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► **COVER:** 'Safe harbour for exploratory biomarkers' image from BrandX, inspired by the Perspective on p435.



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Given the key roles of mitochondria in cellular energy production and apoptosis regulation, it is not surprising that their importance in a wide range of diseases is being increasingly appreciated. Two reviews this month discuss the therapeutic potential of modulating mitochondrial activities. Tseng and colleagues explore the possibility of targeting cellular bioenergetics and mitochondrial metabolism to treat obesity. They consider strategies aimed at increasing energy expenditure, particularly the stimulation of adaptive thermogenesis in the mitochondria of brown adipose tissue — a highly metabolically active tissue recently shown to be present in adult humans. Meanwhile, Fulda and colleagues discuss the mitochondrial dysfunctions that are characteristic of cancer cells, and the potential to exploit these in the development of novel cancer therapies. The most promising agents, particularly those designed to induce mitochondrial membrane permeabilization and specifically activate cancer cell death programmes are discussed. Autoimmune diseases similarly develop because of the formation of abnormal cells exhibiting deregulated activities, namely the autoreactive T cells. In their Review, Faustman and Davis discuss how specific activation of the tumour necrosis factor receptor 2 pathway, which is commonly defective in autoreactive T cells, may selectively destroy these pathological cells, without inducing adverse effects. Finally, in their Perspective, Goodsaid and colleagues present case studies from the first 5 years of the voluntary exploratory data submission programme from the US Food and Drug Administration and the European Medicines Agency, which allows biomarker data to be submitted to these agencies for discussion without an immediate impact on regulatory decision-making. The influence that this programme has had on drug development at companies involved, as well as on the regulatory agencies approach to such data, is highlighted.

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