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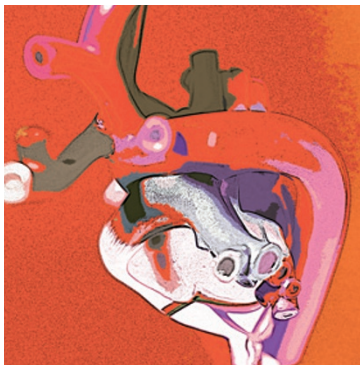

Raising HDL cholesterol p445

Faced with declining research and development (R&D) productivity, many pharmaceutical companies have been making major strategic changes in recent years. In a Perspective article this month, Pangalos and colleagues at AstraZeneca discuss a retrospective analysis of their small-molecule drug pipeline from 2005 to 2010, and highlight five technical factors influencing pipeline quality that are now being used to aid R&D decisions at the company with the goal of reducing late-stage clinical failures. Therapies intended to increase high-density lipoprotein (HDL) cholesterol are among recent high-profile failures in Phase III trials, which has raised controversy around the underlying hypothesis that elevated levels of HDL are cardioprotective. Kingwell and colleagues examine our current understanding of HDL biology, argue that trials so far have yet to adequately test the hypothesis and consider how this knowledge could be used in the development of novel therapies that target HDL. HDL cholesterol is primarily metabolized in the liver, where a class of transcription factors known as liver X receptors (LXRs) regulate lipid homeostasis. In their Review, Hong and Tontonoz discuss strategies to therapeutically target LXRs, which could have potential in treating disorders including atherosclerosis, Alzheimer's disease and type 2 diabetes. Conditions that involve dysregulation of the immune system, such as rheumatoid arthritis and psoriasis, are often co-morbid with type 2 diabetes. In the final Review, Donath discusses the role of inflammation in type 2 diabetes and the rationale for using anti-inflammatory agents —such as those used to treat rheumatoid arthritis — to treat diabetes and other conditions associated with the metabolic syndrome.

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