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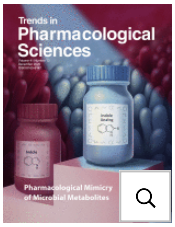

Drug Discovery is fraught with attrition. A new approach to expand the chemical repertoire of drugs is via chemical mimicry of microbial metabolites. In an ... Show more

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Spotlight

A Novel Small Molecule Targets NKCC1 To Restore Synaptic Inhibition

Vineeth A. Raveendran, Jessica C. Pressey, Melanie A. Woodin

Finely tuned excitation–inhibition balance is essential for proper brain function, and loss of balance resulting from reduced synaptic inhibition is associated with neurological disorders. Savardi and colleagues have discovered a novel inhibitor of a cation-chloride transporter that is required for synaptic inhibition, and which restores behaviors associated with Down syndrome (DS) and autism spectrum disorder (ASD).

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Opinions

Drug Mimicry: Promiscuous Receptors PXR and AhR, and Microbial Metabolite Interactions in the Intestine

Zdeněk Dvořák, Harry Sokol, Sridhar Mani

Significant attrition limits drug discovery. The available chemical entities present with drug-like features contribute to this limitation. Using specific examples of promiscuous receptor-ligand interactions, a case is made for expanding the chemical space for drug-like molecules. These ligand-receptor interactions are poor candidates for the drug discovery process. However, provided herein are specific examples of ligand-receptor or transcription-factor interactions, namely, the pregnane X receptor (PXR) and the aryl hydrocarbon receptor (AhR), and its interactions with microbial metabolites.

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Can Growth Factors Cure Parkinson's Disease?

Yulia A. Sidorova, Mart Saarma

Growth factors (GFs) hold considerable promise for disease modification in neurodegenerative disorders because they can protect and restore degenerating neurons and also enhance their functional activity. However, extensive efforts applied to utilize their therapeutic potential in humans have achieved limited success so far. Multiple clinical trials with GFs were performed in Parkinson's disease (PD) patients, in whom diagnostic symptoms of the disease are caused by advanced degeneration of nigrostriatal dopamine neurons (DNs), but the results of these trials are controversial.

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Fluxes for Unraveling Complex Binding Mechanisms

Georges Vauquelin, Dominique Maes, David C. Swinney

A decade ago, many high-affinity drugs were thought to bind to their target via an induced-fit pathway instead of conformational selection. Yet, both pathways make up part of a thermodynamic cycle, and, owing to binding flux-based approaches, it is now rather considered that they act in parallel and also that their relative contribution to the final ligand–target complex depends on the ligand concentration. Those approaches are of increasing interest, but published data still merely refer to the peculiar situation of equilibrium binding.

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Reviews

AKAP Signaling Islands: Venues for Precision Pharmacology

Mitchell H. Omar, John D. Scott

Regulatory enzymes often have different roles in distinct subcellular compartments. Yet, most drugs indiscriminately saturate the cell. Thus, subcellular drug-delivery holds promise as a means to reduce off-target pharmacological effects. A-kinase anchoring proteins (AKAPs) sequester combinations of signaling enzymes within subcellular microdomains. Targeting drugs to these 'signaling islands' offers an opportunity for more precise delivery of therapeutics. Here, we review mechanisms that bestow protein kinase A (PKA) versatility inside the cell, appraise recent advances in exploiting AKAPs as platforms for precision pharmacology, and explore the impact of methodological innovations on AKAP research.

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Critical Assessment of G Protein-Biased Agonism at the μ-Opioid Receptor

Alexander Gillis, Andrea Kliewer, Eamonn Kelly, Graeme Henderson, Macdonald J. Christie, Stefan Schulz, Meritxell Canals

Open Access

G protein-biased agonists of the μ-opioid receptor (MOPr) have been proposed as an improved class of opioid analgesics. Recent studies have been unable to reproduce the original experiments in the β-arrestin2-knockout mouse that led to this proposal, and alternative genetic models do not support the G protein-biased MOPr agonist hypothesis. Furthermore, assessment of putatively biased ligands has been confounded by several factors, includir

assay amplification. As such, the extent to which current lead compounds represent mechanistically novel, extremely G protein-biased agonists is in question, as is the underlying assumption that β-arrestin2 mediates deleterious opioid effects.

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Electroceuticals in the Gastrointestinal Tract

Khalil B. Ramadi, Shriya S. Srinivasan, Giovanni Traverso

The field of electroceuticals has attracted considerable attention over the past few decades as a novel therapeutic modality. The gastrointestinal (GI) tract (GIT) holds significant potential as a target for electroceuticals as the intersection of neural, endocrine, and immune systems. We review recent developments in electrical stimulation of various portions of the GIT (including esophagus, stomach, and small and large intestine) and nerves projecting to the GIT and supportive organs. This has been tested with varying degrees of success for several dysmotility, inflammatory, hormonal, and neurologic disorders.

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Molecular Therapeutics of Pancreatic Ductal Adenocarcinoma: Targeted Pathways and the Role of Cancer Stem Cells

Andrei-Florian Stoica, Chao-Hui Chang, Siim Pauklin

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers in humans due to late detection and highly metastatic characteristics. PDAC cells vary in their tumorigenic capabilities with the presence of a subset of PDAC cells known as pancreatic cancer stem cells (CSCs), which are more resistant to currently used therapeutics. Here, we describe the role of CSCs and tumour stroma in developing therapeutic strategies for PDAC and suggest that developmental plasticity could be considered a hallmark of cancers.

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Drug–Exposome Interactions: The Next Frontier in Precision Medicine

Manuel Pristner, Benedikt Warth

Drug–drug interactions are a known concern during medical treatment. However, in addition to therapeutic drugs, humans are exposed to thousands of environment- and food-related chemicals on a daily basis. The exposome (i.e., the total measure of environmental factors on the human body) is an emerging concept in the field of environmental health. Many chemicals have the potential to interact with drugs and subsequently influence health outcomes. To date, this concept has not been systematically investigated.

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Unintended Effects of GPCR-Targeted Drugs on the Cancer Phenotype

Abigail C. Cornwell, Michael E. Feigin

G protein-coupled receptors (GPCRs) are the most common class of therapeutic targets, accounting for ~35% of all FDA-approved drugs. Cancer patients receive numerous medications not only to combat cancer but also to alleviate pain, nausea, and anxiety, many of which target GPCRs. Emerging evidence has implicated GPCRs as drivers of cancer progression, therapeutic resistance, and metastasis. Therefore, the effects of commonly prescribed GPCR-targeted drugs must be reevaluated in the context of cancer.

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CSF and Blood Biomarkers in Neuroinflammatory and Neurodegenerative Diseases: Implications for Treatment

Lorenzo Gaetani, Federico Paolini Paoletti, Giovanni Bellomo, Andrea Mancini, Simone Simoni, Massimiliano Di Filippo, Lucilla Parnetti

Neuroinflammatory and neurodegenerative diseases are characterized by the interplay of a number of molecular pathways that can be assessed through biofluids, especially cerebrospinal fluid and blood. Accordingly, the definition and classification of these disorders will move from clinical and pathological to biological criteria. The consequences of this biomarker-based diagnostic and prognostic approach are highly relevant to the field of drug development. Indeed, in view of the availability of disease-modifying drugs, fluid biomarkers offer a unique opportunity for improving the quality and applicability of results from clinical trials.

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Selective and Effective: Current Progress in Computational Structure-Based Drug Discovery of Targeted Covalent Inhibitors

Giulia Bianco, David S. Goodsell, Stefano Forli

Targeted covalent inhibitors are currently showing great promise for systems that are normally difficult to target with small molecule therapies. This renewed interest has spurred the refinement of existing computational methods as well as the design of new ones, expanding the toolbox for discovery and optimization of selective and effective covalent inhibitors. Commonly applied approaches are covalent docking methods that predict the conformation of the covalent complex with known residues. More recently, a new predictive method, reactive docking, was developed, building on the growing corpus of data generated by large proteomics experiments.

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Single-Cell Techniques and Deep Learning in Predicting Drug Response

Zhenyu Wu, Patrick J. Lawrence, Anjun Ma, Jian Zhu, Dong Xu, Qin Ma

Rapidly developing single-cell sequencing analyses produce more comprehensive profiles of the genomic, transcriptomic, and epigenomic heterogeneity of tumor subpopulations than do traditional bulk sequencing analyses. Moreover, single-cell techniques allow the response of a tumor to drug exposure to be more thoroughly investigated. Deep learning (DL) models have successfully extracted features from complex bulk sequence data to predict drug responses. We review recent innovations in single-cell technologies and DL-based approaches related to drug sensitivity predictions.

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