating efficacy/safety in both preclinical and clinical settings, and applying biomarkers of biological activity. Information gained in these regards can have direct bearing upon the investment of time and resources for phase 2 trials. Imaging studies allow longitudinal measures in the same subject, and recent developments in small-animal scanners can provide translational data for transition from preclinical into early clinical studies. A new wave of neuroimaging studies that engender useful biomarkers of disease for translational research promise to revolutionize the development of therapeutics for a range of neurological diseases.

*Gerard B. Fox, Chih-Liang Chin, Feng Luo, Mark Day, and Bryan F. Cox*



page 302  
*New vistas in pharmacology*

### 314 Epigenetic Investigations Put the Finger on Histone Modification



page 314  
*Reading the histone code*

We all know the string of usual suspects: A, T, G, and C. And we've known, for some time, that their intimate association with the histones goes much deeper than a mere packaging story: these basic proteins appear to undergo posttranslational modifications that regulate gene activity. Investigators are coming ever closer to understanding exactly how these modifications are being "read" by proteins that—in the case presented here—possess certain zinc fingers (aka PHD fingers). We can now be certain that modifications of specific residues on distinct histones interact with PHD fingers of proteins that in turn recruit additional protein associates to chromatin. The observed complexes can result in specific gene activation or silencing, depending on how the PHD finger-containing proteins "read" the posttranslational cues that reside on histones. In certain instances, mutational alteration of PHD finger-containing proteins has been related to disease; whether new therapeutics can be devised to counter such malfeasance is under ongoing investigation.

*Catherine A. Musselman and Tatiana G. Kutateladze*