Discovering drugs for heart failure?

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The recent conference, *Cardiovascular Summit 2000: Heart Failure Drugs* (London, UK; organized by SMi conferences), set out to address the status of this field and to identify potential novel approaches to the treatment of heart failure. Although current treatment of patients with congestive heart failure (CHF) results in a prolongation and improvement of their quality of life, these therapies do not match up to clinical need.

Heart failure is a complex disease. In the USA:

- 2–3 million people have heart failure;
- 400,000 new cases are identified each year;
- 39,000 people die from heart failure each year; and
- heart failure is part of the cause of another 225,000 deaths each year[1].

However, CHF is a disorder with many causes and its treatment is complex. Molecular biology techniques have played a role in furthering our understanding of heart disease. Similar to other areas of research, this has aided the search for novel therapeutics, incorporating targets such as protein kinases, ion channels and specific receptors. In the past decade, our knowledge of this crucial area has been dramatically enhanced.

New potential targets

Norbert Bender (BASF Pharma, Ludwigshafen, Germany) discussed directions in cardiovascular drug discovery, new targets and developing old targets. In particular, he focussed on the efficiency of existing therapies, unmet clinical needs in CHF and hypertension, efficacy of polypharmacy, directing the development of new therapeutics towards specific cellular targets, and the potential for identifying novel targets.

The sarcoplasmic reticulum (SR) Ca^{2+}-ATPase (SERCA2a; a Ca^{2+} pump located on the membrane of the SR) is a possible therapeutic target in heart failure (Sian Harding, Imperial College School of Medicine, London, UK). The activity of this pump is decreased in ventricular cells (Fig. 1) of patients with heart failure, and thus systolic and diastolic abnormalities arise in the myopathic myocardium. Harding reported that adenoviral gene transfer of SERCA2a in human ventricular myocytes increases SERCA2a expression and activity, decreases diastolic calcium, increases velocity of contraction and relaxation, and normalizes the contractile-frequency response. After Ad.SERCA2a infection, survival of myocytes in culture was improved. In summary, SERCA2a overexpression differs from β-adrenoceptor stimulation, where R_{90} (time it takes for heart cell to reach 90% of its relaxed length) is increased and aftercontractions are accentuated.

Figure 1. An example of an individual isolated adult ventricular myocyte. Kindly provided by the Cardiovascular Research Laboratories, University of Bristol, Bristol, UK.

The ability to use proteome analysis in the identification of therapeutic and diagnostic targets was highlighted by Alison Pearce (Proteome Sciences, Cobham, Surrey, UK). Significant modifications in normal myocardial protein expression cause cardiac dysfunction and influence their development and outcome. The characterization of such modifications will further our understanding of dysfunction in heart disease, and might present novel diagnostic markers and therapeutic opportunities.

Maria Andersson (Gemini Genomics, Uppsala, Sweden) described the advancement of healthcare into the post-genomics era. Andersson discussed the importance of integrating clinical and genetic data from diverse human populations, resulting in the identification of validated targets. Continuing on from this theme, Paul Eisenberg (Eli Lilly, Indianapolis, IN, USA) described strategies to turn a molecular target into a marketable drug and discussed how to choose which targets to study. The validation of genomic targets requires an integrated approach using *in vitro* and *in vivo* models, and this requires much investment.

Clinical trials

The implications of myocyte apoptosis (programmed cell death) were considered by Stephen Mento (Idun Pharmaceuticals, La Jolla, CA, USA) for drug discovery in CHF. Inappropriate apoptosis is thought to be a contributing factor in both acute

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and chronic cardiovascular disease, through involvement of caspase enzymes. *In vitro* evidence shows that caspase inhibitors have a protective effect on enhanced apoptosis in neonatal and adult cardiomyocytes. Mento summarized the various ways in which caspases lead to cell death and how caspases are activated. Idun Pharmaceuticals hope to test their caspase inhibitor INDQ42000 clinically after activity testing in pig models of CHF is complete.

An improvement in cardiac adrenergic responsiveness achieved by gene transfer, using a system that increases the expression of the effector (adenylate cyclase) rather than direct stimulation of the β-adrenoceptor for treating heart failure, was reported (Kirk Hammond, Collateral Therapeutics, San Diego, CA, USA). This increase in endogenous inotropic responsiveness (rather than stimulation) might provide a safe and effective therapy for heart failure. A clinical trial of intracoronary administration of the AdV-FGF4 construct demonstrated that this drug increased time a patient could last on the treadmill compared with placebo. The improvement was similar to the increase seen with coronary artery bypass grafting and percutaneous transluminal coronary angioplasty. The product was well tolerated and crucial clinical trials are due to begin soon.

Hani Sabbah (Case Western University, USA) described the development of a canine model of CHF induced by intracoronary microembolization. The haemodynamic profile mimics that of human CHF. The metabolic modulator, ranolazine, which switches cardiac fatty acid metabolism to carbohydrate, caused a sustained improvement in canine CHF without having acute haemodynamic effects. Trials of this novel approach to CHF are underway.

The future of cardiovascular drug research

The role of integrative biology in cardiovascular drug innovation was discussed by Desmond Fitzgerald (University of Strathclyde, Scotland, UK), who focused on integrative biology and novel drugs for CHF. He discussed the question of whether advances in genomics, proteomics and cell biology can significantly alter the introduction of improved therapy. He suggested that they could, but an important question was 'how and when?' The constraints include the accuracy of aetiological diagnosis and timing

of intervention, current understanding of complex biological systems, limitations of animal models and proof-of-concept studies of therapies in clinical trials. Fitzgerald concluded by saying that these are complex issues with no simple solutions, and there is a vital need for greater communication between payers, patients and associations, basic and clinical scientists, regulators and health economists.

Concerns remain regarding adenobivectors for gene therapy, the possible inhomogeneous uptake in myocardium, with the consequent risk of generating arrhythmias. Further, the lack of reversibility of gene therapy must be considered, particularly with reference to the occurrence of adverse side effects.

In 1999, a total of 29 cardiovascular drugs were approved for different indications. These indications included hypertension, arrhythmias, acute coronary syndromes, hyperlipidaemia, peripheral occlusive arterial disease, prevention and treatment of deep vein thrombosis, acute myocardial infarction, coronary heart disease, CHF, renal failure and stroke[2]. There are 70 cardiovascular drugs currently in Phase III clinical trials and 21 awaiting approval[2] for these indications. The importance of multidisciplinary integrated drug development was highlighted at this meeting and the regulatory hurdles facing novel treatments for CHF were emphasized. Evidence suggests that the prognosis of heart failure might be improving, in clinical trials and in clinical practice[3], but novel therapeutics are still required to improve the treatment of this syndrome.

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