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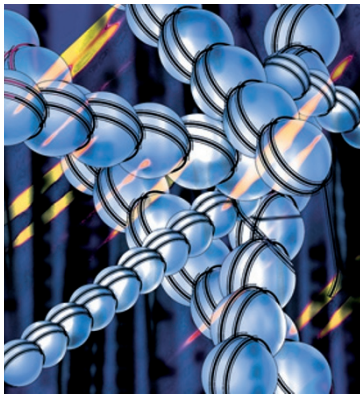

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Reducing attrition rates remains a major challenge in drug development, with the probability of a drug candidate successfully completing Phase II trials currently estimated at only 34%. The physicochemical properties of small-molecule drug candidates are one important factor influencing the chance of success and, importantly, are under the control of medicinal chemists. In their Review, Cummings and colleagues discuss the use of chemical predictive modelling tools — such as quantitative structure–activity relationships — to help guide the selection and optimization of compounds and the challenges associated with their application. Meanwhile, our two other Reviews this month focus on novel anticancer strategies. First, Helin and colleagues discuss the role of histone methylation in the post-translational regulation of gene expression, focusing on the functions of histone lysine methylase enzymes. They present recent evidence supporting a role for members of the lysine-specific demethylase and the Jumonji domain-containing demethylase families in cancer development, highlighting emerging small-molecule inhibitors. Second, Mak and colleagues consider the role of oxidative stress in tumorigenesis and discuss the ability of cancer cells to balance their characteristically high levels of reactive oxygen species with enhanced antioxidant defence mechanisms. They highlight the key cellular sensors and modulators of oxidative stress while assessing the potential to therapeutically target the antioxidant capacity of tumour cells. Finally, in their Perspective, Bloechl-Daum and colleagues discuss the challenges faced by regulatory agencies in determining an appropriate balance between benefit and risk with the limited data that are typically available before drug approval. The adverse effects of regulatory risk-aversion and strategies to better align acceptance of risk and uncertainty by regulators with the interests of public health are presented.

EDITORIAL & PRODUCTION OFFICE
The Macmillan Building, 4 Crinan Street, London N1 9XW, UK
Tel: +44 (0)20 7843 3620
Email: NatureReviews@nature.com
www.nature.com/reviews/drugdisc

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MANAGEMENT OFFICES
NPG LONDON The Macmillan Building, 4 Crinan Street, London N1 9XW, UK. Tel: +44 (0)20 7833 4000
NPG NEW YORK 75 Varick Street, 9th floor, New York, NY 10013-1917, USA. Tel: +1 212 726 9200
NPG ASIA-PACIFIC Chiyoda Building 2-37 Ichigayatamachi, Shinjuku-Ku, Tokyo 16200843, Japan. Tel: +1 212 726 9200
A list of other offices can be found at www.nature.com/npg_/contact/offices.html

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EDITORS

PETER KIRKPATRICK

ALEXANDRA FLEMMING

CHARLOTTE HARRISON

SARAH CRUNKHORN

MONICA HOYOS FLIGHT

MAN TSUEY TSE