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► **COVER:** 'Modulating circadian rhythms' by Susanne Harris, inspired by the Case History on p643.



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**D**rug transport across biological membranes is a key factor influencing drug pharmacokinetics. Although it has traditionally been thought that passive transcellular diffusion was the dominant transport mechanism, this has been challenged recently by growing evidence for a major role of carriers in the transport of some drugs. In their Perspective, Kansy and colleagues review the literature on this subject and conclude that both transportation mechanisms can be important in biological membrane permeation. The contribution of each route, however, should be evaluated on a case by case basis. Understanding interactions with biological membranes is also important in harnessing the potential of nanoparticles to specifically deliver cargo such as drugs to the intended site of action. In their Review, Petros and DeSimone discuss features, such as size, surface characteristics and shape, that influence the biodistribution of nanoparticle carriers. They highlight how such knowledge can be applied in the design of next-generation nanoparticles for therapeutic uses, such as the targeted delivery of anticancer drugs. New insights into the biology of polo-like kinases (PLKs), which have essential roles in cell-cycle events, also offer novel opportunities for anticancer therapy. Strebhardt reviews the role of PLKs in malignant transformation and discusses progress in the development of small-molecule PLK1 inhibitors. Finally, Millan and colleagues present a Case History on the discovery and development of agomelatine — a drug that possesses both melatonergic and serotonergic activity — which was approved by the European Commission in 2009 for treating major depression, thereby becoming the first approved antidepressant to incorporate a non-monoaminergic mechanism of action.

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acid-free paper