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► **COVER:** 'Targeting the vitamin D system' by Susanne Harris, inspired by the Review on p941.



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The development of drugs for rare diseases, known as orphan drugs, is attracting increasing interest and investment. Some of the key questions and issues in the field — from the definition of disease rarity to the pricing of orphan drugs — are considered in a Perspective by Tambuyzer. This is complemented by a Comment article from Coté and colleagues at the US Food and Drug Administration, highlighting the role that regulators can play in catalysing progress with orphan drug development. Three reviews this month cover diverse therapeutic targets. First, Plum and DeLuca summarize therapeutic opportunities related to the vitamin D endocrine system, which has long been appreciated for its role in bone metabolism, but also has potential as a target in autoimmune diseases, infectious diseases and cardiovascular disorders. Tyrosine kinases are being investigated intensively as targets in malignant disorders, but are also involved in a range of other disorders, such as cardiac hypertrophy, pulmonary hypertension, lung fibrosis and rheumatoid disorders, as highlighted in the second Review by Ghofrani and colleagues. And in the third Review, Rupprecht and colleagues focus on the translocator protein (18 kDa) (TSPO), which has an important role in steroid synthesis in the central and peripheral nervous system, discussing the potential of TSPO ligands for the diagnosis and treatment of neurological and psychiatric disorders. Finally, in their Perspective, Di and colleagues consider the effects of plasma protein binding on *in vivo* efficacy, highlighting misconceptions in the application of data on plasma protein binding in the selection of compounds for progression in drug discovery, and propose approaches to address these issues.

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