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► **COVER:** 'Stem cell differentiation' by Susanne Harris, inspired by the Review on p131.



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The dramatic failure of the cholesterol ester transfer protein inhibitor torcetrapib, designed to raise levels of high-density lipoprotein (HDL) as a treatment for cardiovascular disease, in 2006 raised the question of whether raising HDL is a futile strategy for atheroprotection. This month, Joy and Hegele review the complexity of the HDL system, discuss torcetrapib clinical trial data, and evaluate alternative strategies for HDL-based therapies. Meanwhile, in this month's perspective, Jia and colleagues suggest that humans can be viewed as "superorganisms with an indispensable internal ecosystem" — the gut microbiota. The authors propose that systems-oriented technologies such as metabonomics will shed light on complex host–bacteria interactions, providing novel targets and therapeutic strategies to manipulate gut microbiota associated with disease. The nature of the relationship between humans and members of their microbiome is also illustrated by the recent elucidation of the role of commensal bacteria in a physiological pathway that converts inorganic nitrate to nitric oxide (NO). In their Review, Lundberg and colleagues explore the significance of this alternative source of NO, and the possibility of targeting the nitrate–nitrite–NO pathway to treat a diverse range of diseases including myocardial infarction and stroke. Another simple physiological reaction, the conversion of carbon dioxide to bicarbonate ions and protons catalyzed by carbonic anhydrases (CAs), is also emerging as a target for a multitude of diseases. CA inhibitors were originally developed as diuretics and antiglaucoma drugs, but Supuran now discusses their emerging potential as anti-obesity, anticancer and anti-infective drugs. Finally, Klimanskaya and colleagues investigate two key factors that are crucial to the success of stem-cell-based therapies: the ability to find reliable sources of multipotent and pluripotent cells, and to control their differentiation.

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