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Global position paper on cardiovascular regenerative medicine

Scientific statement of the transnational alliance for regenerative therapies in cardiovascular syndromes (TACTICS) international group for the comprehensive cardiovascular application of regenerative medicinal products

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Introduction

Based on the increasingly understood regenerative capacity of the human heart and vascular system,¹ cardiovascular regenerative medicine (CRM) encompasses all potential diagnostic and therapeutic strategies aimed at restoring organ health. Envisioned to enhance the innate regenerative response of cardiovascular tissues, diverse and often complementary products and strategies have been investigated (e.g. stem and progenitor cells, stromal cells, extracellular vesicles such as microvesicles and exosomes, growth factors, non-coding RNAs, episomes and other gene therapies, biomaterials, tissue engineering products, and neo-organogenesis). Despite promising results based on 20 years of research, next generation CRM treatments have yet to transform cardiovascular practice.

Given the compelling need for a thorough critical debate on the past, present, and future of CRM, the international consortium Transnational Alliance for regenerative Therapies In Cardiovascular Syndromes (TACTICS, www.tacticsalliance.org)² summarizes the shared vision of leading expert teams in the field (for a complete list of TACTICS members please see Annex 1). The document addresses key priorities and challenges, including basic and translational research, clinical practice, regulatory hurdles, and funding

sources. The methodological procedure included the following: (i) identification of strengths, weaknesses, opportunities, and threats (SWOT analysis) by means of an open poll; (ii) distribution of the main topics between at least two worldwide key opinion leaders, who prepared proposals for each topic; (iii) open discussion and consensus on each proposal between all members of TACTICS; and (iv) review of the document by an independent committee.

Cardiovascular regenerative medicine in perspective

This section summarizes existing knowledge pertinent to the mechanisms of cardiovascular regeneration, the attempts to apply that knowledge in the preclinical arena, and the main achievements and obstacles in translation to clinical practice.

Mechanisms of cardiovascular regenerative response

Cardiac regenerative response

Available evidence indicates that ongoing cell turnover in the adult human heart involves the death of cardiomyocytes and generation of

new tissue.^{1,3} Furthermore, the myocardium, like other parenchymal organs, contains endogenous stem cells with the ability to proliferate and replace cardiomyocytes that die due to apoptosis or oncosis.⁴ Therefore, the paradigm that cardiomyocytes are terminally differentiated cells incapable of proliferation or renewal has shifted, and the heart is recognized to be a self-renewing organ.

However, the regenerative capacity of the adult human heart is limited and insufficient to overcome the massive loss of cardiomyocytes during acute damage or prolonged remodelling, in which cardiomyocyte death exceeds cardiomyocyte renewal. Such a limitation contrasts with the active cardiomyocyte turnover observed during embryogenesis and with the intense regenerative capacity of the adult heart in some species. In certain mammals, cardiac muscle cells remain mitotically active through the foetal and early perinatal periods, although shortly after birth, mitotic division of cardiomyocytes becomes undetectable, supporting the long-held belief that mature mammalian cardiomyocytes are terminally differentiated. In contrast, an adult zebrafish can fully regenerate its heart even after amputation of 20% of the ventricular mass.⁵ Mammalian neonates have the potential to regenerate injured hearts in much the same way as lower vertebrates.⁶ Although still a controversial concept, the mechanisms by which these processes occur form the basis of regenerative therapies and include various non-exclusive and probably interacting possibilities. These healing mechanisms are still in debate but include the following: (i) *Endogenous cardiac progenitor cells (CPC)*⁷ in distinctive architectural microenvironments known as 'cardiac stem cell niches', which have demonstrated their capacity to differentiate into several cardiac cell types under specific circumstances and constitute a source of new cardiac cells during cardiac regenerative processes; (ii) *Dedifferentiation, proliferation, and reprogramming of pre-existing adult cardiomyocytes* to produce new cardiomyocytes.^{8,9} This process is the main component in the regeneration of damaged myocardium in zebrafish and mammalian neonates. The mechanisms underlying this process may shed light on how to revert the inhibition of the mitotic capability of human adult cardiomyocytes and enable *in situ* cell reprogramming^{10,11}; and (iii) *Activation of cells from the epicardium* as a reminiscence of its involvement in cardiogenesis during embryonic life.¹² Although this mechanism remains controversial, the contribution of epicardial cells to the whole process of heart regeneration, and particularly to the inflammatory response after injury, has been extensively documented and confirms the role of the epicardium in regeneration.¹³

Vascular regenerative response

Cardiovascular regenerative medicine is also a promising approach for refractory angina and peripheral artery disease (PAD).¹⁴ Dysfunction of the endothelial monolayer is the key initiation event of vascular diseases and is caused by a variety of stimuli including hypertension, diabetes, dyslipidaemia, and oxidative stress. After endothelial dysfunction and denudation, endogenous resident endothelial progenitor cells (EPC) tend to proliferate and replace the injured endothelium.¹⁵ However, this endogenous mechanism of regeneration is a relatively slow and inefficient process.¹⁶ Preclinical and clinical studies indicate that a variety of CRM therapies provide growth factors and cytokines for therapeutic angiogenesis, both in the heart and throughout the vascular system.^{17–20} The mechanisms by which those treatments yield positive results are being steadily unmasked.²¹

Cardiovascular regenerative products

Products used for CRM can serve two complementary strategies according to the target processes (Figure 1): (i) *exogenous regenerative responses*, in which implanted products, cells, or tissues are expected to replace the structure of damaged or dysfunctional tissue; and (i) *stimulation of endogenous regenerative responses*, in which the products delivered are aimed at enhancing the efficiency of endogenous reparative mechanisms.

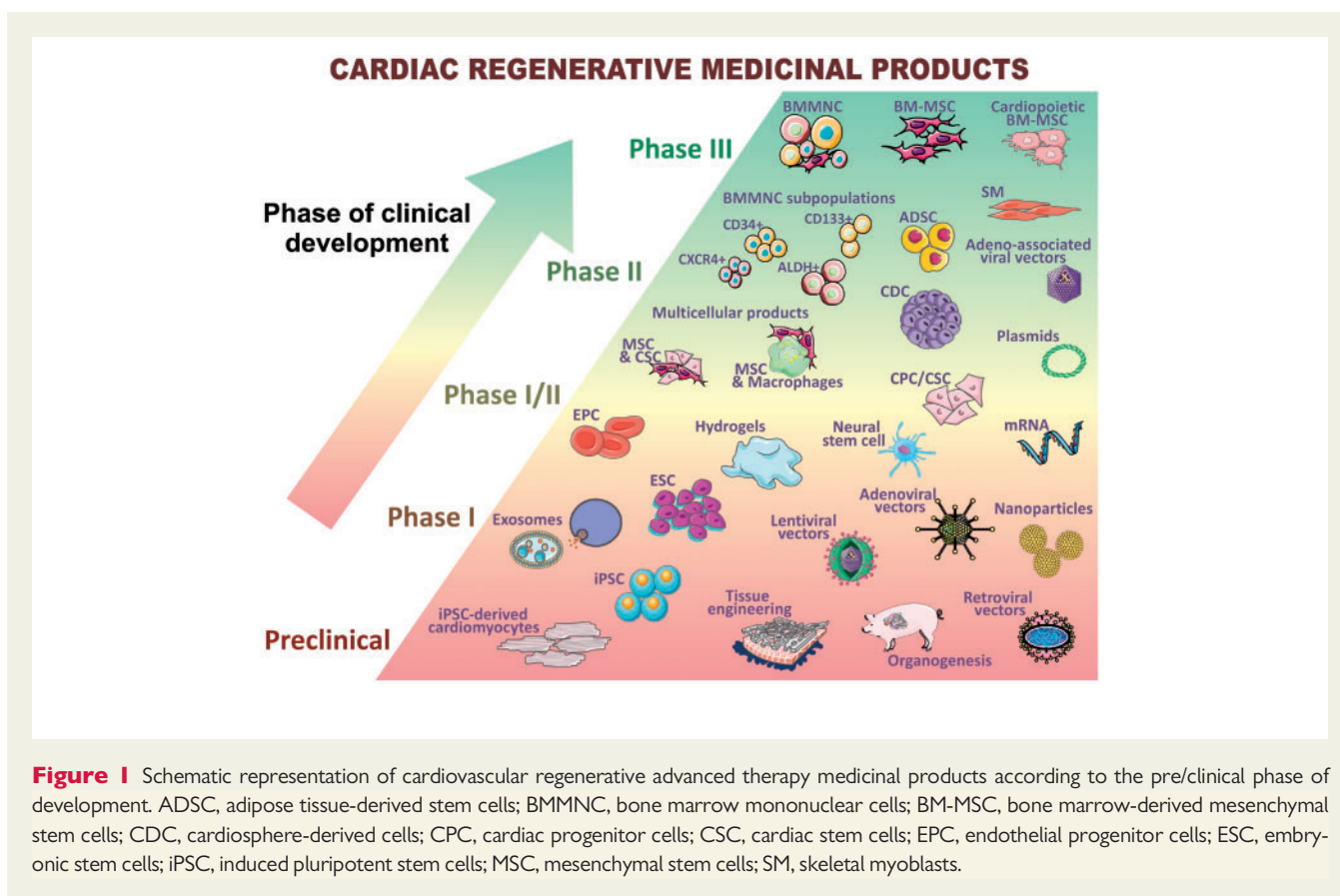
Approaches based on 'exogenous regenerative responses' include *in vitro*-differentiated cardiomyocytes, cardiovascular and EPC, and tissue-engineered cardiac and vascular patches with some degree of electromechanical functional maturation. In recent years, considerable advances have been made with this strategy,^{22–25} which has proven to be effective in primates.^{26,27} However, although the complex mechanisms underlying *in vitro* differentiation and maturation have limited its application in clinical practice, a first-in-man clinical trial is already assessing the feasibility and the safety of the transplantation of human embryonic stem cell-derived cardiovascular progenitors.²⁸

Cardiovascular regenerative medicine products focused on the modulation, enhancement and activation of 'endogenous regenerative responses' can be subdivided into three main groups, which could be eventually combined:

- (1) *Cell implantation*: several types of stem, progenitor and stromal cells have been investigated. These include both pluripotent stem cells, such as embryonic stem cells (ESC) and induced pluripotent stem cells (iPSC), and adult stem cells, including cells of cardiac origin [e.g. CPC and cardiosphere-derived cells (CDCs)] and cells from other sources [e.g. bone marrow-derived mononuclear stem cells (BMMNC), bone marrow-derived mesenchymal stem cells (BM-MSC), adipose tissue-derived mesenchymal stem cells (AT-MSCs), EPC and adventitial progenitor cells]. Excellent reviews summarizing their distinctive characteristics and outcomes have been published elsewhere.^{29,30}
- (2) *Injection of biological or synthetic factors* with active functions in endogenous regenerative processes, which emulate the benefits of cell therapy without the need for living cells. Products in this category include extracellular vesicles (microvesicles, nanoparticles, and exosomes)^{31–33} isolated from *in vitro* cell secretomes and synthetic growth factors. All these products can be generated in clinical grade and injected using various delivery strategies.^{34,35}
- (3) *Genetic and epigenetic modifications* that modulate the expression of genes and mRNA involved in the endogenous regenerative capacity of the heart and vessels. Increasing knowledge of the genetic pathways that govern cardiovascular generation and regeneration processes, which are active during the embryonic and neonatal stages, enables identification of factors that could be reactivated during adult life using genetic approaches.^{11,36} From the administration of mRNA produced *in vitro* to *in vivo* modifications of human DNA, the therapeutic regulation of gene expression and regeneration pathways may dramatically increase the possibilities of repairing the human cardiovascular system.^{37,38}

Preclinical therapeutic application of basic science

Preclinical development depends on the use of appropriate animal models that accurately reflect human disease. In contrast with other areas, cardiovascular *in vitro* models provide limited information, which is restricted mainly to the assessment of drug toxicity and



specific cellular and molecular aspects.³⁹ Functional hearts and vessels are necessary to evaluate and optimize regenerative therapies.

Most of the mechanisms of CRM have been clarified thanks to pre-clinical research on small animals,^{29,30,40} although their practical and translational significance can be undermined by anatomical and functional deviations from human organs. In order to obtain a more comprehensive picture and better translational value, large animals such as pigs, sheep, and perhaps monkeys are needed.^{41–43} It is noteworthy that with large mammals, research has focused on acute myocardial infarction (AMI), chronic ischaemic cardiomyopathy (CIC), and, more sporadically, on dilated cardiomyopathy (DCM) and other forms of non-ischaemic heart disease (NIHD). The study of other cardiovascular diseases, such as Chagas disease,^{44,45} requires more complex animal models, in which the availability of transgenic and knock-out mice is proving particularly useful for assessing genetic factors and inducers of cardiovascular diseases.

Lessons learned from clinical research

Stem cells were first used in to prevent heart failure (HF) in clinical practice in 2002.⁴⁶ Ever since, ischaemic heart disease (IHD) has been the most prominently evaluated disease, with more than 100 and 90 clinical trials carried out in the settings of AMI and chronic ischaemic HF, respectively. *Table 1* provides a brief description of the products and results of individual trials. The literature has been further enriched with 48 systematic reviews and meta-analyses,⁴⁷ which have consistently shown the feasibility and safety of the aforementioned regenerative strategies, as well as promising functional and clinical improvements in patients with AMI and chronic ischaemic left ventricular dysfunction, thus warranting

appropriately powered and well-designed phase III clinical trials. In summary, the application of regenerative strategies in patients with IHD is feasible and safe. However, although promising, regenerative therapies have yet to demonstrate definitive clinical benefit over standard-of-care. *Table 1* also details previous experiences in refractory angina, NIHD, PAD and stroke, for which the results are similar.

Regenerative therapies are currently being investigated in other cardiac conditions (e.g. valvular heart disease, rhythm disorders, and congenital myopathies), although clinical research is currently in very early stages.

The main obstacles that clinical CRM has encountered since its inception and that have hampered its large-scale adoption in daily clinical practice are depicted in *Table 2* and include incomplete understanding of cardiovascular regenerative mechanisms, heterogeneity of study protocols and underestimation of aspects such as delivery methods, extracellular structure, dose, and patient selection. Furthermore, surrogate and clinical endpoints have been inconsistently used and are usually misinterpreted. Finally, multidisciplinary/multinational collaborations to unravel and resolve the limitations identified have been insufficient.

Challenges of cardiovascular regenerative medicine

The following section summarizes the outlook for the next decade. Specifically, the main challenges and priorities of each area involved in the clinical application of CRM are identified.

Table 1 Summary of randomized clinical trials in cardiovascular diseases with regenerative products

Disease (patients treated)	Regenerative product	Safety	Overall efficacy ^a (surrogate endpoints)
Acute myocardial infarction (n = 2732)	BMMNC ^{48–63}	Favourable	Inconsistent
	BM-MSC ⁶⁴	Favourable	Inconsistent
	Specific BM cells ^{65–69}	Favourable	Inconsistent
	ADSC ⁷⁰	Favourable	Inconsistent
	CDC ⁷¹	Favourable	Positive
Ischaemic heart failure (n = 2035)	Growth factors ^{72–77}	Favourable	Inconsistent
	SM ^{78–81}	Favourable ^b	Inconsistent
	BMMNC ^{82–85}	Favourable	Inconsistent
	BM-MSC ^{86–88}	Favourable	Positive
	Specific BM cells ^{89–96}	Favourable	Positive
	CSC ⁹⁷	Favourable	Positive
	Gene therapy ^{37,98–101}	Favourable	Inconsistent
Refractory angina (n = 353)	BMMNC ^{102–106}	Favourable	Positive
	Specific BM cells ^{107–109}	Favourable	Positive
	ADSC ¹¹⁰	Favourable	Positive
Non-ischaemic heart failure (n = 166)	BMMNC ^{111,112}	Favourable	Inconsistent
	Specific BM cells ^{113,114}	Favourable	Inconsistent
	BM-MSC ¹¹⁵	Favourable	Inconsistent
Peripheral artery disease (n = 1217)	BMMNC ¹¹⁶	Favourable	Positive
	Specific BM cells ^{117–119}	Favourable	Positive
	Gene therapy ^{120–124}	Favourable	Inconsistent
Stroke (n = 95)	Neural stem cells ¹²⁵	Favourable	Inconsistent
	BMMNC ¹²⁵	Favourable	Inconsistent
	Specific BM cells ¹²⁵	Favourable	Inconsistent

ADSC, adipose tissue-derived stem cells; BMMNC, bone marrow mononuclear cells; BM-MSC, bone marrow-derived mesenchymal stem cells; CDC, cardiosphere-derived cells; CSC, cardiac stem cells; SM, skeletal myoblasts. 'Specific BM cells' means either modified or selected subpopulations of the bone marrow mononuclear fraction.

^aNote that all randomized clinical trials evaluated efficacy with surrogate endpoints.

^bMain safety concerns after skeletal myoblast transplantation in humans include an increased probability of arrhythmic events, so these cell type should be viewed with extreme caution in further clinical trials.

Priorities in cardiovascular regenerative medicine: diseases and disease stages

The ultimate goal of CRM is the prevention and treatment of cardiovascular failure and its consequences, including the protection and repair of tissue necrosis caused by ongoing myocardial ischaemia and reversal of chronic ischaemic dysfunction at all stages of disease progression. In addition, vascular damage in pulmonary or systemic circulations is a key target in CRM.

The application of regenerative strategies in the setting of AMI takes advantage of preserved extracellular tissue architecture, although it is subject to the inflammatory hostility of the milieu in the context of excellent initial and long-term results of standard-of-care approaches (e.g. reperfusion strategies). Therefore, given the results of research already carried out in this setting, new initiatives should focus on patients at risk of developing HF and should depend on findings from ongoing large-scale clinical trials and from translational and phase I/II clinical studies analysing new regenerative products and mechanistic aspects, such as timing, dose, therapeutic combinations, and single vs. sequential delivery.

In patients with chronic ischaemic or non-ischaemic HF, the histopathological, and functional substrate is crucial and underlies

the choice, design, and methodology of regenerative applications. In this setting, coronary tree status, myocardial perfusion and viability, together with the extent and characteristics of maladaptive myocardial remodelling and influence of chronic inflammatory processes, will help to choose between therapies aimed at stimulating endogenous repair and/or at replacing a functional scar with healthy tissue.

Priorities and methods for basic research

Enhancement of endogenous cardiac regeneration is limited by the lack of knowledge regarding the mechanisms of modulation of the regeneration capacity in the adult mammalian heart. Accordingly, basic research focuses with the potential to revolutionize clinical practice are summarized in Table 3.

Priorities and methods for translational research: animal models

The three stages in the development of new therapeutic products comprise discovery and development of leading products, exploratory studies, and confirmatory studies (Figure 2). The first two stages usually involve small animal models (e.g. zebrafish

Table 2 Main obstacles encountered by clinical CRM

1. The complex molecular, cellular and organ-based mechanisms that govern the cardiovascular reparative process as a whole have yet to be understood. Consequently, it has been difficult to design clinical trials. Since many cardiovascular diseases are syndromes, the future identification of specific molecular or cellular causes will help to increase the chances of success in clinical trials.
2. The results of clinical trials are often contradictory because of non-homogeneous study protocols with inter-trial and inter-patient variability and the lack of standardization and scalability of investigational products.
3. Focus on cell phenotype initially led to underestimation of the importance of delivery methods, thereby leading to low initial cell retention rates, poor survival in the host tissue, and subsequent loss of efficacy.
4. Efforts have focused mainly on the loss of the myocardial parenchyma, thus leading to underestimation of the importance of other key aspects of a functional heart, such as the extracellular matrix or the appropriate cell patterning and electromechanical coupling required for a well-co-ordinated improvement in contractility.
5. Key aspects of clinical trial design that have been systematically underestimated and not sufficiently investigated in phase I trials include optimal dosage (dose-escalation studies), timing of delivery (especially in the case of AMI), cell type and delivery method in the specific condition under study.
6. Patient selection is paramount, given the critical influence that comorbidities, aging and medications have on the quality of source cells (if autologous) and on the response of host tissue to regenerative products. Predictors and scores that would enable appropriate identification of specific target populations that benefit most from CRM have not been described/validated.
7. Surrogate imaging and hard clinical endpoints have been inconsistently used in clinical trials and are usually misinterpreted when translating clinical research for a specific product. In addition, surrogate endpoints need further standardization.
8. Limited multidisciplinary/multinational collaborations to unravel and resolve identified limitations, which could increase our knowledge of regenerative therapies and facilitate definitive large-scale preclinical and clinical trials.

Table 3 Recommendations for basic research**Strategies for the enhancement of endogenous regenerative responses**

1. Better understanding of the underlying biology that leads to significant loss of regeneration capacity in the adult mammalian cardiovascular system.
2. Breakdown of the regeneration process in clinically relevant models, from the niche of adult stem cells to active dedifferentiation, proliferation, and/or transdifferentiation.
3. Identification of molecular mechanisms that control the post-infarction inflammatory response and the remodelling process in order to redirect healing towards regeneration instead of scar formation.
4. Identification of endogenous regeneration triggers that would enable the production of biological or synthetic CRM products, ideally for a prolonged and efficient outcome.
5. Evaluation of potential differences between males and females in terms of their ability to generate a regenerative response.

Strategies for cardiovascular tissue replacement

1. Identification of the most appropriate *in vitro*—and eventually *in vivo*—maturation processes to mimic adult cardiac tissue (e.g. in terms of cell structure and electromechanical function).
2. Evaluation of disruptive organogenesis strategies (e.g. chimeric approaches to produce human organs in pigs).¹²⁶

and rodents), which enable affordable and rapid experiments. Confirmatory studies are typically performed in large mammals, which are more representative of human disease, in order to assess the risks of a new therapy and to predict safety, feasibility, and efficacy. Although studies in large animal models are expensive, complex, and technically demanding, they offer the advantage of being conducted in settings that more closely mimic clinical practice. Therefore, large animal studies are essential if we are to justify the risks and costs of clinical trials and to improve the clinical outcomes of regenerative therapies. However, publication bias is a major concern in preclinical trials. As is the case in other medical fields (e.g. cancer studies), the lack of interest in negative or neutral findings may translate in a disproportional body of positive published results. In order to overcome this overestimation, one

suggestion would be that preclinical research with large mammals follows standards used in clinical trials (see Table 4).¹²⁷

Priorities and methods for tissue engineering and biomaterials

Despite the regenerative capacity of mammalian hearts and vessels, experience with highly damaged tissues indicates that, at a certain point of damage (e.g. homogenous fibrotic scars and highly calcified valves or arteries), endogenous recovery is impossible. In such cases, substitution of the tissue may be the only possible strategy. Given the small number of transplant donors, tissue engineering has emerged as an attractive approach. However, in order to become clinically useful, major challenges have to be resolved (Table 5).

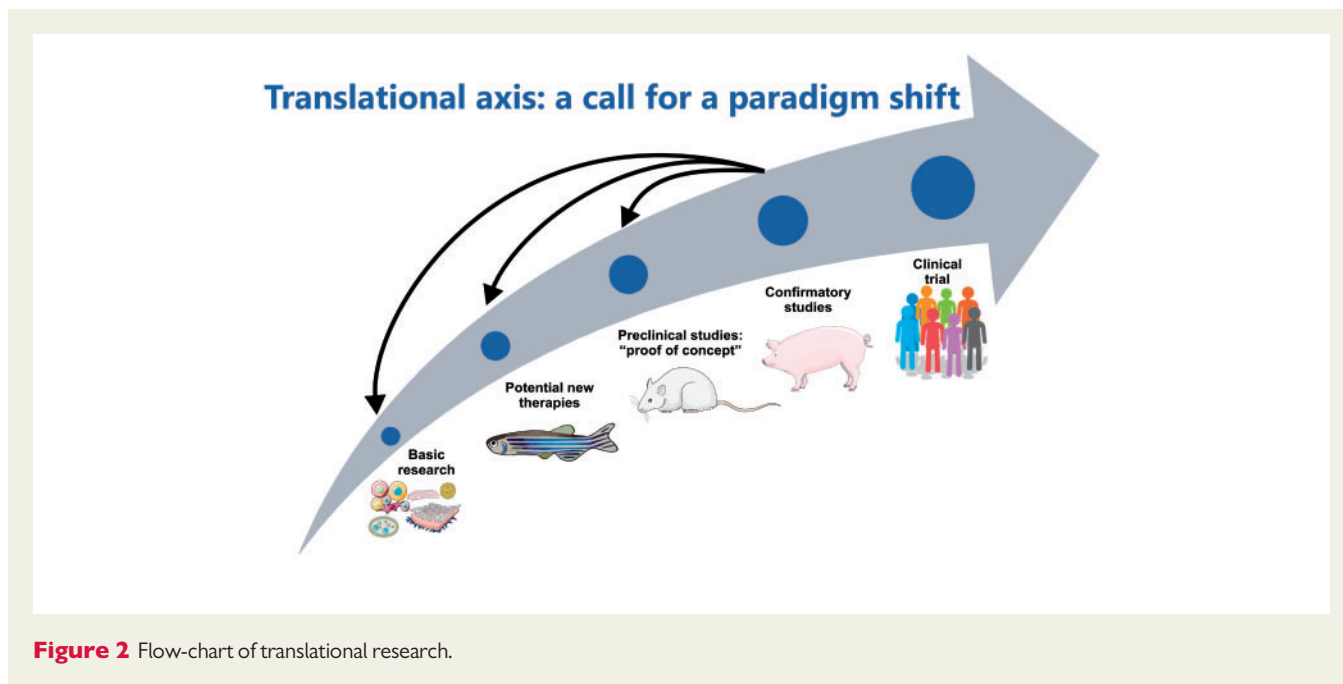
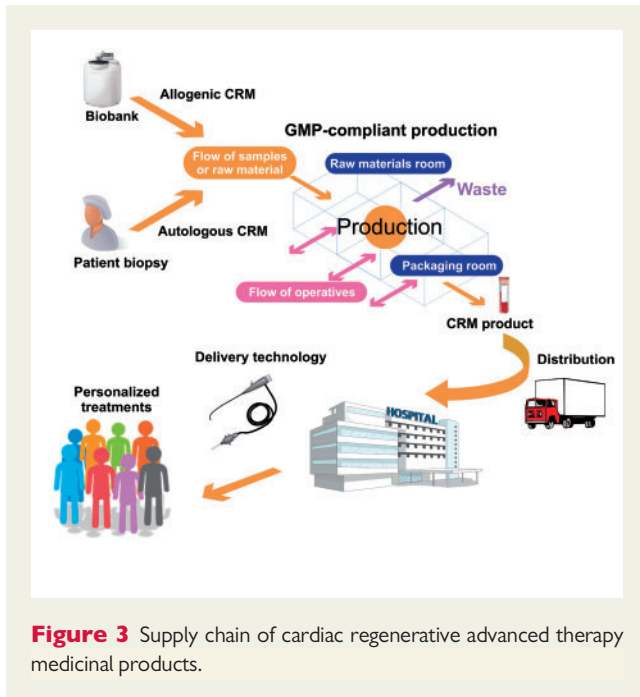


Table 4 Recommendations for translational research with large animal models

1. Prospective online and public registration of preclinical trials, including the description of the study and research model, primary and secondary outcomes, number of animals, and duration of follow-up.
2. Obligatory publication of results required for grant fund release (e.g. funding depends on the dissemination of results, independently of whether they are positive or negative). Use of the ARRIVE guidelines for the reporting of preclinical study results.¹²⁸
3. Prioritization of multicentre studies and development of collaborative consortia consisting of independent core laboratories specialized in large animal models (e.g. the CAESAR consortium).¹²⁹
4. Blinded and randomized studies in the confirmatory stage.
5. Establishment, optimization, and sharing of standard animal models and protocols. Funding agencies should provide guidelines for the generation of animal models, which should include the definition of a standard model for AMI and CIC.
6. Standardization of software protocols for the analysis and quantification of the main outcomes by means of open-source solutions and platforms for data sharing (e.g. scar size, left ventricular ejection fraction).
7. Prioritization of animal models that include comorbidities (e.g. old-animal models), cardiovascular medication use and clinically relevant scenarios (e.g. surrogate cell products or xenoregulated animals that do not require immunosuppression).
8. Mandatory evaluation of gender differences.

Table 5 Main challenges of cardiovascular tissue engineering

1. Enormous number of cells needed to build a heart (e.g. around 10 billion for a whole human heart)¹³⁰
2. Anatomically realistic scaffolds (e.g. natural or synthetic biomaterials with vasculature and anisotropic structures).
3. Differentiation of cells into several cardiac lineages (e.g. endothelial cells, fibroblasts, cardiomyocytes)
4. Mature electrophysiological properties (e.g. action potential duration and conduction velocities, avoidance of autoexcitability) to ensure co-ordinated contraction without arrhythmias.¹³¹
5. Mature mechanical function (e.g. sarcomere constructs, troponin orientation) to achieve efficient contraction.
6. Bioreactors that allow maturation under sterile conditions for long culture periods.
7. Development of easy-to-use and safe, minimally-invasive, delivery technologies.



The aforementioned challenges in the generation of clinically useful cardiac muscle tissue are not present in other cardiovascular structures, for which the tissue engineering approach is already producing clinically viable and useful products. Such is the case of cardiac valves and large vessels.^{132–135} Nevertheless, technical improvements are required in order to extend their applicability to a larger number of patients. These improvements include standardized production units, the identification of the most appropriate materials, control of long-term degradation and integration in the body, and the development of minimally invasive delivery devices.¹³⁶

In addition to the clinical usefulness of cardiovascular tissue engineering solutions, the possibility of producing personalized monolayer cultures and three-dimensional human engineered cardiac tissues heralds a new era for the *in vitro* identification of pathophysiological mechanisms and for the development of tailored novel treatments (e.g. by using human cardiomyocytes obtained by directed differentiation of iPSC derived from patients with cardiomyopathy).^{137,138}

Priorities and methods for production, delivery, tracking, and assessment

Cardiovascular regenerative medicine products have special characteristics that differentiate them from classic pharmacological treatments in terms of production, delivery, tracking, and assessment (Figure 3). The manufacturing of these advanced therapy medicinal products (ATMP) includes multiple step from the acquisition of biological samples to the delivery of a personalized product for each patient. Given the heterogeneity present in the generation of most biological CRM products, the process of manufacturing and the delivery technology need to be considered as part of the CRM product itself. The functionality of a cell-based product is influenced by multiple factors, including the initial source, harvesting and isolation techniques, and manufacturing. Standardization of these procedures and

methods is especially important, as lack of uniformity in cell manufacturing may influence clinical outcome.¹³⁹ Moreover, standardization permits direct comparisons between trials and indirect comparisons through meta-analyses. Several reviews have already provided guidance for the technological progress and challenges towards manufacturing of CRM products based on the principles of Good Manufacturing Practice.^{140–142}

The main objective of delivery technologies is to achieve the optimal dosage of biological material needed to provide benefits in the region of interest of the host tissue. Although all available modalities of regenerative product delivery display—to varying degrees—the four desired characteristics (safety, ease of use, clinical utility, and low cost), after 20 years of research we can conclude the following:

- (1) Surgical transeptal delivery has been relegated to patients with a formal indication for open-chest surgery. However, minimally invasive approaches, such as lateral minithoracotomy, video-assisted thoracoscopy and robotic surgery, are currently being investigated.
- (2) Percutaneous catheter-based delivery has been the most extensively used modality for cardiac diseases. Intracoronary infusion of regenerative products has been the mainstay in the setting of acute coronary syndromes, whereas more sophisticated catheters—with or without navigation platforms—for endomyocardial delivery have been specifically used in HF and refractory angina.
- (3) Intravenous infusion of products was discontinued owing to low selective engraftment rates, subsequent to early trapping in remote organs (primarily the lungs), although it may play a role in the delivery of products with high tropism for the target tissue after AMI (e.g. viral vectors).
- (4) Tissue engineering products require more specific transplantation technologies. These products may prove easier for injection of biomaterials, but will require highly sophisticated systems in the case of matrixes or patches if they are to be minimally invasive or even administered percutaneously.
- (5) In the case of PAD and stroke, intra-arterial and intramuscular injections have been used extensively, and no relevant advances in delivery technologies are anticipated in the short-term.
- (6) Few preclinical studies have compared delivery modalities.^{143–145} It seems that the intracoronary and endomyocardial approaches are the most efficient, depending on the phase of myocardial ischaemia (acute vs. chronic).¹⁴⁶ However, evidence is scarce with humans, and the efficiency of product delivery is a complex, multifactorial variable that is influenced by several factors, including cell type, timing of delivery, device design, and cell dose. Moreover, the implications of these experimental findings for clinical practice are not completely clear, and it is now well known that retention rates may not determine the effect of a given product.^{147–149}

Our recommendations are shown in Table 6.

Identification of regenerative products ready for clinical trials: recommendations regarding clinical investigation tracks

'First-generation' cell types include a series of heterogeneous adult stem cell populations that were first used (unmodified) in CRM at the beginning of this century (e.g. unfractionated BMMNC and selected subpopulations thereof, CPC, EPC, SM, MSC, and ADSC).²⁹ These types of cells are believed to induce myocardial repair through the

Table 6 Recommendations for production, delivery, navigation, tracking, and assessment

1. Identification of optimal delivery technologies for each novel or 'conventional' regenerative product (e.g. viral vectors, stem cells, growth factors and molecules). Other variables, such as timing, dose, microenvironment, clinical scenario, and location, need to be considered when designing new delivery technologies.
2. Development of minimally invasive methodologies, ideally percutaneous approaches, for tissue engineering solutions.
3. Optimization of delivery modalities to improve accuracy by means of fusion imaging tools.
4. New imaging and automated software to guide and improve CRM product delivery and retention: real-time, non-invasive imaging and/or integrating computed tomography, magnetic resonance and ultrasound into the catheter navigation process.
5. New imaging and automated software for *in vivo* tracking of CRM products in humans.

Table 7 Identification of regenerative products ready for clinical trials

1. 'First-generation' and 'second-generation' stem cells (except for iPSC and ESC), including those used in allogeneic transplants, are ready for phase III clinical trials. However, issues such as best tolerated doses, benefits of repetitive administration, optimal timing, and most efficient delivery modality still need further research.
2. Emphasis should be placed on comparison between products, doses and delivery strategies.
3. Cell-based and other regenerative products, especially when evaluated in multicentre/international trials, should be standardized. Standardization includes quality assessments of the final product before release (viability, surface markers, potency, stability, and sterility tests).
4. Safety and efficacy issues in gene therapy should be solved before moving forward to new phase I or more phase II trials. Novel 'cell-free' products and tissue engineering approaches must progressively enter the clinical stage.
5. Efforts should be made to include biomarkers, new imaging/tracking and delivery techniques in phase I trials with the aim of unraveling the complex mechanisms of action of regenerative products.

secretion of cytokines and growth factors that activate innate regeneration pathways (paracrine activity). Most have already been investigated in depth in clinical practice (see 'Lessons learned from clinical research' section) and have passed through phase I and II studies with consistent and solid safety profiles. Furthermore, and although several issues concerning their regenerative capacity remain unresolved (e.g. mechanisms of action, dose, and timing), in some cases, they have already been considered as the most suitable types for investigation in phase III clinical trials.

In contrast, 'second-generation' cells include purified cardiac cell subpopulations (CDCs and CSC), 'potency-enhanced' cells with genetic or pharmacological modifications (e.g. 'cardiopietic' BM-MS), cells of allogeneic origin (MSC and CSC), and novel pluripotent sources (iPSC and ESC). Despite their robust paracrine activity, these cell types are also—theoretically—able to replace the damaged myocardium with the formation of new cardiomyocytes, smooth muscle cells, and endothelial cells to a greater or lesser extent. Although a first experiment with ESC-derived CPCs in chronic HF has been initiated in humans,²⁸ we can consider iPSC and ESC to be at the preclinical stage because of safety concerns (e.g. uncontrolled proliferation, transfection-related mutagenesis in iPSC).¹³⁶ The remaining cell types have also been considered to be ready for phase III experimentation. However, additional safety studies (e.g. immunogenicity and tumorigenicity) are required with some allogeneic sources before genuine phase II clinical trials can be considered.

The field of 'cell-free' products has evolved rapidly from the first unsuccessful experiences with growth factors (e.g. granulocyte colony-stimulating factor) used as soluble injectates to more

sophisticated products, such as episomes, microRNA (mi-RNA), and exosomes, either alone or embedded in hydrogels or encapsulated in nanoparticles. Although these new approaches that mimic the secretome of donor cells could soon be used in clinical practice, further investigations on their characterization, bioavailability (dose, timing), organ distribution (delivery), and efficiency (outcomes) are warranted.

With regards to gene therapy, after 14 years of clinical research, angiogenic factors, calcium-handling proteins, and homing factors have been investigated in phase I/II trials. Given the limited results of gene therapy in clinical trials compared with preclinical models, several obstacles need to be overcome before clinical application of gene therapy can be considered realistic. These obstacles include, but are not limited, to: (i) technical challenges regarding viral and non-viral constructs (e.g. tissue-specific promoters and chemical ligands); (ii) grounded choice of therapeutic targets and clinical conditions; (iii) safety, transfection efficacy, and production costs; and (iv) optimization of delivery systems for precise administration and appropriate bioavailability with minimal off-target effects. Finally, the field of tissue engineering is one of the most promising in CRM and is currently initiating phase I first-in-man experiences.¹⁵⁰

Clinical research tracks in CRM must be based on an evidence-based translational rationale. When ready for clinical testing, any regenerative product should follow the traditional four phases of clinical research (see also Table 8).^{29,151} Of note, some currently researched CRM products do not comply with these principles.

Table 7 summarizes our recommendations on the identification of regenerative products ready for clinical trials.

Table 8 Requirements for each phase of clinical research

	Preclinical, Phase I	Phase II	Phase III
Product regulatory requirements	Kinetics, biodistribution of the regenerative product. Purity, potency, and karyotype stability of particular cells. Ensure traceability	Short-term side effects and risk associated with particular regenerative biologics. Establish efficacy and safety monitoring assays	Performed after preliminary evidence suggesting effectiveness of particular regenerative product
Objective	Safety. Kinetics, dose-dependency, retention, and optimal delivery method	Safety/surrogate endpoints	Safety/therapeutic benefit/improved survival
Patients restriction/criteria	Identify target group (safety analysis)	Identify potential responders and non-responders	Include only responders
Sample size	Usually 20 per cohort	From a few dozen to a few hundred	Several hundred or more
Design	Randomized, open label or placebo/sham	Randomized, double-blind, placebo or sham controlled	Randomized, double-blind, placebo or sham controlled
Endpoints (feasibility/product and procedure related)	Procedural safety, biological activity of the regenerative product	Safety/feasibility of the procedure, adequate number of cells/dose response	Long-term, substantial evidence of previously observed feasibility/safety
Safety endpoints	Patient tolerance, abnormal cell growth, mutagenesis, tumorigenicity	Patient tolerance, tissue injury, clinical major adverse cardiac events, arrhythmias	Clinically relevant endpoints: death, adverse clinical events
Efficacy endpoints	Detect surrogate endpoints that are sufficiently sensitive to track the therapeutic benefit	(1) Further analysis of previously detected surrogate endpoints (2) Exploratory analysis of clinically relevant endpoints	(1) Clinically relevant endpoints <ul style="list-style-type: none"> Objective (single or composite): improved survival, reduced clinical events/number of hospitalizations Subjective: symptom score, health-related quality of life (2) Surrogate efficacy endpoints that correlate significantly with clinical endpoints

Priorities and proposals regarding clinical trial design

Before the promise of biologic-based interventions can be translated into clinical benefits, appropriate endpoints must be selected to facilitate the regulatory path that regenerative interventions are subject to. Regulatory bodies in the US and Europe stipulate generic and disease-specific requirements and rigorous criteria for good clinical practice and clinical research. These requirements are summarized in *Table 8* (reprinted from¹⁵² with permission).

Interestingly, some of the aforementioned variables have been systematically ignored or not investigated in depth in phase I/II trials. The shortcomings of previous approaches include the following:

- (1) Safety and efficacy endpoints have been used consistently, although not in a standardized/uniform manner between trials, and sometimes not correctly according to the corresponding clinical research phase. No novel endpoints that could allow us to increase our knowledge of CRM ('mechanistic' endpoints) have been put forward.
- (2) Surrogate endpoints have been assessed in several trials with very different imaging modalities and sometimes

with high inter- and intra-observer variability (e.g. echocardiography).

- (3) Traditionally, phase II clinical trials have been misused to confirm efficacy, which is the final aim of phase III studies. Ambitious efficacy results have been frequently incorporated into phase II trials with the purpose of shortcutting development expenses and obtaining scientific recognition, frequently resulting in global scientific disappointment.¹⁵³ Phase II trials should be carried out with many primary 'surrogate' endpoints (such as functional and structural measures, biomarkers, quality of life, and functional capacity) to test a range of efficacy domains and to broadly survey the possible benefits of the study product, with little regard for 'P' values. On the contrary, hard clinical endpoints (such as all-cause mortality or cause-specific mortality) that are applicable in daily clinical practice should be tested in well-designed phase III trials, although other endpoints of cardiovascular improvement/impairment may be included.¹⁵²
- (4) Patient-related modifiers: Age, gender, and comorbidities may alter the reparative proficiency of cardiac regenerative products. For instance, patients with cardiovascular disease rarely harbour cells with an acceptable regenerative capacity, an issue that we will be able to assess through the development of biomarkers and potency

Table 9 Recommendations for advanced therapy medicinal product-based translational clinical research

1. Clinical research planning should include 'proof-of-principle' studies, bio-distribution studies, and dose-escalation studies before safety and efficacy can be validated.
2. Confirmatory 'proof-of-efficacy' trials should comply with disease-specific guidelines and target specific, well-defined patient subpopulations.
3. Traditional safety and efficacy endpoints (clinical/surrogate) will be used in the future when appropriate. However, new mechanistic endpoints to corroborate unanswered hypotheses (e.g. on mechanisms of action) should be incorporated after proper validation in the preclinical field and standardized according to regulatory recommendations. In the event that surrogate endpoints are anticipated, the most reproducible techniques must be used (MRI, PET), and core laboratories should be established for centralized analysis.
4. The timing and route of delivery must also be re-considered from the early phases, taking into account the underlying disease, previous hard preclinical observations, and plausible assumptions.
5. Patient selection is crucial. Confounders such as age, gender, comorbidities, disease vulnerability and severity, and concomitant medications should always be taken into consideration when designing a new clinical trial (using predictive scores of outcomes, if possible).
6. Sample size calculations should be rigorous, and general requirements and safety/efficacy profiles for phases I, II, and III should be strictly adhered to. Specifically, phase II clinical trials must be conducted in order to generate hypotheses and foundational (although not significant) evidence for the appropriate design of meaningful confirmatory phase III clinical trials.
7. Adequate inclusion of control/placebo patients should be ensured and strict blinding methods should be followed. The risk/benefit ratio should be defined, and the interference of eventual commercial interests should be avoided.
8. The costs of clinical evaluation phases have been frequently underestimated, thus forcing the interruption of ongoing trials. Strong support and collaboration between academia and industry and an appropriated economic plan are mandatory if we are to provide patients with the most efficient treatments.

assays. Furthermore, clinical trials should include only patients under optimal medical treatments, given that concomitant medications may also modify the final effect of cell/gene therapy, either by affecting the quality of source cells or the response of the host tissue. Some scores predict the impact of these variables on the outcome of regenerative therapies,¹⁵⁴ although their use has been marginal to date.

- (5) Patient selection: Inclusion and exclusion criteria should focus on specific subpopulations with poor prognosis that could benefit the most from CRM and should clearly identify target patient populations. It is increasingly recognized that standard-of-care medications and interventions lead to a high rate of spontaneous recovery in some settings (e.g. post-AMI), thus underpowering the potential beneficial effects of CRM. On the other hand, in many cases regenerative strategies have been applied to 'low-risk' patients, thus also precluding the observation of positive beneficial results. Finally, level of treatment and disease severity must be well balanced between treatment and control groups.
- (6) Sample size has frequently been calculated by imitating the approach adopted in previous trials or based on preclinical models that do not predict human responses and on weak surrogate-based results. These calculations must be drawn only from well-founded and reliable data, once the primary endpoint and the trial objective have been identified and the magnitude of difference for detection and acceptability of errors has been specified. If data are not available, the most reliable resources must be used.
- (7) Cell dosing: As mentioned above, in most cases, the number of cells to be delivered in a clinical trial is empirically determined (e.g. subject to manufacturing capacities) or simply copied from previous trials; genuine dose-escalating studies are lacking. A feasible, safe, and eventually efficient dose of the regenerative product should be anticipated from the results of preclinical research and tested in phase I trials.
- (8) Specific studies to determine the ideal timing for cell delivery (mainly in the acute phase) are lacking. Furthermore, the effect of repetitive injections of CRM products has not been sufficiently assessed.

Other aspects that should be borne in mind when designing future clinical trials include ethics issues (e.g. the choice of control group, which is mandatory in phase II/III trials, and the correct assessment of the risk/benefit ratio), the eventual role of conflicts of interest (mainly commercial interests), and the major impact of CRM results on the scientific community and, in a broader sense, on decision makers and the public.

Table 9 shows our recommendations on translational clinical research with ATMP.

Priorities and proposals regarding regulatory hurdles

Biological products are subject to significantly different regulatory requirements throughout the world. In the United States, regulation of cellular and gene therapy products falls under the auspices of the Center for Biologics Evaluation and Research (CBER). In the European Union (EU), cellular and gene therapies are regulated by the European Medicines Agency (EMA) and undergo evaluation by the Committee of ATMP. In addition, each European country has its own agencies and procedures. In Japan, regulation is the responsibility of the Pharmaceuticals and Medical Devices Agency (PMDA), which recently prioritized biologics, thus enabling the approval of stem cell therapies with only basic demonstrations of safety and trends toward efficacy (phase II clinical trials). Similarly, other countries are developing their own regulations. Each agency periodically publishes its own guidelines, which are frequently subject to discrepancies in terms of objectives and methods. Meanwhile, alternative strategies are often used by small clinics and unscrupulous people to minimize regulatory requirements and obtain profits from patients desperate for 'magic' options.¹⁵⁵

To address the needs of patients, researchers, sponsors, and regulatory agencies, we propose the recommendations detailed in Table 10.

Table 10 Recommendations regarding regulatory hurdles

1. Additional workshops should be organized and sponsored to establish excellence networks comprising patient advocacy groups, researchers, clinical trialists, industry representatives, specialists in clinical-grade production of biologics and representatives of regulatory agencies from around the world.
2. Development of international mechanisms for the oversight of regenerative treatments. To support regulatory mechanisms that would offer patients access to CRM therapies that have proven to be safe and efficient.
3. The standardization of biological therapies presents specific characteristics that cannot be evaluated following the procedures developed for the pharmaceutical industry. Specific tracks need to be considered for measuring the safety, purity, potency, and efficacy of products.
4. Special care and protection needs to be offered to patients with critical diseases who may be subject to hype rather than true hope.

Table 11 Global aims of TACTICS

1. A comprehensive increase in our knowledge of the complex molecular, cellular, and tissue mechanisms that govern regenerative homeostasis and the cardiovascular repair process.
2. Standardization of small and large animal models for cardiovascular research so that they can reach the standards required for clinical research.
3. Collaborative performance of large-scale and optimally designed phase III multicentre clinical trials to demonstrate the clinical efficacy of regenerative therapies and to advance the standard of care in human cardiovascular medicine.
4. Transnational standardization of regulatory requirements to ensure adoption of approved therapies.
5. Communication and demonstration of best practices of all those working in the field of CRM to the scientific community, decision makers and the public. Mitigating a main risk challenging the field—the lack of credibility—requires the organization of robust evidence-based investigational team tracks with the scientific support of a large and committed multidisciplinary/multinational consortium.

Priorities and proposals regarding strategies for public and private funding

The funding challenges facing the CRM community are considerable, and the solutions are demanding. Regenerative medicine raises general questions about the appropriate allocation of government and private resources, thus casting doubt on the relative priority of the translational approach over health care in funding decisions. The research portfolios of pharmaceutical companies and non-profit organizations also reveal an array of promising lines, although neither the public sector nor the private sector can support each and every promising research project. In summary, no single strategy will likely prove itself sufficient to meet the patient's needs. In order to guarantee quality (both in healthcare and research) and private-sector financial support in the CRM field, investors and governments should be prepared to collaboratively support a range of strategies aimed at increasing funding, improving operational efficiency (both administrative and academic) and generating additional revenues through royalties, patent registration, and other models. Only countries and investors with an efficient strategy for market positioning and promotion of translational research in the healthcare system will obtain profits from the revolution of CRM and offer improvements to their citizens in terms of quality of life.

Vision and global perspectives

The TACTICS consortium is the first worldwide cooperative research network in the field of CRM. In this consensus document, the Writing Group of the TACTICS Task Force presents a critical summary of the state of the art in CRM, covering basic and

translational research, clinical practice, regulatory pathways, and funding strategies. Our end objectives are to describe the priorities and challenges in the field for the next decade and to provide evidence-based recommendations to guide the future application of regenerative products in the fight against cardiovascular failure. The most relevant challenges are summarized in *Table 11*.

In conclusion, the opportunity to optimize the regenerative medicine armamentarium and to make real progress in the regeneration of human cardiovascular tissue is through worldwide multidisciplinary cooperation. By pooling the efforts of leading expert groups, we will collectively be able to develop effective treatments that will improve the prognosis of patients with a wide range of heart and vascular diseases.

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Continued

Annex I *Continued*

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