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*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.

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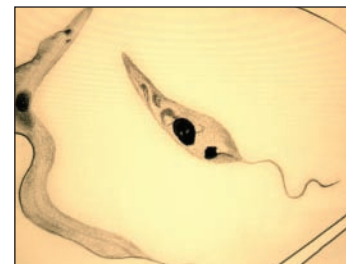
# molecular interventions

pharmacological perspectives from biology, chemistry and genomics

## VIEWPOINTS

### 72 Leishmaniasis: Embracing New Approaches to Fight an Old Scourge

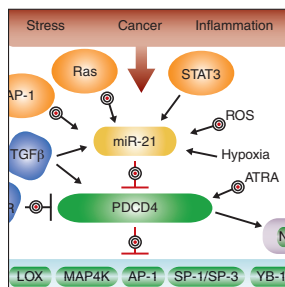
In much of the developing world, leishmaniasis is endemic, infecting millions of people each year, with almost a half-billion people at risk of infection. There are three major clinical manifestations of leishmaniasis, each having significant cultural and socioeconomic impact, owing to disability, disfigurement, and death. Despite its prevalence and profound consequences for human life, leishmaniasis remains a neglected disease with very limited therapeutic options. Recently, some large-scale anti-leishmanial drug-discovery campaigns have been initiated; however, these efforts have focused primarily on one leishmanial manifestation, the visceral form, leaving the cutaneous forms of leishmaniasis even further neglected. We discuss the impact of leishmaniasis and its primary clinical manifestations, the transmission and the life cycle of the *Leishmania* parasite, available treatments, and the new efforts and challenges facing drug discovery.



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Better drugs require  
new strategies

Elizabeth R. Sharlow, Max Grögl, Jacob Johnson, and John S. Lazo

### 76 An Intricate Balancing Act Between Tumor Suppression, Cancer, and Inflammation



A recent article suggests that the well known tumor suppressor PDCD4 also functions as a pro-inflammatory agent. The PDCD4 counteragent miR-21, a pro-oncogenic micro-RNA, is described as an anti-inflammatory agent. The authors of this research article provide evidence that mice lacking PDCD4 are protected from the lethal effects of lipopolysaccharide (LPS). This report also confirms miR-21 as a negative regulator of PDCD4 expression after LPS stimulation. Downstream mediators of the pro-inflammatory activity of PDCD4 include IL-10, an anti-inflammatory cytokine that is negatively regulated by PDCD4, and IL-6, a pro-inflammatory cytokine that appears to be upregulated in a PDCD4 dependent manner, possibly through an increase in NF-κB activity. Is it possible that a tumor-suppressor protein and an oncogenic micro-RNA can be oppositely targeted to control inflammatory disease?

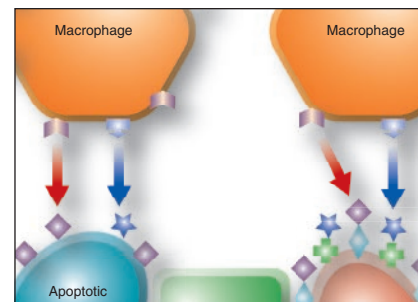
Matthew R. Young, Arti N. Santhanam, Noriko Yoshikawa, Nancy H. Colburn

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A question of balance

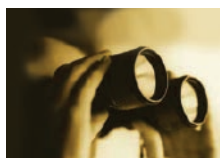
### 80 Learning What from What Not to Eat: Engineering Specific Signals in Acute Pancreatitis

Acute pancreatitis is a common clinical condition, which lacks effective pharmacological treatment. The severity of the disease is determined by the extent of necrotic death of pancreatic acinar cells. This article discusses the idea of developing new pharmacological tools against acute pancreatitis by labeling necrotic pancreatic acinar with apoptotic “eat-me” signaling molecules. This approach could facilitate removal of dead material without activation of inflammatory response and thus would eliminate the main source of damage to the body during acute pancreatitis.

Michael Chvanov, Ole H. Petersen, and Alexei V. Tepikin



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Eat this, not this

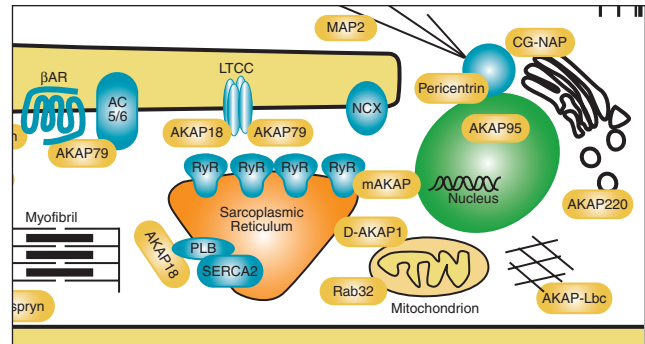


## REVIEWS

### 86 AKAPs Invite Enzymes to the Party

A-Kinase Anchoring Proteins (AKAPs) orchestrate and synchronize cellular events by tethering the cAMP-dependent protein kinase (PKA) and other signaling enzymes to organelles and membranes. The control of kinases and phosphatases that are held in proximity to activators, effectors, and substrates favors the rapid dissemination of information from one cellular location to the next. This article charts the inception of the PKA-anchoring hypothesis, the characterization of AKAPs and their nomenclature, and the physiological roles of context-specific AKAP signaling complexes.

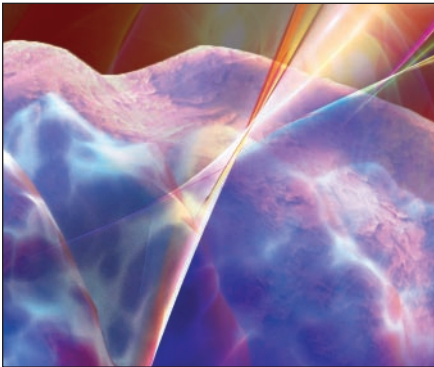
*Emily J. Welch, Brian W. Jones, and John D. Scott*



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*Effective signaling and communication:  
It's all in the networking*

### 98 Mitochondrial Roles Take Center Stage in Drug Hepatotoxicity



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*Cellular signaling centers*

Mitochondria play key roles in aerobic life and in cell death.

Thus, interference of normal mitochondrial function impairs cellular energy and lipid metabolism and leads to the unleashing of mediators of cell death. Traditionally, drug-induced liver injury was viewed as a passive process ensuing from overwhelming insults to mitochondrial and cellular functions. It is now becoming clear that drug hepatotoxicity is an active process, engaging specific signaling pathways that are integrated through mitochondrial input. Reactive radical species, once seen merely as by-products of aerobic metabolism, may in fact be key to concerted processes by which the cell senses and regulates essential redox reactions. The activation of cell trafficking mechanisms and kinase pathways in programmed cell death reflects mitochondrial dynamics extending far beyond default responses to free radical damage. These and other new insights may have far-reaching clinical implications, because mitochondrial dysfunction and oxidative stress are important components of liver injury caused by a broad range of drugs and toxicants.

*Dean P. Jones, John J. Lemasters, Derick Han,  
Urs A. Boelsterli, and Neil Kaplowitz*