

DEPARTMENTS

152 Reflections

The Drug That Launched a Thousand Sleds
Stanley Scheindlin

159 Nascent Transcripts

Emerging concepts from the literature

160 Significant Deciles

ASPET celebrates its centennial anniversary

185 Beyond the Bench

Smell You Later
Dan Collinge

187 Net Results

Sites of Interest on the World Wide Web

188 Professional Opportunities

Position openings

191 On Deck

Upcoming meetings

196 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, *UCSD*
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

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.



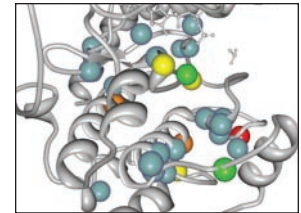
Photo Credit: Gary Carlson / Photo Researchers, Inc.

VIEWPOINT

162 Separating the Wheat from the Chaff: Identifying SNPs Associated With Disease

Non-synonymous single nucleotide polymorphisms (SNPs) that result in amino acid substitutions may have no appreciable effect on protein function, but those that involve critical residues may cause or contribute to disease. Large-scale gene sequencing studies have revealed a daunting number of non-synonymous SNPs with unknown functional consequences. Both predictive techniques and functional assays can aid in the identification of disease-relevant SNPs, as illustrated by two recent reports. An insightful comparison of known disease-causing vs uncharacterized SNPs in protein kinases sheds new light on regions of the catalytic core. The observed prevalence of disease-causing SNPs in substrate binding and regulatory regions—but paucity thereof in residues directly involved in the catalytic reaction—will likely extend to other enzymes as well. A clever functional bioassay using mouse ES cells distinguishes neutral from deleterious mutations in the breast and ovarian cancer-related BRCA2 gene, which may aid in the interpretation of patient BRCA2 screening data.

Joan L. Cmarik

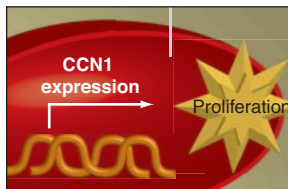


page 162
SNPs: Improving the signal-to-noise ratio

REVIEWS

165 GPCR Signals and Integrin Backtalk

G protein-coupled receptors are a mainstay of pharmacology and remain the most targeted molecules in clinical history. Typically, soluble ligands reach GPCRs and initiate cascades of protein-protein and enzymic interactions that affect cytoplasmic and nuclear metabolism. Migration, survival, and proliferation are some of the basic cell functions that are regulated by means of GPCR signaling. Increasingly, the extracellular matrix has become appreciated for its active role in nuancing these functions and integrating cell-cell communication essential to tissue physiology. The matricellular protein CYR61/CCN1 has recently been shown to be expressed in response to canonical GPCR-activated signaling pathways. Furthermore, secreted CYR61/CNN1 interacts with integrins and other elements of the ECM and thereby adds a novel dynamic to GPCR and ECM signaling. Recognition of CYR61/CCN1 as a regulator of crosstalk between intra- and extracellular signaling pathways also opens up new opportunities for experimental therapeutics.



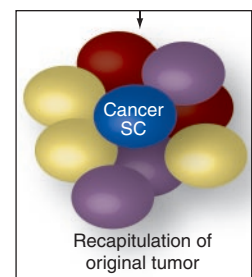
page 165
GPCRs and the ECM

Colin T. Walsh, Dwayne Stupack, and Joan Heller Brown

174 Using Phytochemicals to Fight Cancer

Recent research into the origins of cancers suggests the cancer stem cell is the source of both initial tumor formation and eventual patient relapse. Cancer stem cells have the ability to self-renew as well as to give rise to the multiple cell types present within the tumor. Investigations into the biology of cancer stem cells have revealed that they express large amounts of drug pumps and have active self-renewal and anti-apoptosis pathways that involve the participation of well-characterized signaling proteins and transcription factors. These characteristics may render cancer stem cells susceptible to pharmacological intervention. Intriguingly, certain plant-derived compounds interfere with the capacity of cancer stem cells to pump out cytotoxic agents, differentiate, or resist programmed cell death. Indeed, many phytochemicals are currently under evaluation in clinical trials and may prove themselves as valuable adjuncts to front-line cancer therapies.

Brian T. Kawasaki, Elaine M. Hurt, Tashan Mistree, and William L. Farrar



page 174
Finding adjunct therapies in plants