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► **COVER:** 'Combining targeted anticancer drugs', inspired by the review on p649.



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The concept of a 'magic bullet', targeted at the molecular culprit responsible for a particular disease, has inspired scientific drug discovery from its very beginnings. In this issue, Drews discusses the case history of five modern drugs, and uses these to retrospectively analyse factors that relate to success or failure in modern drug research. In particular, he asks whether it is time to consider 'magic bullets of the second order' — compounds addressing a few selected targets rather than one only. Another way to achieve multi-targeting is, of course, by combining different drugs, and Dancey and Chen explore the challenge of developing strategies for optimizing combinations of molecularly targeted anticancer drugs. One such class of molecularly targeted agents are mTOR inhibitors, and the development of this promising class is reviewed by Raymond and colleagues. And as an example of a drug with relatively high specificity but many uses, Ghofrani *et al.* trace the chameleon-like properties of sildenafil, the active ingredient of the 'little blue pill'. Mainly targeting phosphodiesterase 5 (PDE5) and affecting local blood supply, it was originally developed for the treatment of angina. As Viagra it became a blockbuster for treating erectile dysfunction, and as Revatio it is now approved for treating pulmonary hypertension. PDEs on 'the other side' of the blood–brain barrier are also attracting attention, and Menniti *et al.* examine the potential of PDE inhibitors to treat psychiatric and neurodegenerative disorders by modulating neuronal activity. Finally, Mossialis and Brogan discuss call options for vaccines designed to stimulate research into neglected diseases, and Fresh from the Pipeline presents the first vaccine to prevent cervical cancer.

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