

## DEPARTMENTS

### 120 Reflections

The Whittemore Peterson Institute  
*Annette Whittemore*

### 127 Speaking of Pharmacology

Human Patient Simulation in Pharmacology  
Graduate Education  
*W. Bosseau Murray, Jody Wood, Maura Schwab,  
Melissa Fritz, and Kelly Dowhower Karpa*

### 179 Beyond the Bench

Heated Water-Cooler Talk  
*Dan Collinge*

### 181 NetResults

*Sites of Interest on the World Wide Web*

### 182 On Deck

*Upcoming Meetings*

#### 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*  
Joan Heller Brown, *UCSD*  
Bryan Cox, *Abbott*  
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*  
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*  
Michael R. Vasko, *U Indiana*  
Mary Vore, *U Kentucky*

#### BOARD OF PUBLICATIONS TRUSTEES

James E. Barrett, Chair  
P. Jeffrey Conn  
Randy A. Hall  
Michael F. Jarvis  
Eric F. Johnson  
John S. Lazo  
Edward T. Morgan  
Kim A. Neve  
David R. Sibley  
Mary Vore  
Jeffrey M. Witkin

#### 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.: \$298 for institutions and \$60 for individuals. Outside the U.S.: \$322 for institutions and \$70 for individuals. The subscription price to ASPET members (\$30) is included in membership dues. Single issue: \$54. 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

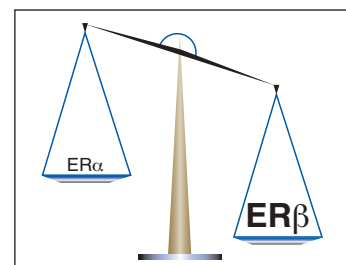
pharmacological perspectives from biology, chemistry and genomics

## VIEWPOINTS

### 133 ER $\beta$ : Selective Activation not Involving the Ligand Binding Site

Estrogen action is mediated by binding to two specific estrogen receptors (ERs), ER $\alpha$  and ER $\beta$ . The discovery of ER $\beta$  in 1996 changed our understanding of estrogen action and sparked intense research efforts to discover its role in normal physiology and its potential as a drug target. Several ER $\beta$ -selective and clinically active ligands have since been developed. The first compounds described were those that have a high selective binding affinity for ER $\beta$ , such as ERB-041. A second class of agents that have been identified bind to ER $\beta$  and ER $\alpha$  with similar affinity but selectively activate ER $\beta$ , such as liquiritigenin, a flavanone. A recent study has identified 3,3'-diindolylmethane (DIM) as a member of a new class of ER $\beta$  activator that does not bind to the ligand binding site, but rather selectively activates ER $\beta$  possibly through cellular kinase pathways that target the receptor's ligand-independent activation domain. Although more studies are needed, these findings suggest that compounds that modulate of ER $\beta$  activation without directly binding to the receptor might prove to be of significant clinical importance in the future.

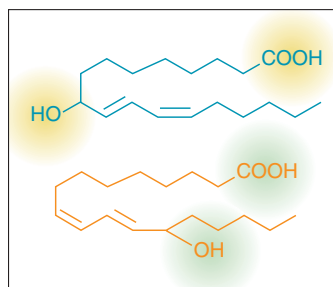
Raymond Lo and Jason Matthews



page 133  
Tipping the scale:  
ER $\beta$ -selective activation

### 137 TRPV1 Deorphanized: Octadecadienoids Emerge as Novel Lipid Transmitters

Nearly fifty years ago, the existence of a “pain receptor” was postulated through which capsaicin could exert its “stimulatory and desensitizing” actions. More recently, that receptor, the transient receptor potential vanilloid



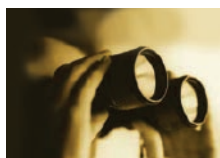
page 137  
Hot topic: Endogenous  
ligands of TRPV1

1 (TRPV1) has been molecularly cloned and characterized. Much research has been devoted to identify those molecules serving as endogenous agonists for TRPV1. Various eicosanoids may act as these so-called endovanilloids, but new, exciting findings indicate that oxidized metabolites of linoleic acid (OLAMs) satisfy a number of critical criteria to be classified as endogenous activators of TRPV1. Intriguingly, OLAMs may also participate as peripheral neurochemical conduits of heat itself. Thus, TRPV1 may not only be deorphanized, but OLAM “octadecadienoids” may represent a novel class of algogenic substances. These findings raise critical questions regarding the precise role(s) of TRPV1 in nociceptive transduction and about the importance of fatty acids in the modulation of pain and related functions. Moreover, these findings may inform the potential development of novel therapeutic strategies to treat pain.

Christopher M. Flores and Michael R. Vasko

#### Erratum

*Close Encounters of an Oily Kind: Regulation of Transporters by Lipids*  
*Mol. Interv.* 9, 252-262 (2009) Christopher B. Divito and Susan G. Amara.  
In Table 2, the five double bonds inherent to eicosapentaenoic acid were not shown. The article also lacked acknowledgment that the authors' work was supported by the National Institutes of Health [Grants DA07595, MH80726].

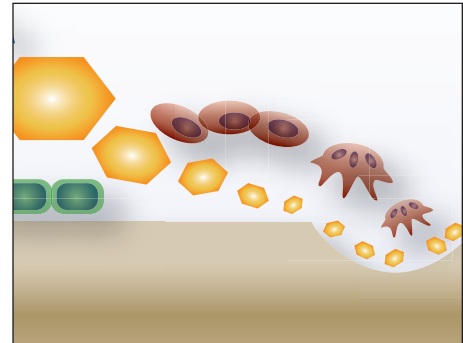


## REVIEWS

### 141 Bisphosphonate Therapeutics in Bone Disease

With annual sales well over three billion dollars, bisphosphonate drugs have been widely prescribed to maintain bone density in patients who are at risk for fractures, such as those afflicted with osteoporosis. Paradoxically, bisphosphonate treatment has in the past few years been linked to rare adverse events, such as osteonecrosis of the jaw, marked by bone deterioration. Such side effects tend to occur within particular clinical contexts, such as cancer and dental surgery, but they have raised concern in light of the widespread use of bisphosphonate therapeutics. The mechanisms of bisphosphonate action and the dynamics of bone turnover are intricately related, and the interplay between drug and bone explains, at least in part, the paradoxical effects of bisphosphonate drugs on bone development. An understanding of this interplay may also provide routes to potential new therapeutics to ward off bone loss associated with disease.

*Matthew T. Drake and Serge C.L.M. Cremers*

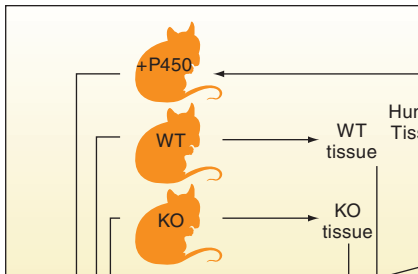


page 143  
*Bone pharmacology*

### 153 Orphan Cytochrome P450 Enzymes

With the rapid completion of genomic sequences of organisms today, we have far more gene products than functions we can ascribe. A number of experimental strategies have been developed and applied, both in vitro and in vivo, to put functions to these orphan proteins. The “deorphanization” of human and *Streptomyces* cytochrome P450 enzymes is considered quite important for pharmacology, with ramifications for the use of clinical therapeutics. The myriad of possibilities is too enormous to screen one reaction at a time, and the development of metabolomic and proteomic screens with complex biological samples is thus essential.

*F. Peter Guengerich, Zhongmei Tang, S. Giovanna Salamanca-Pinzón, and Qian Cheng*

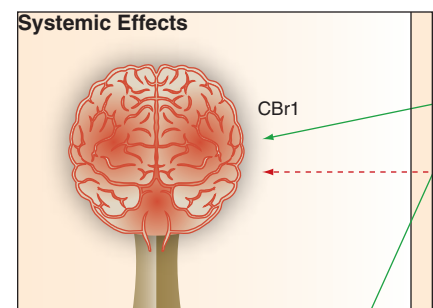


page 155  
*Genomic homing devices*

### 164 The Cancer Microenvironment: Sources of Pain

Cancer pain is a formidable clinical problem, reflecting a complex series of cellular, tissue, and systemic changes that occur during proliferation, invasion, and metastasis. Primary afferent nociceptors are modulated by a number of mediators released by cancer cells, and immune cells that are drawn into the cancer further complicate pain perception. The peripheral neuropathic changes and the influence of tumors upon neurons in the elaboration of pain and central sensitization are beginning to be understood in some detail. The judicious design and exploitation of animal models continue to help researchers unravel the complexities of cancer-evoked pain.

*Brian L. Schmidt, Darryl T. Hamamoto, Donald A. Simone, and George L. Wilcox*



page 171  
*Cancer pain*