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► **COVER:** 'Targeting proteases' by Susanne Harris, inspired by the Review on p399.



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The renin–angiotensin system has a key role in regulating blood pressure, and is the target for several highly successful drugs for cardiovascular disease. However, although renin — the protease at the top of the cascade — has been pursued as a target for more than two decades, it was only in 2007 that the first renin inhibitor, aliskiren, received regulatory approval. In a 'Case history' this month, Jensen and colleagues describe the challenges that were overcome in the discovery and development of aliskiren, and consider the future potential of this class of inhibitor. Another promising but challenging target is the endocannabinoid system, which has diverse functions in pain, feeding behaviour and metabolism. Highlighting the complexity of this system, Di Marzo discusses compounds in development that are designed to modulate endocannabinoid activity, and their potential to treat conditions including metabolic dysfunction and cardiovascular disease, pain, and neuroaffective disorders such as anxiety and depression. Increasing evidence also supports an important role for the glutamatergic system in the pathophysiology and treatment of affective disorders. In their Review, Sanacora and colleagues focus on the therapeutic potential of modulating ionotropic glutamate receptor activity. Another receptor currently receiving much research attention is the cytokine receptor Fn14, as is its ligand — the multifunctional TNF-family member TWEAK. The recent discovery and functions of the TWEAK–Fn14 axis are summarized by Winkles, who proposes strategies to modulate TWEAK–Fn14 signalling that may be beneficial in the treatment of cancer and autoimmune diseases, as well as acute ischaemic stroke. Finally, in our Perspective this month, Goldstein and colleagues highlight the potential of novel high-throughput profiling approaches for kinase inhibitors to expedite the identification and development of candidate drugs.

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