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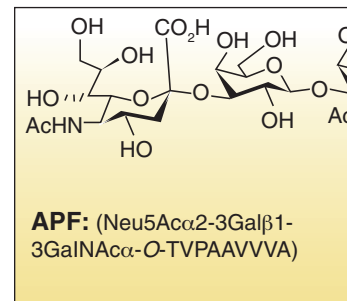
pharmacological perspectives from biology, chemistry and genomics

VIEWPOINTS

14 A Sweet Tale: An Anticancer Lead from Diseased Bladders

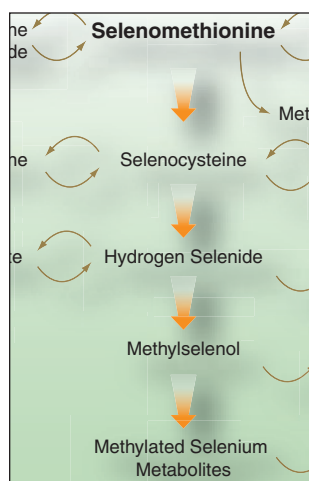
Glycopeptides are a class of molecules that comprise two distinct families of biologically important scaffolds, peptides and oligosaccharides, each playing important roles in cellular communication and signaling. Rarely are small, endogenous secreted glycopeptides found that have significant impact on the progression of a specific disease state, but such is the case for the antiproliferative factor (APF) found in the urine and tissue of patients with the poorly understood bladder diseases collectively referred to as interstitial cystitis (IC). APF is a 9-mer peptide containing a sialylated *O*-linked trisaccharide glycan attached to the N-terminal threonine. APF dramatically inhibits normal bladder cell proliferation and is thought to cause some of the characteristic pathological changes in the bladder of IC patients. Importantly, APF also potently inhibits the growth of certain tumor cells. The details of the cellular receptors to which APF interacts, and the structural features that are critical for its potency are now beginning to unfold. This interesting molecule is a powerful model for the design of new treatments and diagnostic tests for IC, as well as an unprecedented lead agent for novel anticancer drug design.

Joseph J. Barchi, Jr. and Piotr Kaczmarek



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APF: Activity against tumor cells

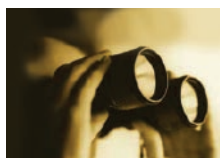
18 Clarifying Selenium's Role in Prostate Health



The recently completed Selenium and Vitamin E Cancer Prevention Trial (SELECT) was one of the largest human cancer prevention trials ever undertaken. Its purpose was to assess the role of selenium and vitamin E in prostate cancer prevention, but SELECT found no decline in prostate cancer. Comparison of this study to other clinical trials involving selenium and to the results of animal studies suggests that the source of the selenium supplement, L-selenomethionine, and the relatively high initial levels of selenium in the enrolled men may have contributed to this outcome. Further analysis of the clinical and animal data highlights the need for mechanistic studies to better understand selenium biology in order to target dietary selenium to appropriate subsets of the human population: those individuals most likely to benefit from this micronutrient.

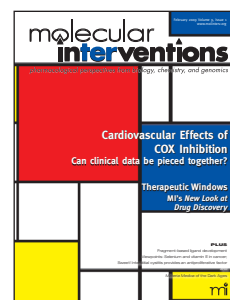
Dolph L. Hatfield and Vadim N. Gladyshev

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Subtlety to selenium's effectiveness



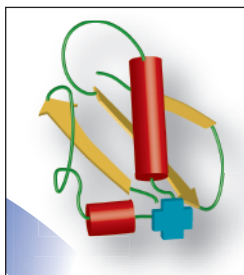
The Art of Mondrian and Therapeutic Windows: De Stijl!

Our cover is inspired by Piet Mondrian (1872–1944), who attempted to capture the dichotomous concepts of complexity and simplicity within each work of art. In this issue of MI, we also introduce a new department—Therapeutic Windows (pages 12–13)—that will explore examples of drug discovery and the development of therapeutics. Pharmacologists are very familiar with the exhilarating challenges that informed Mondrian's work. From the molecular to the integrative, pharmacological research thrives by bringing multiple perspectives to drug discovery and the design of novel therapeutics. 🍷



REVIEWS

22 Of Ligands and LEGOs: Fragment-Based Drug Design



page 22
Drug tinkering

From home building and decor to mass production, modular design is a standard feature of the modern age. The concept also promises to define drug discovery efforts in the near future, as a wide range of methodologies, from NMR to X-ray crystallography, are being adapted to high-throughput platforms. In particular, “fragment-based ligand discovery” describes the laboratory-driven evolution of drugs from libraries of chemical building blocks. “Evolution” is an apt word for the process, as a wide array of methods are used to define how compound fragments can be best fit into the binding sites of medically relevant target biomolecules. A number of compounds that evolved from fragments have entered the clinic, and the approach is increasingly accepted as an additional route to identifying new hit compounds in pharmaceutical discovery and inhibitor design.

Marcus Fischer and Roderick E. Hubbard

31 Cardiovascular Health: What is it about the NSAIDs?

Aspirin has been a commercial drug for over a century, although for most of this history, an understanding of its mechanism of action, as an inhibitor of cyclooxygenase (COX) activity and thus of prostanoid synthesis, was lacking. Over the past fifty years, a large number of other nonsteroidal antiinflammatory drugs (NSAIDs) have been developed, and a much deeper understanding of inflammation and prostanoid action has emerged. Indeed, a new class of selective inhibitors of the cyclooxygenase-2 isozyme was introduced, about ten years ago, and these so-called coxibs quickly became regarded as preferable, in certain clinical contexts, to avoid side effects associated with the use of aspirin and previously developed NSAIDs. This regard for coxibs has been challenged, sometimes infamously, as cardiovascular events associated with coxib use have become apparent. A variety of clinical trials have led to seemingly conflicting data concerning the roles of COX-1 and COX-2, and the implications of their relative inhibition, in cardiovascular health and disease. In this Review, the authors offer an assessment of drug pharmacokinetics and enzyme physiology that reconciles cardiovascular appraisals from a wide array of clinical data.

Carlo Patrono and Colin Baigent



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Aspirin and company