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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, $\text{ET}_A$ and $\text{ET}_B$, 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 $\text{ET}_A$ receptor antagonists, such as ambrisentan and sitaxentan, have been approved for the same indication in most countries. However, debate remains as to whether selective $\text{ET}_A$ blockade or dual $\text{ET}_{A/B}$ 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

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. 📚
REVI EWS

79 Therapeutic Regulation of K⁺ Channel Surface Expression:
Antifibrillatory Agents as “Drug–Traffickers”
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 antiarrhythmic
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