**VIEWPOINTS**

**133 ERβ: Selective Activation not Involving the Ligand Binding Site**

Estrogen action is mediated by binding to two specific estrogen receptors (ERs), ERα and ERβ. The discovery of ERβ in 1996 changed our understanding of estrogen action and sparked intense research efforts to discover its role in normal physiology and its potential as a drug target. Several ERβ-selective and clinically active ligands have since been developed. The first compounds described were those that have a high selective binding affinity for ERβ, such as ERB-041. A second class of agents that have been identified bind to ERβ and ERα with similar affinity but selectively activate ERβ, such as liquiritigenin, a flavanone. A recent study has identified 3,3′-diindolylmethane (DIM) as a member of a new class of ERβ activator that does not bind to the ligand binding site, but rather selectively activates ERβ possibly through cellular kinase pathways that target the receptor’s ligand-independent activation domain. Although more studies are needed, these findings suggest that compounds that modulate of ERβ activation without directly binding to the receptor might prove to be of significant clinical importance in the future.

*Raymond Lo and Jason Matthews*

**137 TRPV1 Deorphanized: Octadecadienoids Emerge as Novel Lipid Transmitters**

Nearly fifty years ago, the existence of a “pain receptor” was postulated through which capsaicin could exert its “stimulatory and desensitizing” actions. More recently, that receptor, the transient receptor potential vanilloid 1 (TRPV1) has been molecularly cloned and characterized. Much research has been devoted to identify those molecules serving as endogenous agonists for TRPV1. Various eicosanoids may act as these so-called endovanilloids, but new, exciting findings indicate that oxidized metabolites of linoleic acid (OLAMs) satisfy a number of critical criteria to be classified as endogenous activators of TRPV1. Intriguingly, OLAMs may also participate as peripheral neurochemical conduits of heat itself. Thus, TRPV1 may not only be deorphanized, but OLAM “octadecadienoids” may represent a novel class of algogenic substances. These findings raise critical questions regarding the precise role(s) of TRPV1 in nociceptive transduction and about the importance of fatty acids in the modulation of pain and related functions. Moreover, these findings may inform the potential development of novel therapeutic strategies to treat pain.

*Christopher M. Flores and Michael R. Vasko*

---

**Erratum**

*Close Encounters of an Oily Kind: Regulation of Transporters by Lipids*  
In Table 2, the five double bonds inherent to eicosapentaenoic acid were not shown. The article also lacked acknowledgment that the authors' work was supported by the National Institutes of Health [Grants DA07595, MH80726].
REVI EWS

141 Bisphosphonate Therapeutics in Bone Disease
With annual sales well over three billion dollars, bisphosphonate drugs have been widely prescribed to maintain bone density in patients who are at risk for fractures, such as those afflicted with osteoporosis. Paradoxically, bisphosphonate treatment has in the past few years been linked to rare adverse events, such as osteonecrosis of the jaw, marked by bone deterioration. Such side effects tend to occur within particular clinical contexts, such as cancer and dental surgery, but they have raised concern in light of the widespread use of bisphosphonate therapeutics. The mechanisms of bisphosphonate action and the dynamics of bone turnover are intricately related, and the interplay between drug and bone explains, at least in part, the paradoxical effects of bisphosphonate drugs on bone development. An understanding of this interplay may also provide routes to potential new therapeutics to ward off bone loss associated with disease.

Matthew T. Drake and Serge C.L.M. Cremers

153 Orphan Cytochrome P450 Enzymes
With the rapid completion of genomic sequences of organisms today, we have far more gene products than functions we can ascribe. A number of experimental strategies have been developed and applied, both in vitro and in vivo, to put functions to these orphan proteins. The “deorphanization” of human and Streptomyces cytochrome P450 enzymes is considered quite important for pharmacology, with ramifications for the use of clinical therapeutics. The myriad of possibilities is too enormous to screen one reaction at a time, and the development of metabolomic and proteomic screens with complex biological samples is thus essential.

F. Peter Guengerich, Zhongmei Tang, S. Giovanna Salamanca-Pinzón, and Qian Cheng

164 The Cancer Microenvironment: Sources of Pain
Cancer pain is a formidable clinical problem, reflecting a complex series of cellular, tissue, and systemic changes that occur during proliferation, invasion, and metastasis. Primary afferent nociceptors are modulated by a number of mediators released by cancer cells, and immune cells that are drawn into the cancer further complicate pain perception. The peripheral neuropathic changes and the influence of tumors upon neurons in the elaboration of pain and central sensitization are beginning to be understood in some detail. The judicious design and exploitation of animal models continue to help researchers unravel the complexities of cancer-evoked pain.

Brian L. Schmidt, Darryl T. Hamamoto, Donald A. Simone, and George L. Wilcox

Bone pharmacology

Genomic homing devices

Cancer pain