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▸ **COVER:** 'Targeting subcellular compartments' by Susanne Harris, inspired by the review on p29.


PETER KIRKPATRICK


ALEXANDRA FLEMMING


CHARLOTTE HARRISON


SARAH CRUNKHORN


BETHAN HUGHES


MONICA HOYOS FLIGHT

Since the discovery of gene silencing by small interfering RNAs, there has been considerable investment in therapeutically applying this technology, with clinical trials now in progress for several diseases. However, progression into the clinic has been hampered by a lack of target specificity, leading to data misinterpretation, poor efficacy or adverse effects. A Review this month by Jackson and Linsley considers the importance of recognizing the various off-target effects of small interfering RNAs and potential strategies to mitigate them. Improving the specificity and efficacy of drugs is also discussed by Simons and colleagues, who review membrane trafficking and subcellular organization, presenting strategies that exploit endogenous mechanisms to direct drugs to the specific cellular compartments in which their targets lie. Various applications of such approaches, including targeting cancer, Alzheimer's disease and HIV, are highlighted. Retrospective analysis reveals that best-in-class HIV protease inhibitors and statins are those for which the enthalpic component of the interaction with their respective targets is optimized. Ladbury and colleagues propose that evaluating the enthalpic component of compound–target interactions using isothermal titration calorimetry may aid in the selection and optimization of lead compounds in general. In their Review, Wagner and Frank focus on the complement system and its role in disease, including allergic, infectious and neurological disorders, highlighting emerging therapeutic strategies, while Bialer and White review advances in understanding of the pathophysiology of epilepsy, and discuss existing antiepileptic drugs and those in development. Finally, as 2010 begins, we would like to thank our authors, advisors, referees and readers for their support in the past year.

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