

DEPARTMENTS

240 Speaking of Pharmacology

John S. Lazo

244 Nascent Transcripts

Emerging concepts from the recent literature

284 Beyond the Bench

Trouble in Mind
Dayle Houston

286 NetResults

Sites of Interest on the World Wide Web

287 Professional Opportunities

Position Openings

290 On Deck

Upcoming Meetings

292 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/NIH*
Susan Amara, *U Pittsburgh*
Leslie Z. Benet, *UCSF*
Helen Blau, *Stanford U*
Floyd Bloom, *Scripps*
Joan Heller Brown, *UCSD*
Bryan Cox, *Abbott*
Raymond Dingledine, *Emory U*
Sue Duckles, *UC Irvine*
Alfred G. Gilman, *U Texas SW*
Michael Gottesman, *NIH/NCI*
Randy Hall, *Emory U*
Ken Harden, *U North Carolina*
John Hickman, *Servier*
Dayle Houston*, *U North Carolina*
Robert J. Lefkowitz, *Duke U*
Victor Ling, *U British Columbia*
Rochelle Long, *NIGMS/NIH*
Benedict Lucchesi, *U Michigan*
Kenneth P. Minneman, *Emory U*
Perry Molinoff, *U Pennsylvania*
Richard R. Neubig, *U Michigan*
Carlo Patrono, *U Rome*
David Roman**, *U Michigan*
Alan Sartorelli, *Yale U*
Glenn Sipes, *U Arizona*
Boris Tabakoff, *U Colorado*
Palmer Taylor, *U San Diego*
Robert Tomko*, *U Pittsburgh*
Ted Torphy, *Johnson&Johnson*
Roger Tsien, *UCSD*
Mary Vore, *U Kentucky*

* 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

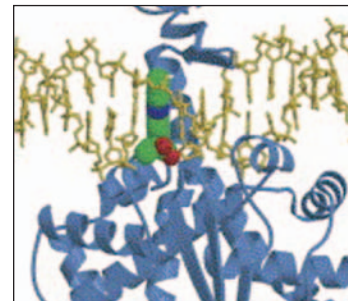
pharmacological perspectives from biology, chemistry and genomics

VIEWPOINTS

245 Finding the Achilles' Heel in Variola Virus

Smallpox is a serious and highly contagious disease that is caused by the variola virus. It is one of the most severe infectious human diseases known, with mortality rates as high as 30%. A successful worldwide vaccination program led to the eradication of smallpox in 1980. However, the high transmission rate of variola virus, coupled with the deadly nature of smallpox, makes this virus a potentially devastating weapon for bioterrorism. Currently, there is no specific treatment for smallpox. However, a recent article on the structure of a variola topoisomerase IB–DNA complex provides an intriguing starting point for the rational design of drugs with potential activity against smallpox.

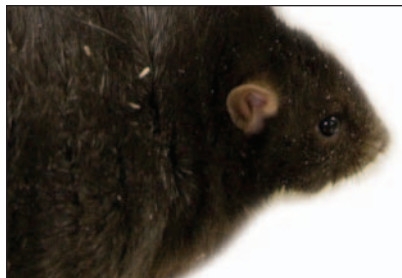
Neil Osheroff



page 245
*Untangling the web of death
smallpox weaves*

249 Blocking Ghrelin to Fight Obesity

In the battle to treat the pandemic of obesity, one therapeutic strategy is to block endogenous signals that stimulate appetite and control body weight. One such molecule is ghrelin, a gut peptide that is the only known orexigenic hormone and is a likely contributor to mealtime hunger. The relative importance of ghrelin in long-term



page 249
First steps toward a vaccine

body-weight regulation (and thus its promise as an anti-obesity target) is uncertain, however, because genetic and pharmacologic blockade of ghrelin signaling have yielded variable results to date. Using a novel approach of vaccinating rats against their own ghrelin, Zorilla et al. report that animals with high ghrelin-specific antibody titers displayed restricted body weight, without evidence of non-specific inflammation following the vaccine. These results favor a meaningful role for ghrelin in energy homeostasis, hinting at a possible new anti-obesity approach. More broadly, the work of Zorilla et al. supports the feasibility of vaccinations directed against specific autologous targets—immunopharmacotherapy that could potentially be developed to target a wide array of medical conditions.

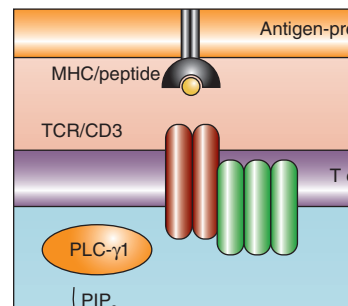
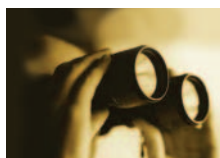
Molly J. Carlson and David E. Cummings

253 Novel Genetic Lesion Leads to SCID: Calcium Influx in T Cell Activation

Severe Combined Immunodeficiency (SCID) is a rare primary immunodeficiency disease often characterized by a block in T cell development, which may also affect the normal development of B cells and NK cells. Several different mutations are known to give rise to SCID, and multiple genes are involved. Consequently, there are several different forms of SCID, which can be classified according to the metabolic and cellular defects that impede normal lymphocyte function. The two most prevalent forms of SCID are X-linked SCID and adenosine deaminase (ADA) deficiency SCID, together accounting for approximately 70–80% of disease cases. Other genetic abnormalities associated with this syndrome range from defective T cell receptor rearrangement to non-functional signaling molecules. Recently, a new genetic defect has been described in which

mutations in a key component of Ca^{2+} release activated–channels (CRAC) result in T lymphocyte malfunction.

Helen P. Carroll, Benjamin B.A. McNaull, and Massimo Gadina



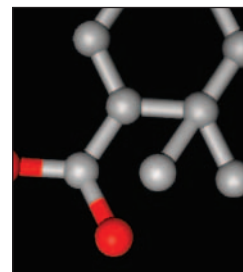
page 253
*CRAC'ing open the regulation
of T cell activation*

REVIEWS

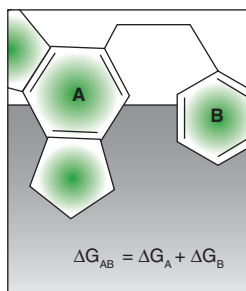
257 Magic Mint Targets the κ -Opioid Receptor

The hallucinogenic plant *Salvia divinorum*, a member of the mint family, has traditionally been used by the Mazatec natives of southern Mexico to induce ritual visions and is increasingly used in the US for recreational purposes. The main active ingredient in the plant is the diterpene salvinorin A, which is structurally distinct from other chemical classes of hallucinogens. In recent high-throughput screening experiments, salvinorin A was found to bind to the κ -opioid receptor (KOR) with high specificity. Chemical analogs of the compound are now under study, in concert with functional characterization of KOR, to determine whether modulation of KOR activity could provide a basis for new psychotropic medications. Indeed, there are indications that salvinorin A or its congeners may prove useful in both psychiatric and non-psychiatric diseases.

Timothy A. Vortherms and Bryan L. Roth



page 257
Divine molecules

266 Getting Better Lead Compounds Through Better Technologies

Constructing novel drug leads from small molecular building blocks is a powerful new approach to drug discovery. This field, called fragment-based drug design, relies on the experimental detection and structural characterization of very weakly binding, low molecular-weight ligands that can be rapidly increased in potency using structure-based drug design. Numerous examples of fragment-based drug design now exist in the literature, and several compounds derived using this approach have made it into the clinic. This review will describe the concept of fragment-based drug design, discuss why it works, and use two case studies to illustrate the power of the approach.

Philip J. Hajduk

page 266
SAR by NMR takes a lead role

273 Appraisal of Choice in Drug-Use Behavior

The abuse liability of a drug is closely related to its ability to maintain self-administration behavior in laboratory subjects. But how do researchers gauge the reinforcing value of a self-administered drug in the preclinical laboratory? One approach is to determine the "preference" for that drug, that is, the allocation of behavior to drug taking, when alternative reinforcers are concurrently available. Careful analyses of such "choice" behavior in laboratory subjects can lead to a scientific understanding of the pharmacological and behavioral determinants of the reinforcing strength of a drug and, ultimately, to a more useful preclinical evaluation of abuse liability.

Jack Bergman and Carol A. Paronis

Component	
Cocaine Unit Dose	S
% Injection Lever Responding	
# Injections	

page 273
Measures of choice