Identifying needs and opportunities for advancing translational research in cardiovascular disease†

Karin R. Sipido1*, Alain Tedgui2, Steen D. Kristensen3, Gerard Pasterkamp4, Heribert Schunkert5, Martin Wehling6, Philippe G. Steg7, Wolfgang Eisert8, Frank Rademakers9, Barbara Casadei10, Valentín Fuster11, Elisabetta Cerbai12, Gerd Hasenfuss13, Francisco Fernandez-Aviles14, David García-Dorado15, Maria Vidal16, Manuel Hallen16, and Virginija Dambruosskaite16

1Experimental Cardiology, University of Leuven, KUL Campus Gasthuisberg O/N 7th floor, Herestraat 49, B-3000 Leuven, Belgium; 2INSERM U689, Hôpital Lariboisière, Paris, France; 3Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark; 4Experimental Cardiology Laboratory, Utrecht Medical Center, Utrecht, The Netherlands; 5Medizinische Klinik II, Lübeck University, Lübeck, Germany; 6Clinical Pharmacology Mannheim, University of Heidelberg, Mannheim, Germany; 7Department of Cardiology, Hôpital Bichat-Claude Bernard, Paris, France; 8Boehringer Ingelheim, University of Hannover, Hannover, Germany; 9Cardiac Imaging, University of Leuven, Leuven, Belgium; 10Department of Cardiovascular Medicine, University of Oxford, Oxford, UK; 11Mount Sinai School of Medicine, Mount Sinai Hospital, New York, NY, USA; 12Center of Molecular Medicine, University of Florence, Firenze, Italy; 13Department of Cardiology and Pneumology, Georg-August-University, Göttingen, Germany; 14Department of Cardiology, Hospital General Universitario Gregorio Marañon, Madrid, Spain; 15Hospital Universitari Vall d’Hebron, Barcelona, Spain; and 16DG Research, Directorate Health, EC, Brussels, Belgium

Online publish-ahead-of-print 5 June 2009

1. The success of cardiovascular research: two sides of a story

In Western Europe, as in the USA, mortality of cardiovascular disease (CVD) has declined significantly in the last 30 years. Life expectancy for patients with coronary heart disease in the USA increased on average by 3 years between 1970 and 2000.1 Several epidemiological analyses support this positive evolution. An analysis of the underlying causes identifies improvements in quality of care and treatment as a major cause, accounting from 50 up to 75% of the success depending on the study samples, the remainder being accounted for by changes in lifestyle and prevention.2 Research and development in several areas of CVD have contributed to this success. In acute coronary events, the identification and development of efficient and safe thrombolytic agents followed by percutaneous coronary intervention with stent implantation were milestones in the reduction of acute mortality and salvage of myocardium.3–5 Statins have brought a major advance in preventing the progression of atherosclerotic disease and have been recognized for their wide mode of action.6 In heart failure (HF), beta-blockers and ACE-inhibitors have increased life expectancy by a leap.7 Some of these improvements have been the result of a classic bench-to-bedside development of a targeted treatment, such as the statins, others have known a more serendipitous development, such as beta-blockers.

In other areas, progress in terms of treatment has been less spectacular and fraught with difficulties. Development of antiarrhythmic agents received a large boost from basic insights into cardiac ion channel structure and function, but translation into pharmacology unveiled unexpected pro-arrhythmia risks of some of the highly specific ion channel blockers in class III.8 Automatic defibrillators have taken an important role in the treatment of life-threatening arrhythmias and save lives, but are not without burden and come at a high cost.9

This latter example is but one highlight of the more sobering and darker side of this medical success story: the improved survival and quality of life of patients with CVD comes at a high economic cost. In the US hospitalizations for CVD have tripled and the cost of care is estimated at 386 billion USD per annum (AMA, Kaiser Family Foundation). Within the EU, the annual cost for healthcare systems for CVD was just under €110 billion in 2006 (British Heart Foundation statistics at www.heartstats.org). Interventions, device therapy, and imaging take up a large share of the cost. Ageing of the population, without further improvement in care and prevention, will lead to a high increase in prevalence of CVD. This is already noticeable in the statistics of the last 10 years, showing a decrease in mortality but an increase in prevalence.10 In addition, in countries with less access to medical care, the incidence of CVD is rising and is expected to continue to increase dramatically.11,12 The WHO has estimated that rising life expectancy coupled with adverse trends in major cardiovascular risk factors including obesity and...
type II diabetes could lead to a doubling in the absolute incidence of CVD by 2050.

There is thus a clear need for continued investment into improving our approach to CVD and thus into cardiovascular research. In addition to the remaining need, the major progress that has been made constitutes a strong incentive for priority funding of cardiovascular research in order to build on this success. Addressing the economic need to contain cost, as well as the necessity to provide better care for a growing patient population, a new paradigm is put forward focusing on promoting health and intervening at the early onset of CVD.\(^\text{13,14}\) This requires that we (i) improve our physiological and molecular understanding of mechanisms of health and disease so we can implement earlier preventive interventions and better-targeted diagnosis and therapy, (ii) that we develop personalized preventive and therapeutic regimens, and (iii) that we streamline the processes involved in translating knowledge into practice to accelerate implementation of new knowledge.

2. The framework of translational research

The concept of translational research can be interpreted and defined in many ways by scientists. A consensus view is that the end-target of translational research is the patient, with the goal to improve care. The classic or traditional one-dimensional track of translational research is a sequence of events: discovery of a new mechanism and potential therapeutic target in an experimental or basic research setting, with a drug or device being developed, the approach being validated in the clinical setting and eventually being introduced into clinical practice. This concept is still valid, but in recent years it has come under increasing pressure. The drug development and validation in clinical trials come at a huge cost, largely carried by industry, and in a number of cases, the expected clinical benefits have been disappointing. For example, the development of the CETP inhibitor, torcetrapib, was halted in 2006 when phase III studies showed excessive mortality in the treatment group receiving a combination of atorvastatin and the study drug.\(^\text{15}\) Therefore, the willingness of industry to take risks has decreased. In this 'traditional' approach, the principal actors partake in sequence: basic, industry, and clinical researchers.

More recent models of translational research give up on this traditional sequence and can start, for example, from clinical data, feeding into experimental or basic research for further mechanistic insight, or from clinical observations on unexpected drug effects, feeding into new applications ('reverse' translational research), with many variations in iterative interactions between the different stages, as illustrated in Figure 1.

Such approaches have been quite successful, as can be illustrated by the example of post-conditioning as a mechanistic of cardiac protection. The phenomenon was discovered in experimental research, and early studies in the hospital prompted further basic research to propose a drug alternative to be tested again in the clinic.\(^\text{16,17}\) Molecular and genomic studies on patient material also have introduced unique input for basic mechanistic studies that can be again validated in patient material.

High-quality translational research should involve a more active participation and exchange among basic, clinical, and industry researches, with emphasis on a re-iterative scheme. For a specific project, the approach and the relative input of each component will be tailored to the area of research, depending on the needs and opportunities in the particular field, but always respecting the prime directive of translational research, namely with the end-target of improving individual health.

The introduction of the term 'translational medicine' reflects the increasing demand for a successful, reproducible, and efficient way of translating results from animals/test tubes to humans. This process is thus not new, but the quality of the process is not sufficient to meet the current demands for fast application of major innovations in medicine. The crucial question is thus how this can be achieved and by which methods. Some key elements are:

(i) A translational plan. For projects starting from experimental research, a comprehensive roadmap to implementation should guide the design of new research projects in order to maximize the translational potential. In current practice, this is far from being implemented consistently or even taken into consideration, and valuable opportunities may be lost. Important reasons for this 'failure' are a lack of knowledge and experience in the academic environment as well as insufficient exchange and interaction between the different stages in translation. Ways to improve this situation are education and improved training of researchers as well as intensifying the interactions in more formal translational institutes or centres that could lend expertise to individual researchers.

(ii) Specific tools. The experimental tools/methods used for translational processes in medicine should be clearly defined and used in reproducible, objective, and measurable translational algorithms. Thus, the strategies described in translational development plans need to be standardized, decision trees developed and tested, validated, and exercised. We need tool boxes with appropriate biomarkers that must be validated for predictive power, biostatistical methods to cope with multiple read-out problems, and decision tree (stop/go decisions) algorithms.

(iii) Qualifications of the investigators. Education and training of young scientists and clinicians are cornerstones to promoting translational research and the proper methodological approach.\(^\text{18}\) An example of successful recruitment and training of highly capable young people is the new Spanish research initiative, CNIC, where private and public funding have acted together to support training initiatives starting at high school age up to the level of young professionals (http:// www.cnic.es/index1.php?inc=6&sec=formacion).
The training of physicians in translational research also requires a targeted program. In a time when there is huge potential for translational medicine, there is a paradoxical shortage of clinician scientists. In contrast, the basic cardiovascular research is expanding and increasingly led by non-medically trained scientists. A dichotomy between the different activities carries a risk for reduced translation efficiency and requires active measures to ensure communication and exchange.

Another point of concern in the particular needs for translational research is the waning knowledge and expertise in integrative physiology. New leads from clinical research require mechanistic insights to be investigated in the laboratory using valid models spanning from molecular to cellular to in vivo studies in large animals. While the first two are well-developed, with transgenic mice for validation now widely available, the availability and expertise in preclinical large animal models, such as the pig, are becoming rare. Collaboration within the European Research Area can make better use of the available sites, but also offers opportunities for training and expanding the expertise.

3. The case of clinical research through randomized trials

In the traditional translation of bench-to-bedside research, randomized clinical trials establish safety and efficacy of new treatments, largely funded by the company which developed the compound or device with the intention of marketing it. Several limitations and drawbacks to this approach have called for alternative strategies, necessitating alternative funding. A first consideration that has been made is that the traditional approach creates a dependence on industry for decisions on the initiation of clinical trials. This is already widely recognized, and the investigator-driven clinical trial (IDCT) has come into its own right as an important tool in translational research. The IDCT faces, however, a major funding problem. Several types of IDCT can be distinguished based on goals, size, and financial cost.

A first category is the small-scale trial that seeks a proof-of-concept. Although the cost of such smaller-scale studies is relatively moderate, they require extensive supporting evidence from basic experimental studies and preclinical data to justify the financial commitment and risk.

A different category of studies is aimed at evaluating new treatment strategies that rely on the use of approved drugs or devices, or evaluate new uses of ‘old’ drugs. These require larger patient groups, but carry less risk. The financial cost is variable depending on the required data. For a number of studies, no additional interventions or studies may be required beyond those that are part of the standard optimized treatment in effect already.

A last category is evaluation of implementation, outcome, and compliance, studies that carry no risk need little financial investment in terms of diagnostic studies or treatment, but require registries and large data collections. They are an essential part of the final evaluation of translation of new concepts and approaches into practice.

Can and should the European Community fund IDCT? Within the 7th Framework Programme, there is the possibility of funding of clinical research, articulated already before for the proof-of-concept studies. The need for a solid scientific basis of such proof-of-concept studies must be emphasized. Earlier calls had not always been successful in attracting applications in which the clinical studies were considered of sufficiently high quality by the expert scientific review panels. This could reflect a problem of insufficient involvement from the scientific community, as there are more than enough high-quality potential candidates. On the other hand, the current drive towards early translation carries a risk of reducing quality. Nevertheless, the inclusion of such studies in broader translational projects is fitting. For larger implementation studies of new compounds or devices, there is a consensus that such studies cannot depend fully on public/EC funding. A partnership with industry and private funding must be sought. EC funding can provide start-up money and facilitate the search for partners.

Clinical studies that would rely on patient data collected as part of the normal practice with limited additional financial investment represent a category that hitherto has not received specific support. It is a category with potentially major impact and that typically will need a European scale of study. A cost–benefit analysis will be critical and can only be done on a case-to-case basis. Examples of such studies are offered in the next sections.

4. The need for a long-term view

As already mentioned above, there is a paradigm shift from aiming for improvement in treatment towards prevention of disease and improving health. Primary prevention may have the largest economical impact on health costs, but it carries the inherent difficulty that it targets people before the onset of disease. Although this is no problem for general measures designed to improve health through lifestyle changes, it poses a problem once an intervention carries certain risks and additional costs, e.g. through medication. Therefore, identifying early onset of disease, mechanisms that promote repair, and targets for early treatment are important goals.

A long-term view is also needed in funding policy. Although current EU policy prefers ‘seeding’ funding, a more sustained or careful long-term plan for sustaining efforts will amplify results from the funding investment. Data-driven investigations starting from patient samples and clinical data require a long-term follow-up through databases and carefully annotated biobanks. Secure funding is needed to optimize and maximize gain from these projects. This type of investigation can generate a wealth of data and often also leads to new hypothesis-driven research that can then be translated, as illustrated by the case of the discovery of Apo-Al variants through genetic screening and the subsequent demonstration of the protective effect of apoAl_6_1 in atherosclerosis.

The ultimate goal of translation, namely improving health and patient treatment, also needs outcome studies. These are typically long-term studies via registries that require a long-term commitment and do not necessarily imply a huge cost. They are, however, typically trans-national, European-scale projects. Partnership with existing efforts is a possible approach.

Building on success is another aspect of a long-term view. Although projects are expected to be contained and self-sustaining at the time of completion, building on successful projects has a high potential to guarantee quality and outcome.
Finally, explorative basic experimental research remains a cornerstone in all studies, an essential element of translational projects. Even though a knowledge-driven study not linked to an identified health problem does not fit the category of translational research, in the long-term view, the continued financial support of explorative research is vital. Non-committed research is a major source of new ideas for further development into translational research that must be vigorously maintained.

5. Needs and opportunities in cardiovascular research

5.1 Atherosclerotic disease

Major advances have been made in understanding the mechanisms underlying the development of atherosclerotic plaque in a multidisciplinary approach including clinical studies, imaging, genomics, proteomics, cellular, and animal studies. A success story of (ongoing) translation from gene discovery to therapy is the targeting of ApoA1 \(^{20,21}\) and the developing story for haptoglobin. \(^{22}\) The potential of statin therapy in prevention, even in the absence of dyslipidaemia (JUPITER), is still being uncovered and will go through another bench/bedside interactive study.

Yet, at the same time, progress is stalling. Looking back, there is a large discrepancy between the success of genomic studies and the translation from studies in mice to the introduction of new drugs. It is important to consider the limitations of our current views. The concept of the vulnerable or high-risk plaque is largely based on cross-sectional studies in patients, and the animal models for verification may not have been adequate or the approach may have been oversimplified. There is a need for new concepts and the inclusion of complexity in the investigational approach. The bioinformatics/systems biology approach that integrates multiple levels, i.e. clinical, genomics, proteomics, and metabolomics, could play an important role in understanding the progression of the disease. Data- and hypothesis-driven researches are complementary and interactive, not parallel, tracks.

5.1.1 New concepts for translation

The concept that atherosclerosis is an inflammatory disease has led to new discoveries on the role of specific elements in the immune system, especially innate and adaptive immunity, that orchestrate lesion development. \(^{24,25}\) These paradigms have been identified in experimental animal studies and validated against clinical data. Different subpopulations of T-cells have been identified, some pro-atherogenic, mainly Th1, and some protective, regulatory T-cells. In addition, natural antibodies against various components of oxidized (phospho)lipids have been found to protect against atherosclerosis. These findings have opened new lines of investigation based on immunomodulation of atherosclerosis, by either stimulating regulatory immunity or raising protective antibody titres. The potential benefit of vaccination has been explored in several animal studies: active immunization using oxidized LDL (oxLDL), passive immunization, and induction of immune tolerance by oral oxLDL have shown protection against lesion development in atherosclerosis-prone mice. \(^{26-28}\) As a specific antigen, oxLDL appears to play a major role. There is a clear opportunity here for further translation, but major questions need to be addressed. As a concept, the approach is different from classic vaccination, where immunization is sought against foreign, hostile elements. The long-term risk of immunization against cells that partake in immune responses is currently unknown. This avenue is a novel one that must be further explored in collaborative efforts that bring together laboratories with molecular, cellular, and physiological expertise. Better disease models than transgenic mice must be tested, and large animal models such as the pig will be needed. Limited availability of facilities that comply with current rules and regulations as well as the high costs is currently hampering this much needed pre-clinical step.

A further distinction of different subtypes of lymphocytes and macrophages and recognizing this cell diversity can further fine-tune current insights into the role of the immune system in atherosclerosis. \(^{29}\) The diversity of lymphocytes and macrophage populations has in addition a broader application to metabolic syndrome, characterizing the inflammatory state, and may provide important biomarkers. Collecting patient samples and data are a necessary part of this concept.

Summary: The concept of atherosclerosis as an inflammatory and immune disease offers opportunities for translation of concepts. Priorities are: exploring the potential of vaccination and immunomodulation as treatments for atherosclerosis and identifying new biomarkers for vascular disease using monocyte diversity.

5.1.2 Thrombosis research

Mechanisms underlying thrombosis are complex and are related to the different anatomical location (arterial, venous, central) and the different players involved, i.e. the vascular wall, platelets, and plasma factors. Development of thrombolytic agents has been a success story of interaction between basic and clinical research, with efficient translation into practice and industrial development. \(^{30}\) The field has not been further pursued, however, as attention shifted to primary angioplasty and subsequent stent implantation for treatment of acute coronary syndromes. Despite the success of these interventional approaches a need remains for improved non-invasive treatment, in particular the long-term adjuvant therapy and anticoagulation. A specific problem is the in-stent thrombosis, which represents a rare but serious complication of stent implantation. \(^{31,32}\) The potential market for improved antithrombotic therapy is huge, and there is an ongoing drug hunt by industries. The market-driven approach, however, is likely to fail in addressing a number of unmet needs and opportunities. To advance the field in new ways, a ‘back-to-the-bench’ approach should lead investigation into platelet biology, using proteomics, studying production, and turnover rate, and assessing platelet interaction and vessel wall interaction. Thrombosis research should include valid animal models and develop standardized methods for study to be imposed on clinical research. Large registries are needed at the multinational scale, but can only be useful if standardized.

Despite the availability of a broad spectrum of targets to achieve anticoagulation, there is need for improved
and—most importantly—safer drugs. The development of new anti-thrombotic drugs will decrease thrombotic risk, but the major drawback of all current and future therapy is increased bleeding. Current management of correct dosage depends on costly tests that are not flexible and insufficiently standardized. Simple, low-cost, and reliable blood tests are urgently needed to closely monitor therapy and allow individualized, tailored anti-thrombotic therapy. Smaller companies are presently developing such devices but are not able to provide financial support for clinical trials. Large pharmaceutical companies, on the other hand, are not much interested in individualized therapy in anticoagulation. Yet, there is a particular need for tailored individualized treatment for patients on antithrombotic therapy. This concept has large potential, but is currently underdeveloped because of the complexities involved. The different responses in patients are likely to be partly due to genetic modifiers directly related to the process itself, but also to modifiers of the stress response. Current animal models tend to be uniform and address only one type of response. Diversity in animal models is needed.

Summary: Further ‘classic’ drug development in thrombosis will be led by industry, but to develop new approaches, basic research in platelet biology and coagulation is needed, combined with experimental animal studies that more faithfully reproduce the diversity in patient responses. To effectively translate into better patient management, better monitoring requires appropriate device development to allow individualized treatment.

5.1.3 Generating new hypotheses from large-scale (post)-genomic studies

The power of bioinformatics allows for an open, non-committed, large-scale screening of gene expression and, more recently, protein expression. In the area of atherosclerosis, a screening of gene and protein expression in carotid plaque has been combined with a prospective study and follow-up of the patients, currently a cohort of some 1500. At this scale, the approach has already been successful in identifying novel markers for active atherosclerotic disease. The matching of future events with expression in the plaque has also hinted at some unexpected correlations, such as drug therapy for non-CVD (G.P., unpublished). This successful approach needs a large-scale follow-up, looking more in depth beyond genomics to proteins and post-translational modification. A more sophisticated analysis of the data, using bioinformatics to integrate knowledge on vessel genomics, proteomics, and transcriptomics will generate new ideas and should be complemented by bench verification of the generated hypotheses. This will lead to a next phase of data-driven genomic research.

Genome-wide searches have enlarged their scope because of the availability of better and faster high-throughput analysis techniques. This has led to breakthrough findings in the area of myocardial ischaemic disease, a result of a European collaborative effort, pooling and (re)analysing several patient cohorts. Some of the newly identified gene products modulate known risk factors such as LDL cholesterol, but most genes found in association with myocardial infarction were hitherto not implicated in the pathogenesis of vascular disease. In fact, at some chromosomal loci such as 9p21.3, neither genes nor causative mechanisms responsible for the strong association with myocardial infarction have been identified. Nevertheless, it is expected that these studies will markedly improve risk prediction, validation of biomarkers, and identification of novel disease mechanisms. Further analysis of genomic data may help to clarify the functional relevance and the relationship between biomarkers and disease: causative markers, associative markers, or markers of intermediate steps. Novel genetic tools for analysis of existing data, such as Mendelian randomization, may distinguish between these possibilities. Proof-of-concept studies in the laboratory, i.e. reverse translation, are needed to validate a suspected functional relationship.

Epigenetic processes such as DNA methylation and histone modification in response to environmental triggers in utero and in early life may provide another basis for increased susceptibility to CVD in adult life. In particular for the development of obesity and metabolic syndrome, such early life events may be of prime importance. In addition, the epigenetic modification can be passed on to future generations. This field is still in expansion and is not without controversy.

Summary: Large-scale studies based on patient materials have a high translation potential towards risk prediction and novel biomarkers, but are also generating new hypotheses. They call for European collaboration in collecting patient data and maintaining well-annotated biobanks and cannot be disconnected from bench research. The role of epigenetic modification in CVD needs to be further explored.

5.2 Cardiovascular imaging

The recent advances in imaging modalities and the opportunities for improved diagnosis and treatment have led to their increased utilization, which is only expected to expand as the population ages. The consequence is an expected cost increase that will exceed available healthcare budgets. This is a general phenomenon in analyses of future healthcare costs, but particularly important in imaging, as this represents a large fraction of the budget. It calls for a new direction, focusing on prevention and early identification of disease, so-called pre-emptive medicine, which would reduce the cost of late-stage curative medicine. Such an approach requires a thorough understanding of susceptibility to disease and the early molecular events.

Most imaging modalities combine anatomy, function, and some tissue characterization, which has led to early stage recognition of events such as microvascular obstruction and myocardial haemorrhage, or local ischaemia in hypertrophic cardiomyopathy entities that previously could not be recognized in vivo and which are early, strong predictors of subsequent events [reviewed in Nat Clin Pract Cardiovasc Med 2008;5(Suppl. 2)]. A strong start has been made in the development of probes of molecular function for in vivo imaging, using nuclear, CT, and MR imaging techniques. Such probes can report on plaque vulnerability, myocardial ischaemia and viability, stem cell homing, and gene therapy, with the potential
5.3 Arrhythmias

Ventricular arrhythmias remain a major cause of mortality, in particular in the setting of HF. Because of this latter connection, it is a problem that is expected to further increase substantially in the next 10 years. With the exceptions where ablation therapy is possible, there is currently no cure for arrhythmias. Drug and device therapy aim to prevent and suppress arrhythmias, but are a lifelong commitment. In the setting of HF, device therapy has rapidly expanded as a best option for life-threatening ventricular tachycardia. Some clinical follow-up and outcome studies, however, suggest a variable number of implantations that might have been unnecessary. Given the cost and adverse effects, there is a clear need for better identification of patients who will benefit. Biomarkers may help to identify responders, but this field is still to be explored. Non-invasive tests such as microvolt T-wave alternans are being explored and show promise. There is at present, however, need for better insight into the mechanisms underlying this event in different aetiologies of HF and potential links to associated pharmacotherapy.

Alternative pharmacological approaches are badly needed to complement and, if possible, replace the invasive and costly device approach for life-threatening arrhythmias. Classical pharmacology, directly targeting ion channels, may need to be re-invented, considering the many alternative and additional mechanisms that contribute to arrhythmogenesis. Alternative strategies include the modulation of ion channels through post-translational modification, the direction of trafficking and expression levels, and non-conventional targets such as calcium handling proteins. Upstream targets that modify the arrhythmic substrate in HF and atrial fibrillation, i.e. the remodelling process, are another novel approach.

Atrial fibrillation may in itself be rarely lethal through cardiac arrest, but it is associated with a high burden of morbidity, predominantly through stroke. It is the most common arrhythmia. The prevalence is increasing with the ageing population and is expected to further rise with a tripling by the year 2050. Therapy remains suboptimal. Ablation therapy has offered a cure to a number of patients, but carries a risk of atrial structural and functional damage and cannot be seen as a first resort. It also carries a serious economic cost. Pharmacological therapy remains suboptimal and very often does not reverse the arrhythmia. Recent insights into the mechanisms underlying the persistence of atrial fibrillation emphasize the remodelling processes, both structural and functional, that form the substrate of the disease. Inflammation and oxidative stress may be common mediators in pro-arrhythmic remodelling in the ventricle and atria. General systemic approaches of anti-inflammation and antioxidant therapy have had partial success, but more clinical data are needed in addition to animal experimental data to elucidate mechanisms and refine targets. In analogy to the tissue collection for genomic studies in myocardial infarction, an initiative for atrial fibrillation could be the starting point of a major translational research effort. Human tissues collected at the time of cardiac surgery, well annotated for clinical phenotype and stored in a biobank at the European level, can be mined for...
genomic as well as functional hypothesis-generating studies. Like for other omics-type approaches in clinical tissue samples, these hypotheses will need to be verified and mechanistically studied in the experimental setting. Large animal models of chronic disease will be the ultimate benchmark, offering the possibility of longitudinal studies and relevant pharmacological testing.68

In arrhythmic disease, genetic causes are a small fraction but inflict a particularly serious burden on individuals and families.69,70 From a scientific point of view, study of these rare diseases has offered invaluable insight into mechanisms of arrhythmias, identifying specific ion channel mutations but also the role of calcium handling proteins. From these observations specific and new antiarrhythmic targets have been identified.71 As mentioned above for acquired ventricular arrhythmias, the current therapeutic approaches still fall short. New paradigms to be tested are the role of modifier genes and interaction with environmental stressors.

A neglected field is foetal and perinatal mortality due to arrhythmias.72 They may result from developmental defects, and there is a novel awareness of the potential role of antenatal exposure to toxins as a cause of the perinatal arrhythmias. This is a new research area that is relevant for perinatal health, but that could also offer insights into more general principles of environmental control of arrhythmias through structural and functional defects in normal development. Such a study would require an integrated approach from developmental biology, using (stem) cell models, animal models, and clinical data.

Summary: Arrhythmias remain a major burden in terms of morbidity and mortality, but also constitute an economic burden. Device therapy has improved outcome but requires better identification of patients. The search is on for new, non-classical targets for pharmacotherapy, including identification of remodelling processes upstream of arrhythmogenesis. An orphan area of research deals with arrhythmic perinatal mortality. Studies integrating current paradigms of developmental biology, novel pharmacology, and clinical data could identify new therapeutic approaches. A translational strategy starting from a large annotated collection of tissue samples from patients with atrial fibrillation will open new avenues for therapy of this common disease.

5.4 Heart failure

A new focus in healthcare promoting healthy lifestyle, early detection of disease, and secondary prevention should curb the increase in HF. This does not eradicate the disease, however, and because of demographics we can predict that in absolute numbers, HF will be a major problem and burden in the next 10–20 years.73 More than 10% of people over 65 years will suffer from HF, and the lifetime risk of a person of 40 years is 20%. The advances in treatment, combining pharmacological, surgical, and device therapy, have postponed death, but do not cure the patients. We need new treatments, and there is still room to improve the impact of our current tools.74 For the latter aspect, assessing and improving the application of guidelines is a major task. Recent data show that between 40 and 65% of eligible patients do not receive appropriate treatment.1 Improving patient adherence and compliance are essential to obtain results. A simplification of the medication in a polypill may help to achieve this, and this is currently under study for secondary prevention of ischaemic disease.75,76 Furthermore, non-pharmacological treatment, such as exercise, has a potential that has not yet been fully exploited. Exercise relies on physiological mechanisms and can provide benefit at low risk and cost.77 It is an area where further reverse translation may help to enhance the impact of treatment.

For the large group of patients with HF secondary to myocardial infarction and ischaemic heart disease, a true regenerative/replacement treatment will be the major step forwards (see the next section). This goal, however, must not distract from the potential for better pharmacological, small-molecule treatment. A new paradigm being developed in animal studies is targeting the pathways leading to hypertrophy and contractile dysfunction, rather than the mechanisms underlying the established dysfunction.78 Data-driven approaches in both animal models and patient material are identifying different networks of signalling involved in cardiac remodeling.79 Several checkpoints are to be explored to modulate the pathways. Control of gene expression through different transcription factors may identify clustering of different pathways and a possibility for central targets. MicroRNAs have emerged as master modulators of post-transcriptional regulation. The attractiveness lies in the possibility of manipulation through antagonirs, which may be more amenable to translation than classic gene therapy.80,81 All these approaches need to be further expanded and require contribution from basic research into cell growth, differentiation, and de-differentiation processes.

HF with preserved systolic function represents a large subgroup of patients, estimated at 1.5–2 millions patients in Europe. It typically develops at an older age, is more prevalent in women, and occurs mostly in a setting of hypertension, but also with obesity and renal and pulmonary disease.82 Diagnosis relies on clinical signs of HF with preserved left ventricular dimensions and systolic function, but disturbed filling. Diastolic HF has a mortality that is comparable to systolic HF, around 50% over 5 years, and thus higher than most cancer diseases. The response to the classic HF pharmacological treatment is poor.83,84 All mega-trials with drugs proven to be beneficial in systolic HF have failed so far in patients with diastolic HF. The underlying molecular and cellular mechanisms that distinguish it from systolic HF remain poorly defined and the cause of death is not well known. In a small study, exercise had a beneficial effect on diastolic function parameters and symptoms (G.H. et al., unpublished). This indicates that means to improve diastolic HF are available and need to be explored. At present, randomized trials using sufficient endpoints are lacking.

In defining the needs for research, diastolic HF is a priority focus for socio-economic reasons, but also because of new opportunities. We have acquired tools to elucidate molecular mechanisms and identify biomarkers. A system biology approach using patient data to generate hypotheses will
need a multinational and translational approach with strong experimental input. In this particular form of HF, the prevalence of sudden death is currently unknown, but likely to be important, whereby underlying arrhythmias may have distinct mechanisms. A large-scale translational European research project including basic and clinical research could be of tremendous added value for Europe. In particular, exploring the mechanism by which exercise improves the disease in animal models and clinical studies could be very promising.

Summary: HF therapy has prolonged life but not cured the patient. Prevalence is expected to further increase. Small-molecule therapy is to be developed in the area of signalling pathways and post-translational modifications. Exercise is a physiological means of modulating pathways that could be exploited and needs to be pursued in clinical and mechanistic studies. Diastolic HF escapes current treatment and needs specifically targeted research in mechanisms, treatment, and management.

5.5 New potential for stem cells

Loss of protective endothelial function is one of the early events in the process towards atherosclerosis and results from defective repair by circulating endothelial progenitor cells (EPCs).85 Studies on the genesis and biology of the various types of EPCs and their possible pharmacological induction hold promise for the future for the protection from vascular disease. In a later stage, insufficient organ perfusion following thrombotic vessel obstruction of the feeding artery is the major determinant of post-ischaemic tissue injury, ultimately leading to atrophy of the affected territory, important loss of function, and serious health consequences. Therapeutic angiogenesis is viewed as a highly promising strategy to ensure revascularization of ischaemic tissues by promoting the growth of new vessels or the maturation of pre-existing ones.86 Particularly, administration of growth factors or transplantation of vascular progenitor cells, including EPCs, constitutes the most promising pro-angiogenic therapies.

In addition to angiogenesis, the advances in stem cell biology have offered the hope for repair and replacement of damaged myocardium. In experimental research, embryonic stem cells (ESCs) have been among the most potent and efficient, but remain far from clinical practice because of the risk of teratogenicity, the need for donor compatibility and, in particular, with regard to clinical implementation and potential use of human ESCs, the ethical barriers.87,88 In contrast, other cell types such as autologous bone marrow stem cells (BMSCs) and EPCs have been tested in clinical trials with significant improvements of function in a number of these studies.89,90 There remains a big gap, however, between the extent of clinical improvement and the expectations created by the in vitro and experimental results. Several factors account for this and need to be addressed.

The lack of standardization and uniformity in protocols (timing, cell preparation, numbers) between clinical trials reduces the power of the studies. Larger multicenter trials will eventually be needed, but there is concern that the investment in such an effort may not have the needed return with the use of BMSCs. This concern is based on the remaining controversy and paucity of data that this cell type can form cardiomyocytes in vivo. As there are promising new candidates under development in experimental laboratories, a larger effort should be directed towards an improved pre-clinical definition of the type, means, and conditions for successful cell therapy. The discovery of the inducibility of differentiated cells into pluripotent stem cells opens a totally new area for research that could be beneficial for vascular and cardiac regeneration.91–93 On the basis of earlier experience, we can move more rapidly towards characterizing the conditions for translation. Large animal studies may answer the issues of dose, administration route, and expected benefit. A factor currently unaddressed in animal studies is the role of the chronic disease state on the success of graft implantation or endogenous stem cell mobilization.94 This will require long-term studies, which are by nature difficult and costly, but these may yield critical information to adapt protocols for application in patients. This further experimental development should be closely followed by clinical proof-of-concept studies.

Summary: Major progress has been made in the biology of stem cells, supporting their potential for regenerative medicine. The implementation remains only moderately successful, however, and calls for further research. Priorities are: deciphering the mechanisms of stem cell mobilization, migration, and homing; identification and targeting of the factors defining the ‘hostile’ environment; defining the requirements for successful maturation and differentiation in situ; combining the power of gene therapy with that of stem cell replacement therapy; identification of new pro-angiogenic molecules.

5.6 New potential for cardiac protection in ischaemia

Ischaemic heart disease is the major cause of HF. Myocardial infarction and its location and extent are a major determinant of the progression to HF. Consequently, reducing infarct size is one of the most desirable goals. Early reperfusion of a closed coronary artery is a direct target that has received a good deal of attention with important successes. Early thrombolysis made possible by the introduction of streptokinase and tissue plasminogen activator and the subsequent development of successful new angioplasty techniques and stents have effectively reduced early mortality and the area of infarction.95 However, experimental studies did demonstrate quite early that reperfusion in itself extends the damage occurred during the preceding period of ischaemia, thus limiting the benefit obtained by emergent coronary artery recanalization (reviewed in Yellon and Hausenloy96). If this could be prevented through cardioprotective measures applied at the time of reperfusion, the gain in viable myocardium would translate into
improved prognosis and quality of life of patients with acute myocardial infarction.97

The molecular pathways that lead to further cell death upon reperfusion are multiple with two major late endpoints: an increase in intracellular calcium, which activates proteases, and mitochondrial damage, both leading to cell fragility, sarcolemmal rupture, and cell death. This mechanism reveals multiple potential targets, and several appear to be valid experimentally, showing a redundancy in the pathways.

Several approaches have been tested in the experimental setting to reduce this reperfusion injury. Early on, preconditioning was shown to be very powerful, reducing infarct size (the gold standard endpoint) by more than 50% and could be mimicked pharmacologically. Yet, it has taken a long time to translate the concept of cardioprotection and to convince the clinicians of the potential benefits and importance of the concept.106 One reason may be the focus on the implementation of fast reperfusion that was improving survival, and there was little apparent need for adjuvant therapy. Negative results in some early attempts with drugs aimed at not-well-founded targets and mechanisms, such as infusion of superoxide dismutase, SOD, deterred further interest in clinical implementation.68 Another reason was the practical difficulties involved in testing strategies at the time of reperfusion where, in contrast to experimental conditions, the window for treatment was poorly controlled. Yet some recent studies using pharmacology derived from the experimental studies on preconditioning were successful.99-101

Some major recent advances increase the opportunity to translate and implement ischaemic protection into clinical practice. Post-conditioning applied at the time of reperfusion can reduce the infarct size in experimental models.102,103 Translation of this concept has been considerably faster, and post-conditioning was shown to reduce myocardial damage as measured by enzyme release in a proof-of-concept clinical study.104 The mechanism is not fully understood but probably reduces the opening of the mitochondrial permeability transition pore and mitochondrial damage. A reduction in the permeability transition pore can also be obtained with cyclosporine, and a single dose of cyclosporine appears to mimic post-conditioning protection.17 Several questions and potential pitfalls need to be addressed. Experimental studies suggest a high vulnerability to the protective effects, and the confounding factors in patients are not readily identified in the laboratory. Further advances will need clinical studies based on strict reperfusion algorithms with extensive data collection and feedback of data into further experimental research. Currently, the different pathways have mostly been studied in isolation, and major experimental advances can be made by a systems approach and identification of networks that may reveal new targets.

This approach will be part of the broad and inclusive approach to ischaemic heart disease: prevention/treatment of atherosclerosis/thrombosis, reperfusion strategies and patent vessels, and cell replacement therapies. Support and recovery of function in chronic ischaemic areas is currently an orphan area with few specific targets for therapy that awaits translational studies and could further improve the outcome in ischaemic heart disease.

Summary: The field of myocardial protection against reperfusion injury is entering a phase of translation to humans in the form of proof-of-concept studies. The acute, single-dose administration of these treatments limits to a certain extent its commercial interest. This and the need for rapid recruitment of large populations make clinical trials on protection against reperfusion injury adequate targets for European funding. We need IDCTs integrating cardioprotection in reperfusion algorithms, with relevant endpoints and evaluation of patient/disease modifiers. In addition, mechanistic studies involving the use of central platforms and relevant animal models are strongly needed for optimization and development of new therapeutic strategies in an integrated basic/cellular/industry translational approach.

6. General conclusions

Translational research in the cardiovascular field must be seen as a re-iterative process among basic, experimental, and clinical research, in partnership with industry. There is a strong need of support for clinical investigator-driven research, not as a stand-alone entity but as a component of this re-iterative process, including basic experimental research. Training initiatives are necessary to form both clinical and basic researchers in the translational approach. Research should focus more on the identification of early disease, protective mechanisms and promotion of health. In the post-genomic area, emphasis is on data integration from the different '-omics' approaches and the interaction between environment and genetics.

Conflict of interest: There are no conflicts to declare in relation to this manuscript.

References

1. Lenfant C. Shattuck lecture—clinical research to clinical practice—lost
2. Fox KA, Steg PG, Eagle KA, Goodman SG, Anderson FA Jr, Granger CB et al. Decline in rates of death and heart failure in acute coronary syn-
   627–630.
   et al. Management of acute myocardial infarction in patients presenting
   with persistent ST-segment elevation: the Task Force on the Manage-
6. Ray KK, Cannon CP, Ganz P. Beyond lipid lowering: what have we learned
   about the benefits of statins from the acute coronary syndromes trials?
   Am J Cardiol 2006;98:18P–25P.
7. McMurray JJ, Pfeffer MA. New therapeutic options in congestive heart
   cardioverter-defibrillator therapy for the prevention of sudden cardiac


