

DEPARTMENTS

178 Editorial

John S. Lazo

183 Reflections

A Career in Pharmacology
Sue Duckles

190 Significant Deciles

ASPET celebrates its centennial anniversary

224 Beyond the Bench

A Sewage Treatment
Christie Carrico

226 Nascent Transcripts

Emerging concepts from the recent literature

227 NetResults

Sites of Interest on the World Wide Web

228 Professional Opportunities

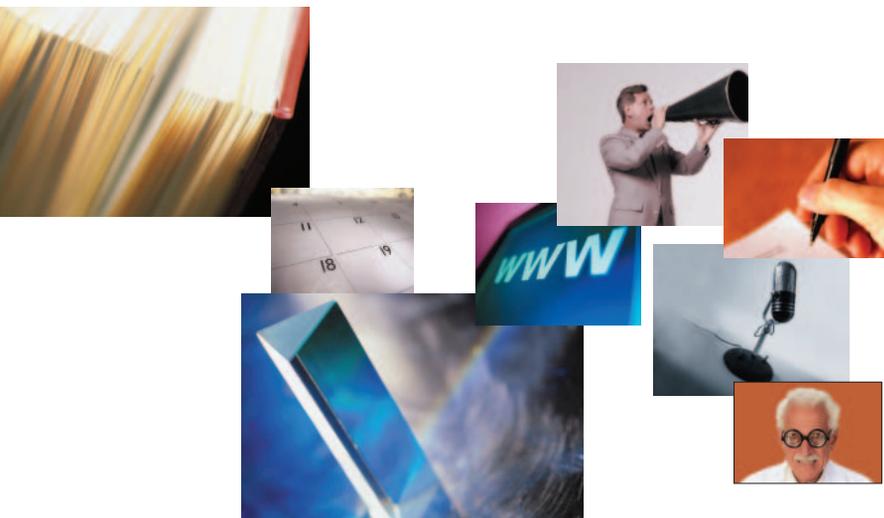
Position Openings

229 On Deck

Upcoming Meetings

232 Outliers

mi cartoon



EDITOR

Harry B. Smith

ASSOCIATE EDITOR

John W. Nelson

DESIGN & LAYOUT

Vizuäl, Inc.

EDITORIAL ADVISORY BOARD

John S. Lazo, Chair, *U Pittsburgh*
Darrell R. Abernethy, *NIH/NIA*
Susan Amara, *U Pittsburgh*
Leslie Z. Benet, *UCSF*
Joan Heller Brown, *UCSD*
Bryan Cox, *Abbott*
Raymond Dingleline, *Emory U*
Sue Duckles, *UC Irvine*
Alfred G. Gilman, *U Texas SW*
Randy Hall, *Emory U*
Ken Harden, *U North Carolina*
John Hickman, *Servier*
Dayle Houston*, *U North Carolina*
Robert S. Kass, *Columbia U*
Serrine S. Lau, *U Arizona*
Rochelle Long, *NIH/NIA*
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*
David Roman**, *U Michigan*
Alan Sartorelli, *Yale U*
Boris Tabakoff, *U Colorado*
Palmer Taylor, *U San Diego*
Robert Tomko*, *U Pittsburgh*
Ted Torphy, *Johnson&Johnson*
Roger Tsien, *UCSD*
Michael R. Vasko, *U Indiana*
Mary Vore, *U Kentucky*
Richard M. Weinsilboum, *Mayo*

* Student representative; ** Postdoctoral representative

BOARD OF PUBLICATIONS TRUSTEES

Brian M. Cox
Darrell R. Abernethy
P. Jeffrey Conn
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.

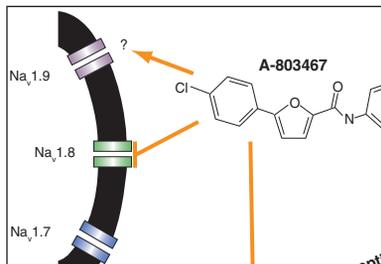
Postmaster: Send address changes to *Molecular Interventions*, ASPET, 9650 Rockville Pike, Bethesda, MD 20814-3995.

molecular interventions

pharmacological perspectives from biology, chemistry and genomics

VIEWPOINTS

192 Overcoming Neuropathic Pain: A New Lead in Pain Management



Voltage-gated sodium channels in nociceptive neurons are attractive targets for novel pain therapeutics. Although drugs that target voltage-gated sodium channels have proven value as pain therapeutics, the drugs that are currently available are non-specific sodium channel inhibitors, which limit their usefulness. Recently, a selective small-molecule inhibitor of Na_v1.8, a voltage-gated sodium channel isoform that participates in peripheral pain mechanisms, has been developed. This exciting new compound shows efficacy in several animal models of pain and is anticipated to be only the first of many new isoform-specific sodium channel blockers.

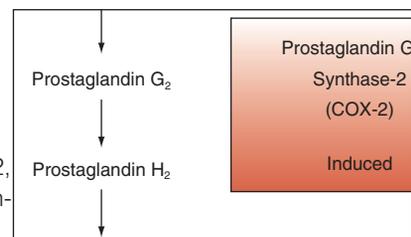
Anthony M. Rush and Theodore R. Cummins

page 192
Na_v gating neuropathic pain inhibition

195 Outflanking the Side Effects of COX-2 Inhibitors

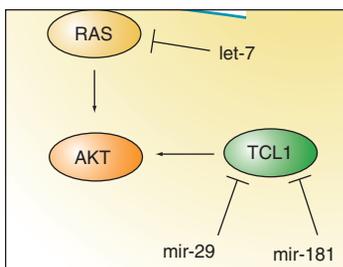
Non-steroidal anti-inflammatory drugs (NSAIDs) are inhibitors of the cyclooxygenase (COX)-1 and -2 activities of prostaglandin G/H synthase-1 and -2, respectively. They have been extensively used in the treatment of prostaglandin E₂-mediated chronic inflammatory diseases. Selective COX-2 inhibitors (coxibs), which were developed to provide an alternative with reduced gastrointestinal risk for the traditional NSAIDs, have been associated with an increased incidence of major adverse cardiovascular events. Could the targeting of microsomal prostaglandin E₂ synthase (mPGES-1) lead to novel anti-inflammatory drugs with possibly reduced risks of gastrointestinal and cardiovascular side effects?

Leo Timmers, Gerard Pasterkamp, and Dominique P.V. de Kleijn



page 195
mPGES-1 vs PGHS-2: Better anti-inflammatory drugs?

199 Anti-Oncomirs: First Steps in Exploiting Natural Inhibitors of Oncogene Expression



MicroRNAs (miRNAs or mirs) are small, non-coding RNAs that bind specific mRNAs and decrease their translation or increase their degradation. miRNAs may modulate the formation and maintenance of tumors by regulating oncogene and tumor suppressor expression. For example, overexpression of a subset of miRNAs has been inversely correlated with certain tumor phenotypes, suggesting a role in tumor suppression. Pairs of oncogenes and the corresponding miRNAs that attenuate their expression have been recently identified. These miRNAs, or "anti-oncomirs," can act as natural inhibitors of oncogene function, indicating the possibility that they might be developed as novel therapeutics.

page 199
Suppressing tumors with anti-oncomirs

Andrei Goga and Christopher Benz

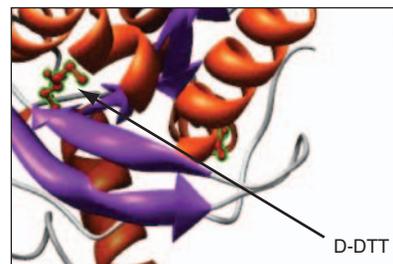


REVIEWS

203 **Boot cAMP for Trypanosomes: Exploiting the Differences between Human and Parasite Enzymes**

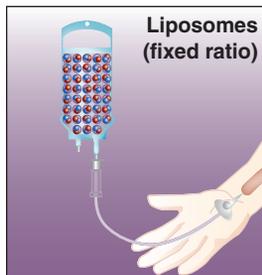
Trypanosomatid parasites cause numerous human diseases, including African sleeping sickness and Chagas disease, affecting millions of people worldwide. There are few effective therapeutic options presently available to treat these diseases, and new anti-trypanosomal drugs are urgent needed. The adenosine 3',5'-monophosphate (cAMP) signaling pathway in these parasites appears to be an attractive target for new therapeutics, as the enzymes that create and destroy cAMP are regulated differently from their mammalian counterparts. This review briefly summarizes the current knowledge of cAMP signaling in trypanosomes and highlights studies of enzymes in the cAMP signaling pathway that are crucial for the survival of the parasite and are, therefore, good targets for new anti-trypanosomal drugs.

Sunil Laxman and Joseph A. Beavo



page 203
Interfering with cAMP-mediated signals

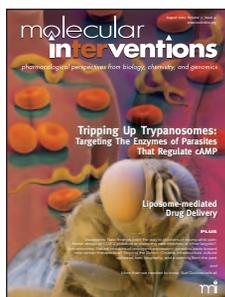
216 **Controlled Delivery of Synergistic Drug Ratios to Tissue Targets In Vivo**



page 216
Synergy on delivery

Cancer chemotherapy treatments typically employ drug combinations in which the dose of each agent is pushed to the brink of unacceptable toxicity; however, emerging evidence indicates that this approach may not be providing optimal efficacy due to the manner in which drugs interact. Specifically, whereas certain ratios of combined drugs can be synergistic, other ratios of the same agents may be antagonistic, implying that the most efficacious combinations may be those that utilize certain agents at reduced doses. Advances in nano-scale drug delivery vehicles now enable the translation of in vitro information on synergistic drug ratios into improved anticancer combination therapies in which the desired drug ratio can be controlled and maintained following administration in vivo, so that synergistic effects can be exploited. This "ratiometric" approach to combination chemotherapy opens new opportunities to enhance the combinatorial effectiveness of existing and future therapeutic agents across a spectrum of human diseases.

Lawrence D. Mayer and Andrew S. Janoff



*This month's cover depicts an image of the Tsetse fly (*Glossina* sp.) and Trypanosomes. *T. brucei* is the cause of African sleeping sickness in humans. The ribbon-like *T. brucei* are carried in the saliva of the blood-drinking tsetse fly. The protozoa enter a human host through the wound made by the fly when it feeds. The protozoa infect the blood, lymph and spinal fluid, and begin to divide. Damage to the nervous system by the infection eventually leads to lethargy, tremors, and mental & physical deterioration. The sufferer finally enters a comatose state and dies. Photo Credit: Eye of Science / Photo Researchers, Inc. 🍌*