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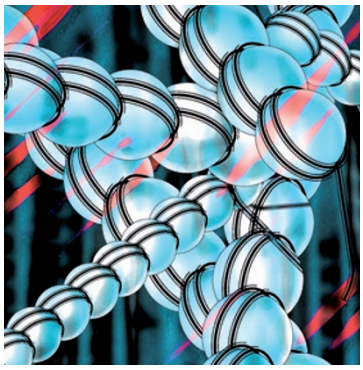

Epigenetic drug targets p384

The importance of epigenetic processes in many diseases has been increasingly appreciated in the past decade. In their Review, Arrowsmith and colleagues focus on protein families that mediate epigenetic signalling pathways through histone acetylation and methylation, discussing their links with disease and recent progress in their pharmacological modulation in the treatment of cancer, inflammation and neuropsychiatric disorders. Cancer is also among the diseases in which members of the serine protease proprotein convertase family have been shown to have a role. Seidah and Prat overview the biological functions of members of this family, reviewing studies of rodent knockout models and analyses of natural human mutations. They also discuss those proprotein convertases that may represent viable targets for therapeutic inhibition in various indications, highlighting recent advances in the clinical development of monoclonal antibodies targeting proprotein convertase subtilisin kexin 9 (PCSK9) for the treatment of hypercholesterolaemia. Denosumab is a monoclonal antibody targeting the receptor activator of NF-κB ligand (RANKL), and is approved for use in postmenopausal osteoporosis as well as some oncology indications. In a Case History, Lacey and colleagues describe how an increased understanding of the mechanisms of bone resorption — particularly the identification of the osteoprotegerin–RANKL–RANK pathway — led to the discovery of denosumab, and summarize its clinical development. Finally, in a Perspective, Hann and Keserü integrate findings from a range of analyses of the physicochemical properties that are associated with successful drugs. They discuss reasons why current medicinal chemistry practices may still be producing compounds with suboptimal drug-like characteristics, and propose guidelines to help improve the quality of compounds selected for clinical development.

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