Vascular biology: a route to novel cardiovascular drugs

Despite advances in awareness, prevention and treatment, cardiovascular disease (CVD) remains the largest cause of death and disability world-wide. With this view of the future, a major mission for the pharmaceutical industry is to develop new CVD therapies that significantly increase life span and improve quality of life for patients. Building on a solid foundation of cardiovascular drug development, beginning in the 60s with beta-blockers and continuing through the 70s and 80s with calcium antagonists and ACE-inhibitors, AstraZeneca is now firmly focusing on the next therapeutic breakthrough opportunities for patients suffering from CVD.

Atherosclerosis, the degenerative process underlying a major part of CVD, is a complex trait arising from the interaction of multiple susceptibility genes with a range of environmental stimuli. Metabolic dysfunction, such as diabetes and dyslipidaemia, accelerates the growth and impact of atherosclerotic lesions. Remodelling of the atherosclerotic vessel wall results in a wide spectrum of plaque architecture, from large, fibrotic lesions typically causing stable angina, to the angiographically occult, lipid rich plaques, prone to rupture. The consequences of plaque rupture can be prevented by antithrombotic therapies. Recent progress in resolution of protein structures in the coagulation cascade has allowed structure based design of highly selective anticoagulants, and AstraZeneca is committed to be a leading scientific force in the development of effective and safe antithrombotic drugs. However, there is also clear need to intervene in the causes of atherosclerotic lesion progression and instability of occult plaques.

The endothelium is important for regulating vascular tone, haemostasis and transport into the blood vessel. Endothelial dysfunction is an early sign of vascular disease, with consequences for atherosclerotic lesion progression and risk of thrombosis. Lack of sufficiently predictive animal models, disease surrogate markers and the need for large cumbersome clinical trials have hampered clinical evaluation of new anti-atherosclerotic drug concepts. During the last decade, advances in transgenic technology have led to successful development of humanized cardiovascular disease models in the mouse. This has established integrative physiology in transgenic mice as a powerful approach for target validation. Evaluation of new atherosclerosis therapies using noninvasive surrogate markers, such as endothelial dysfunction, may offer a simplified bridge between transgenic disease models and rapid concept studies in atherosclerotic patients.

There is now growing interest in therapeutic angiogenesis to induce collateral vessel growth in peripheral and myocardial ischaemic diseases. The contribution of neoangiogenesis in controlling growth and dissemination of solid tumours has led to successful attempts to treat experimental tumours with antiangiogenic approaches. Understanding the fundamentals of angiogenesis is of relevance for therapeutic management of both cardiovascular and cancer diseases.

In the future, treatment of cardiovascular diseases will include tailoring of therapy to the individual, according to a variety of metabolic and genetic profiles. AstraZeneca is therefore participating in extensive genetics programs to identify CVD susceptibility loci and to establish a molecular disease management. Our sponsorship of this Nature Insight reflects the high priority we attach to scientific excellence as the foundation to drug discovery. We look forward to seeing the outcome of advances in vascular biology contributing to improved future therapeutic opportunities for patients suffering from cardiovascular diseases.

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