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245 Finding the Achilles’ Heel in Variola Virus

Smallpox is a serious and highly contagious disease that is caused by the variola virus. It is one of the most severe infectious human diseases known, with mortality rates as high as 30%. A successful worldwide vaccination program led to the eradication of smallpox in 1980. However, the high transmission rate of variola virus, coupled with the deadly nature of smallpox, makes this virus a potentially devastating weapon for bioterrorism. Currently, there is no specific treatment for smallpox. However, a recent article on the structure of a variola topoisomerase IB–DNA complex provides an intriguing starting point for the rational design of drugs with potential activity against smallpox.

Neil Osheroff

249 Blocking Ghrelin to Fight Obesity

In the battle to treat the pandemic of obesity, one therapeutic strategy is to block endogenous signals that stimulate appetite and control body weight. One such molecule is ghrelin, a gut peptide that is the only known orexigenic hormone and is a likely contributor to mealtime hunger. The relative importance of ghrelin in long-term body-weight regulation (and thus its promise as an anti-obesity target) is uncertain, however, because genetic and pharmacologic blockade of ghrelin signaling have yielded variable results to date. Using a novel approach of vaccinating rats against their own ghrelin, Zorilla et al. report that animals with high ghrelin-specific antibody titers displayed restricted body weight, without evidence of non-specific inflammation following the vaccine. These results favor a meaningful role for ghrelin in energy homeostasis, hinting at a possible new anti-obesity approach. More broadly, the work of Zorilla et al. supports the feasibility of vaccinations directed against specific autologous targets—immunopharmacotherapy that could potentially be developed to target a wide array of medical conditions.

Molly J. Carlson and David E. Cummings

253 Novel Genetic Lesion Leads to SCID: Calcium Influx in T Cell Activation

Severe Combined Immunodeficiency (SCID) is a rare primary immunodeficiency disease often characterized by a block in T cell development, which may also affect the normal development of B cells and NK cells. Several different mutations are known to give rise to SCID, and multiple genes are involved. Consequently, there are several different forms of SCID, which can be classified according to the metabolic and cellular defects that impede normal lymphocyte function. The two most prevalent forms of SCID are X-linked SCID and adenosine deaminase (ADA) deficiency SCID, together accounting for approximately 70-80% of disease cases. Other genetic abnormalities associated with this syndrome range from defective T cell receptor rearrangement to non-functional signaling molecules. Recently, a new genetic defect has been described in which mutations in a key component of Ca2+ release activated-channels (CRAC) result in T lymphocyte malfunction.

Helen P. Carroll, Benjamin B.A. McNaull, and Massimo Gadina
257 Magic Mint Targets the κ-Opioid Receptor

The hallucinogenic plant Salvia divinorum, a member of the mint family, has traditionally been used by the Mazatec natives of southern Mexico to induce ritual visions and is increasingly used in the US for recreational purposes. The main active ingredient in the plant is the diterpene salvinorin A, which is structurally distinct from other chemical classes of hallucinogens. In recent high-throughput screening experiments, salvinorin A was found to bind to the κ-opioid receptor (KOR) with high specificity. Chemical analogs of the compound are now under study, in concert with functional characterization of KOR, to determine whether modulation of KOR activity could provide a basis for new psychotropic medications. Indeed, there are indications that salvinorin A or its congeners may prove useful in both psychiatric and non-psychiatric diseases.

Timothy A. Vortherms and Bryan L. Roth

266 Getting Better Lead Compounds Through Better Technologies

Constructing novel drug leads from small molecular building blocks is a powerful new approach to drug discovery. This field, called fragment-based drug design, relies on the experimental detection and structural characterization of very weakly binding, low molecular-weight ligands that can be rapidly increased in potency using structure-based drug design. Numerous examples of fragment-based drug design now exist in the literature, and several compounds derived using this approach have made it into the clinic. This review will describe the concept of fragment-based drug design, discuss why it works, and use two case studies to illustrate the power of the approach.

Philip J. Hajduk

273 Appraisal of Choice in Drug-Use Behavior

The abuse liability of a drug is closely related to its ability to maintain self-administration behavior in laboratory subjects. But how do researchers gauge the reinforcing value of a self-administered drug in the preclinical laboratory? One approach is to determine the “preference” for that drug, that is, the allocation of behavior to drug taking, when alternative reinforcers are concurrently available. Careful analysis of such “choice” behavior in laboratory subjects can lead to a scientific understanding of the pharmacological and behavioral determinants of the reinforcing strength of a drug and, ultimately, to a more useful preclinical evaluation of abuse liability.

Jack Bergman and Carol A. Paronis