molecular interventions
pharmacological perspectives from biology, chemistry and genomics

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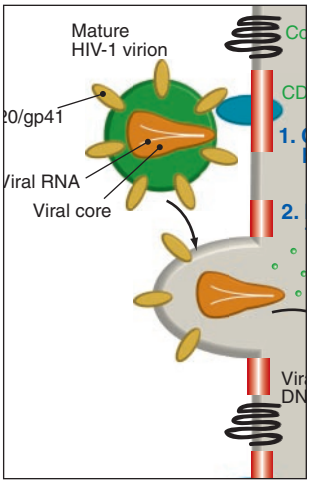


page 70
Can new agents deliver?

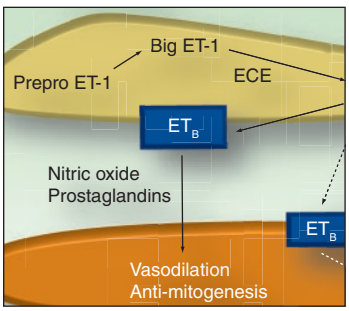
VIEWPOINTS

70 **New Ways of Killing: Novel Targets to Inhibit HIV-1 Replication**
More than twenty-five years after its discovery, HIV-1 remains one of the world's most formidable and destructive pathogens. Several classes of anti-HIV-1 agents are currently in widespread clinical use in developed nations; however, viral resistance to these drugs limits their effectiveness in a growing number of patients. It is therefore imperative that novel drugs be developed. Recent advances in the fields of HIV-1 molecular virology and cell biology have revealed possible new targets for drug discovery. The current status of antiretroviral therapy and some of the promising new targets against which novel antiviral agents could be developed are discussed.

Catherine S. Adamson and Eric O. Freed

75 **Does Improved Lipophilicity Improve Dual Endothelin Receptor Antagonism?**
The widespread actions of endothelin-1 (ET-1) and its receptors, ET_A and ET_B, have led to extreme interest in endothelin antagonists for the treatment of various cardiovascular and other disorders. The first commercially available antagonist, bosentan, blocks both receptors and has been successfully marketed for the treatment of pulmonary arterial hypertension. Similarly, selective ET_A receptor antagonists, such as ambrisentan and sitaxentan, have been approved for the same indication in most countries. However, debate remains as to whether selective ET_A blockade or dual $ET_{A/B}$ blockade would provide a therapeutic advantage. Despite the demonstrated clinical utility of endothelin receptor antagonists, there is much room for improvement in the "-sentan" class of drugs. Recently, investigators reported the development of a new dual endothelin receptor antagonist, macitentan. A specific goal of the drug discovery process, of which macitentan was the end product, was to improve tissue-targeting by selecting lipophilic agents for development. This is a potentially exciting discovery if it can be demonstrated that such compounds partition into local tissue environments to obtain a more preferable pharmacological profile in targeting the largely autocrine-paracrine endothelin system.

David M. Pollock, Erika I. Boesen, Stephen M. Black



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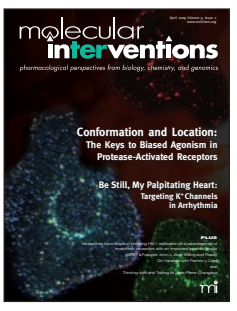
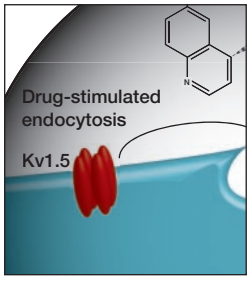
Better tissue partitioning through chemistry

Location, Location, Location!
MI's review articles in this issue stress the cellular placement (and conformation!) of proteins as a parameter of cell signaling, function, and potential pharmacological regulation. The cover image comes from Jeffrey Martens and his studies of cardiomyocyte potassium channels—including their trafficking through cellular compartments—as targets of antifibrillatory drugs.



REVIEWS

79 Therapeutic Regulation of K^+ Channel Surface Expression: Antifibrillatory Agents as "Drug–Traffickers"



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Block the pore, and more

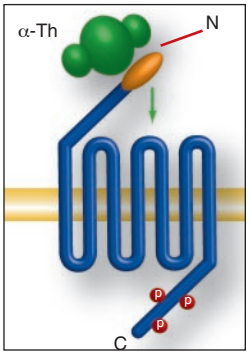
Atrial fibrillation (AF) is the most common cardiac arrhythmia. The preferred therapy for AF is sustained sinus rhythm control; however, the efficacy of currently used antiarrythmic drugs is limited by adverse side effects resulting from both a lack of ion channel selectivity and nonspecific ventricular activity. The role of the voltage-gated potassium channels in atrial myocyte repolarization and the subsequent control of action potential duration renders them attractive targets for antiarrhythmic drugs in the treatment of AF. Conventional antiarrhythmic drugs generally target the ion permeability of potassium channels. This review discusses the limitations of this traditional approach and introduces, as a novel paradigm for antiarrhythmic pharmacology, the decrease of ion channel cell surface density through the modulation of ion channel trafficking pathways.

Dyke P. McEwen and Jeffrey R. Martens

87 Biased Agonism Requires Good Location and Receptors to Conform

An activated receptor residing on the cell surface stimulates several intracellular signaling pathways. But what if a cell needs only to activate a subset of those possible pathways? Cells have evolved many ways of tailoring responses, including the use of particular enzyme isoforms and isozymes that have different binding affinities or substrate specificities or are located in differing subcellular compartments. Receptors themselves can regulate what pathways get activated by using the least well-understood mechanism, known as functional selectivity or biased agonism. Depending upon the conformation a receptor adopts and its location on the cell surface, a receptor may specify what intracellular signals are activated. The protease-activated receptor (PAR) family consists of four members that are activated by proteolysis of their extracellular N termini, which unmasks an intrinsic cryptic ligand capable of binding the receptor's ligand-binding domain. Differing proteases elicit distinct responses through the activation of the same PAR. This phenomenon can involve localization of the receptors to caveolae-rich lipid rafts and stabilization of distinct active PAR conformations that facilitate selective coupling to different effectors.

Angela Russo, Unice J. K. Soh, and JoAnn Trejo



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Conforming to expectations?