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► **COVER:** 'Modulating protein homeostasis' by Susanne Harris, inspired by the Review on p29.


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Vitamin K antagonists such as warfarin have been the mainstay of oral anticoagulant therapy for more than 50 years, despite limitations such as the need for careful monitoring of their effects. However, several new oral anticoagulants with the potential to replace warfarin are emerging. In a 'Case History' this month, Perzborn and colleagues describe the discovery and development of one of these drugs, rivaroxaban (Xarelto; Bayer), which received European approval in 2008 for the prevention of venous thromboembolism. This first-in-class agent inhibits factor Xa — a serine protease that has a central role in the blood coagulation pathway, where it catalyses the production of thrombin. Several G protein-coupled receptors (GPCRs), including those for thrombin, chemokines, endothelin and prostaglandins, have recently been linked to cancer metastasis and angiogenesis. Lappano and Maggiolini review our current understanding of the role of GPCRs in tumour progression, and discuss the potential of GPCRs as future anticancer targets. Cancer, immuno-inflammatory disorders and cardiovascular disease are among the conditions in which the ubiquitin–proteasome system and ubiquitin-like protein conjugation pathways have been shown to be involved. Recent advances in our understanding of the roles of specific pathway components and strategies to therapeutically target them are reviewed by Brownell and colleagues. Finally, in their Perspective, DiMasi and Faden analyse the development and patent filing histories of new drug classes in the United States over the past 50 years. They show that instead of simply categorizing agents as 'first in class' and imitation 'follow on' drugs, the development of multiple drugs in a given class should be viewed as a competition in which members race to gain regulatory approval.

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Printed in Wales by Cambrian Printers on acid-free paper