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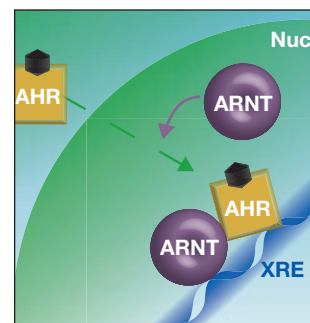
pharmacological perspectives from biology, chemistry and genomics

VIEWPOINTS

116 AHR-ARNT Interrupted: EGF May Inhibit the Development of Chloracne

The aryl hydrocarbon receptor (AHR) mediates most, if not all, of the many toxicological effects of the environmental pollutant 2,3,7,8-tetrachlorodibenzo-p-dioxin [(TCDD) or dioxin]. The “classical” pathway of AHR action involves dimerization of the liganded AHR with the aryl hydrocarbon nuclear translocator (ARNT) protein, and the AHR-ARNT dimer specifically associates with the enhancer regions of dioxin-responsive genes, leading to their increased transcription. Sutter and coworkers recently reported that epidermal growth factor (EGF) represses the dioxin-mediated induction of CYP1A1 in cultured normal human keratinocytes by inhibiting the recruitment of the transcriptional coactivator protein p300 to the CYP1A1 gene. EGF also inhibits the dioxin-dependent induction of certain parameters in keratinocytes that are reflective of dioxin-induced chloracne. These findings point to the potential usefulness of EGF for the treatment of chloracne and also describe a novel mechanism for repression of dioxin-induced gene transcription.

Oliver Hankinson



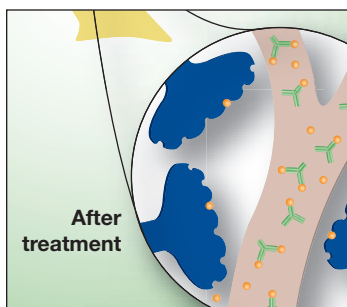
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Blocking dioxin's devastation

119 Antibody-Based Therapies for Treating Drug Addiction

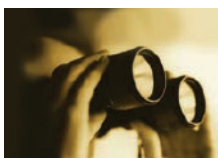
Immunotherapy for treating illicit drug abuse is a rapidly advancing field. There are currently two major approaches to developing drug-specific immunotherapies: active and passive. Active immunotherapy involves conjugating a drug-like hapten to a carrier protein and using traditional immunization approaches to generate a drug-specific immune response in the patient. In contrast, passive immunotherapy utilizes preformed monoclonal antibodies. Whether generated by active immunization or delivered passively, antibodies act as pharmacokinetic antagonists by binding the drug in the bloodstream and reducing the amount and rate of drug delivery to receptors in the brain. A newly emerging technology in anti-drug immunotherapy is the use of antibody fragments, or scFvs, rather than intact immunoglobulin G (IgG). These scFvs can retain the same binding properties as the original mAbs, and are one-third the molecular weight, providing a scaffold for creating antibody treatments with more customizable properties. Another nascent area of research utilizing the scFv scaffold is in creating drug-specific scFv-nanoparticle conjugates.

These conjugates could improve upon current drug-specific antibody paradigms by increasing multivalency and allowing pharmacokinetic customization, while avoiding interactions with endogenous antibody receptor pathways. These parallel approaches to immunotherapy are moving rapidly toward the clinic and may soon provide new therapies for treating drug abuse.

Eric C. Peterson and S. Michael Owens



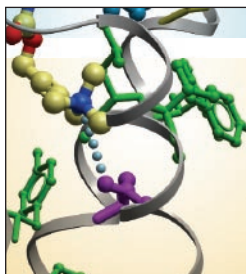
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Breaking addiction: King mAb?



REVIEWS

125 Allosteric-orthosteric ligands: Probing alternative functions of GPCRs

G protein-coupled receptors (GPCRs) can adopt multiple biologically active states that can be differentially stabilized by ligands that bind to topographically distinct sites (e.g., orthosteric ligands and allosteric modulators). Recent studies in the field are now demonstrating the utility of linking orthosteric and allosteric pharmacophores to yield hybrid, or bitopic, ligands, with improved affinity and/or receptor subtype selectivity. Interestingly, this approach can also engender functional selectivity in the actions of orthosteric ligands, highlighting a viable means of further sculpting GPCR ligand responses. Indeed, some previously identified functionally selective agonists may actually represent hitherto unappreciated bitopic ligands.



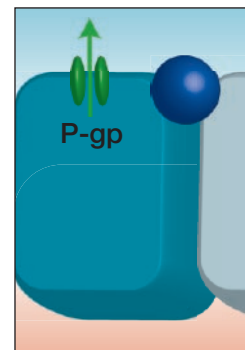
Celine Valant, Patrick M. Sexton, and Arthur Christopoulos

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Bitopic ligands

136 Know your ABCs! Clinical implications of drug transporter knockout mice

ATP-binding cassette (ABC) multidrug transporters are cellular efflux pumps with broad and often widely overlapping substrate specificities. They can have a major impact on the pharmacokinetics and hence overall pharmacological behavior of many drugs. To study their separate roles and functional overlap, or complementarity, a collection of mice deficient in two or more ABC transporters has been generated. This review discusses recent findings obtained with these models, focusing on pharmacokinetic studies with a number of clinically relevant drugs. In addition, the characterization of these mice and some physiological aspects of ABC multidrug transporters are addressed.

Jurjen S. Lagas, Maria L.H. Vlaming, and Alfred H. Schinkel



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The right combination