In This Issue

Antibiotic Renaissance

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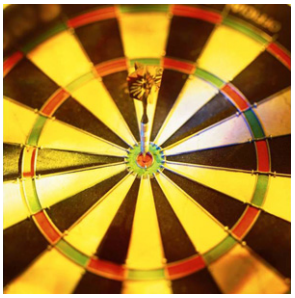
Antibiotic resistance is one of the most significant challenges to the health care sector in the 21st century, yet at the same time there have been ever fewer new antibiotics brought to market and the pharmaceutical industry increasingly sees antibiotics as a poor investment. Paradoxically, we are in a goldenage of understanding how antibiotics work and where resistance comes from. In this Perspective, Wright discusses how this knowledge is fueling a renaissance of interest and innovation in antibiotic discovery, synthesis, and mechanism that is poised to inform drug discovery to address pressing clinical needs.



Chemoproteomics to the Rescue

PAGE 11

One of the important issues that current drug discovery efforts are facing is how to navigate large genetic information space to produce new first-in-class medicines. In this Perspective, Moellering and Cravatt argue for the critical role of pharmacology in early phases of drug discovery campaigns, to bridge the current divide between early and later stages of the process. The authors discuss the potential role chemoproteomics are poised to play in mining the proteome for new drug targets, as well as new biological insights.

Systems Biology in Drug Discovery

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Current drug design strategies are able to successfully optimize structure of a small molecule to improve the specificity. Although this "one-to-one" drug design approach has been fruitful, adverse drug reactions due to ligand and protein promiscuity have been well documented. Brown and Okuno describe the need to refine the drug design strategy such that it includes the possibility of multiple interactions from both ligand and target perspectives. The authors argue that interpretation requires zooming our perspective out to the larger, network-wide level, and they review some of the recent developments in systems-level research for drug design and discovery.

Computational Drug Discovery

PAGE 29

Bioinformatics and chemoinformatics approaches contribute to hit discovery, hit-to-lead optimization, safety profiling, target identification, and enhance our overall understanding of the health and disease states. The review by Taboureau et al. explores several computational methods used in the field of drug discovery and chemical biology, with a special emphasis on compound collection preparation, virtual screening, protein docking, and systems pharmacology. The review also includes a list of generally freely available software packages and online resources, to encourage wider community use.

Structural Biology in Drug Discovery

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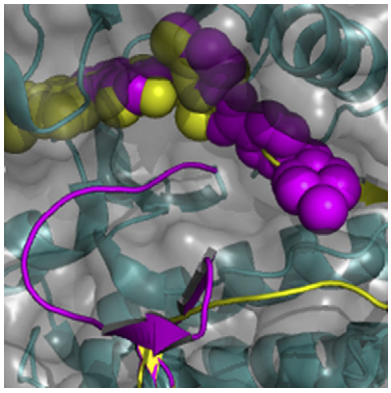


Over the past decade, researchers in the pharmaceutical industry and academia have identified features of drug targets that are considered undesirable and some that make them "unligandable." The review by Surade and Blundell focuses on the factors that make targets difficult. The authors discuss the challenges of targeting protein-protein interfaces, protein-ligand interactions where adaptive changes are required to configure a binding site, and binding sites with metal ions, high lipophilicity, and other features that lead to lack of selectivity.

Targeting the Orphans

PAGE 51

The nuclear receptor (NR) superfamily is composed of 48 members in humans and includes receptors for steroid hormones, thyroid hormone, various lipids, and oxysterols. This superfamily has been a rich source of drug targets for myriad diseases including inflammation, cancer, and metabolic disorders. Here, Burris et al. review recent discoveries that yield important insight into the druggability of three orphan nuclear receptors: the retinoic acid receptor-like orphan receptors (RORs), peroxisome proliferator-activated receptor γ (PPARγ), and liver receptor homolog-1 (LRH-1).

The Power of RNA

PAGE 60

Over the last three decades, RNAs have gone from being viewed as a DNA/protein go-between to a key player in regulating cellular function, displaying functional and structural diversity. Improved understanding of multifaceted roles of RNAs led to the emergence of different types of RNA-based therapeutics. In this review, Burnett et al. discuss RNA-based therapeutics, their mechanism of action, current state of the development, and challenges faced with moving these drugs to the clinic.

Proteomics in Preclinical Drug Discovery

PAGE 72

The environment in which drugs need to act is extremely complex and includes numerous intra- and extracellular pathways, as well as cell and tissue variability. Thus, application of proteomics in the drug discovery process can offer large scale analysis and enable target identification and deepen biological insight. In this review, Schirle et al. summarize the current status of proteomics in drug discovery and provide an overview of early applications in this area, the most recent methodological improvements, and how proteomics can be successfully applied in both target-based and phenotype-based workflows for preclinical drug discovery.

Finding Drugs in the Sea

PAGE 85

The world's marine habitats are a rich source of natural products with remarkable chemical diversity. Here, Moore and Gerwick provide a historical perspective of marine natural product research, as well as discussing the state of the art efforts to improve our understanding of biosynthetic pathways that lead to diverse chemical structures and manners in which this information can be used for re-engineering existing pathways to produce more potent derivatives. Finally, the authors also provide a vision of an exciting future fueled by rapid development of methodology.

Proteasome Inhibitors

PAGE 99

Bortezomib (Velcade, PS-341) is the oldest FDA-approved drug that acts as a proteasome inhibitor. Bortezomib was approved for treatment of multiple myeloma (MM) in 2003, and the interest in small molecule proteasome inhibitors has been high ever since, with five other proteasome inhibitors in clinical trials. Here, van der Linden et al. review the current state of drug discovery and development aimed at the proteasome as the target.

Ganging up on Malaria

PAGE 116

Malaria is a notorious mosquito-borne disease with a large death burden and a significant economical impact in the most affected countries of the sub-Saharan region. The arsenal of weapons against malaria includes insecticide impregnated bed nets, localized spraying, and chemotherapy, which is the dominant component of malaria control. Here, Guiguemde et al. describe key challenges for currently available chemotherapy and summarize recent success from both academia and industry in applying phenotypic screening campaigns to identify compounds acting on *Plasmodium falciparum*. Additionally, authors elaborate on further innovation needed to produce new viable therapeutic options, including changing the way in which information and resources are shared between both academic and industrial scientists involved in the process.

Heparan Sulfate-Mimetic Peptide against HIV-1

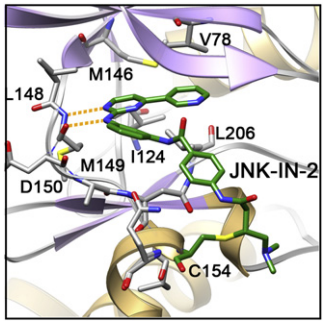
PAGE 131

HIV-1 entry requires the interaction of the viral gp120 with the cell surface CD4 and either one of the two coreceptors CCR5 or CXCR4. The CCR5/CXCR4 binding site represents an attractive pharmacological target; however, it remains cryptic until the gp120 has been bound by CD4. A new compound, mCD4-P3YSO3, described by Connell et al., gets around this defense mechanism: it comprises a CD4 mimetic (mCD4), which interacts with gp120 and exposes the CCR5/CXCR4 binding site and a sulfated peptide (P3YSO3), which then targets this newly exposed domain. The molecule thus blocks two gp120 conserved domains and inhibits HIV-1 replication with an IC50 of 1 nM.

Covalent Inhibitors of JNK

PAGE 140

C-Jun N-terminal kinases (JNKs) are members of the MAPK (mitogen-activated protein kinase) superfamily and central to cellular stress response. Zhang et al. now report selective covalent inhibitors of JNK. Two cocrystal structures of the inhibitors with JNK3 show covalent modification of cysteine 154. JNK-IN-8 and JNK-IN-12 exhibit nanomolar potency in biochemical and cellular assays and extensive kinase selectivity profiling was performed to establish the selectivity of these inhibitors. JNK-IN-8 and JNK-IN-12 will be useful pharmacological probes of JNK-dependent phenomena.



Yeast Screen Yields PDE11-Selective Inhibitors

PAGE 155

Cyclic nucleotide phosphodiesterases (PDEs) comprise an enzyme superfamily encoded by 21 genes whose products act on only two substrates, cyclic AMP and cyclic GMP, yet regulate distinct processes. By screening 198,382 compounds for inhibition of human PDE11A using a fission yeast growth assay, Ceyhan et al. identify four potent PDE11A-specific inhibitors. Compound BC11-38 elevates cAMP levels and cAMP-regulated functions in adrenocortical cells, mimicking the effect of PDE11A mutations associated with Cushing Syndrome. This compound can serve as a research tool to study biological roles of PDE11A and as a lead compound to develop therapeutics to treat adrenal insufficiencies such as Addison's Disease.

