Title: Global Overview of the Transnational Alliance for Regenerative Therapies in Cardiovascular Syndromes (TACTICS) Recommendations. A Comprehensive Series of Challenges and Priorities of Cardiovascular Regenerative Medicine

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Circulation Research Review Series

Section: Unmet Needs in Cardiovascular Science and Medicine
Title of the Series: Cardiovascular Regenerative and Reparative Medicine

Chapter 1

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Running title: Priorities of Cardiovascular Regenerative Medicine

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Introduction

Cardiovascular regenerative medicine (CRM) has been defined as an innovative research field that includes all diagnostic and therapeutic strategies aimed at restoring cardiovascular health by enhancing the innate regenerative response of cardiac and vascular tissues[1]. The Transnational Alliance for Regenerative Therapies in Cardiovascular Syndromes (TACTICS) was created in 2015 with the vision of advancing CRM through synergy of basic discoveries and translational clinical efforts in the fight against cardiovascular failure, and has grown to include more than 100 research groups worldwide[2]. This unprecedented initiative stated as specific missions the redefinition of CRM and advanced therapy regenerative products, the establishment of discovery and development priorities for the next decade and the attainment and dissemination of a consensual strategy to reinforce the field increasing its credibility.

The first milestone of TACTICS has been achieved with the publication of a Global Consensus Document[1]. However, given the amplitude and relevance of its different chapters, a more detailed description of all of them has been deemed necessary, following the same scheme of the Global Consensus Document and therefore discussing the main topics and priorities of the CRM field.

This is the final aim of this "Cardiovascular Regenerative and Reparative Medicine" Circulation Research Review Series. In this first chapter, the following ones are presented and summarized in the form of and index of consecutive manuscripts, which will cover biological fundamentals, preclinical models and all clinical research-related issues. These manuscripts will be regularly and subsequently published in this journal, on behalf of the TACTICS Consortium (Figure 1).

Chapter 2. Translational Research in Cardiovascular Repair: a Call for a Paradigm Shift

The hypothesis of CRM being able to revolutionize cardiovascular clinical practice has been based on the mainly positive and overall consistent results of preclinical research. However, the lack of homogenous definitions in preclinical models and of blinded and multicentre studies have hampered eventual comparisons between them, and could explain the discrepancies observed between the results of preclinical studies and human clinical trials. Despite the inherent limitations of preclinical studies (which exist not only in CRM, but in all areas of biomedical research), the need for infrastructures, protocols and technologies that would allow the translation of CRM products to clinical practice is increasingly recognised. In this chapter, specific recommendations will be made to overcome the aforementioned limitations of translational research. Specifically, solutions to guide researchers and regulatory bodies to conduct more efficient preclinical studies will be presented.

Chapter 3. Cardiovascular Regenerative Products and Mechanisms of Cardiac Regeneration

The paradigm that cardiomyocytes are terminally differentiated cells with no capacity for proliferation or renewal has been abandoned, and the heart is now recognized to be a self-renewing organ. However, the mechanisms involved in this natural process of renewal in the cardiovascular system remain under debate. From lower vertebrates to mammals,

cardiac regenerative capacities extensively differ but probably share similar pathways and mechanisms. The main effectors of the process of regeneration and their interactions will be described in this chapter (ie, cardiac aging, cell-to-cell communications, differentiation and dedifferentiation, inflammatory responses, proliferation processes, etc). Furthermore, latest achievements in the development of effective therapeutic approaches to modulate these regenerative and reparative processes will be presented.

Chapter 4. IMPACT: Preclinical Studies of Cell Therapy for Human Diseases

Focusing on cell therapies, chapter 4 will critically discuss promising preclinical studies using a variety of stem cells with innovative approaches in different models of cardiac disease. The beneficial effects of certain types of stem cells when delivered in a single dose or the use of just one cell source may be negligible. Conversely, the development of novel strategies such as the combination of different types of stem cells, the repetitive administration of cells or the implementation of techniques designed to improve engraftment and retention rates are being increasingly investigated. These innovative preclinical approaches have showed better results and will pave the way for future – and hopefully positive – clinical trials. Finally, preclinical research needs to be designed simultaneously with future clinical trials in order to ensure a cost-effective and time-efficient development.

Chapter 5. Priorities in Fundamental Regenerative Knowledge and Innovative Research: from Genes to Tissue Engineering

Basic research is the cornerstone of clinical advances. This chapter will summarize and discuss those areas of research where more extensive knowledge is needed in order to develop more effective regenerative treatments. The identification of biological processes involved in embryonic development and in innate mechanisms of regeneration are mandatory in order to identify therapeutic targets and novel strategies for the enhancement of endogenous regenerative responses. In addition, disruptive therapies such as cell-free modalities, safe and controlled gene-editing technologies, tissue engineering approaches or even the creation of chimeric organs are under evaluation and will be critically discussed.

Chapter 6. Identification of Regenerative Products Ready for Clinical Research

This chapter will be focused on advanced therapy medicinal products for cardiac and vascular repair. First, second and third-generation stem cells, episomes and gene therapies, cell-free solutions (ie, mRNA, microvesicles, exosomes and growth factors), biomaterials and tissue engineering products will be presented and analysed in terms of readiness and convenience for full clinical assessment. Taking into account that all these products and all clinical research tracks must be grounded on evidence-based translational rationales and have to undergo the traditional four phases of clinical research, a critical reflection will be offered with a special focus on unsettled issues with implications on outcomes. In some cases, these uncertainties should be further explored before moving into new clinical trials. They include best tolerated doses, benefits of repetitive administration, optimal timing, comparative experiments with different products, combinatorial approaches and most efficient delivery modalities for each product and condition. Final considerations will be also offered on product standardization and on mechanistic trials that will increase our knowledge on mechanisms of action.

Chapter 7. Priorities of Clinical Cardiovascular Regenerative Research. Design of Clinical Trials. Methods for Delivery, Tracking and Assessment

One of the most controversial debates in the CRM field is the design of future clinical trials. Indeed, the main obstacles that clinical CRM has encountered since its inception and that have hampered its large-scale adoption in daily clinical practice include heterogeneity of study protocols and underestimation of aspects such as patient selection, delivery methods and imaging-based assessment of the outcomes. Furthermore, surrogate and clinical endpoints have been inconsistently used and are usually misinterpreted. In this chapter, objectives, selection criteria, safety and efficacy endpoints (hard, surrogate and composite), sample size calculation, design modalities and clinical research phases will be discussed in the light of available evidence.

As part of trial design, the use of biomarkers, new imaging and tracking modalities and reflections on delivery techniques will be included. Special emphasis will be laid on the development of minimally invasive methodologies for tissue engineering solutions and on the optimization of delivery modalities to improve accuracy by means of fusion imaging tools. Finally, new automated software to guide and improve product delivery and retention (ie, real-time integration of computed tomography, magnetic resonance and ultrasound into the catheter navigation process) and novel imaging technologies for *in vivo* tracking of regenerative products in humans will be presented.

Chapter 8. From the Lab to the Market: Recommendations Regarding Regulatory, Funding Strategies and Final Interaction with Public Opinion

The goal of this chapter will be to provide recommendations regarding important aspects which may accelerate the translation of advanced therapy regenerative products into the clinics. The standardization of biological therapies presents specific characteristics that cannot be evaluated following the procedures developed for the pharmaceutical industry. The essential role of competent authorities to identify international mechanisms for the oversight of regenerative treatments (avoiding unregulated scenarios) and the need for customized regulatory pathways that would facilitate CRM research, will be discussed. Linked with this, funding strategies may be enhanced by cooperative networks (ie, TACTICS), underscoring the importance of true international collaboration to move the field definitely forward. Last but not least, the interaction with public opinion, media, decision makers and the rest of the scientific community is of utmost importance, given the negative climate that has been created around the whole field during the last years and that should be revisited.

Chapter 9. Role of Immunology and Inflammation on Cardiovascular Regenerative Medicine

The biological basis of all types of damage to the cardiovascular system involve cellular effectors and molecular signals that regulate the inflammatory and reparative responses after those insults. The field of CRM is closely related to these mechanisms, which are not yet completely understood and which may be modulated to improve the efficacy of regenerative products in patients with acute myocardial infarction, stroke, peripheral artery disease and heart failure. Furthermore, the increasing use of allogeneic products because of their distinctive immunological behavior with immunomodulatory beneficial

effects, their strictly quality-controlled manufacturing and their readily availability, warrant further investigations. Both topics (ie, inflammation and immunology) will be discussed in this chapter.

Summary

The main objective of this series of articles is to describe and reflect on the priorities of cardiovascular regenerative research from a critical point of view, promoting an open discussion about the lights and shadows of the field, increasing its credibility and facilitating the advance of CRM to definitely repair the failing cardiovascular system.

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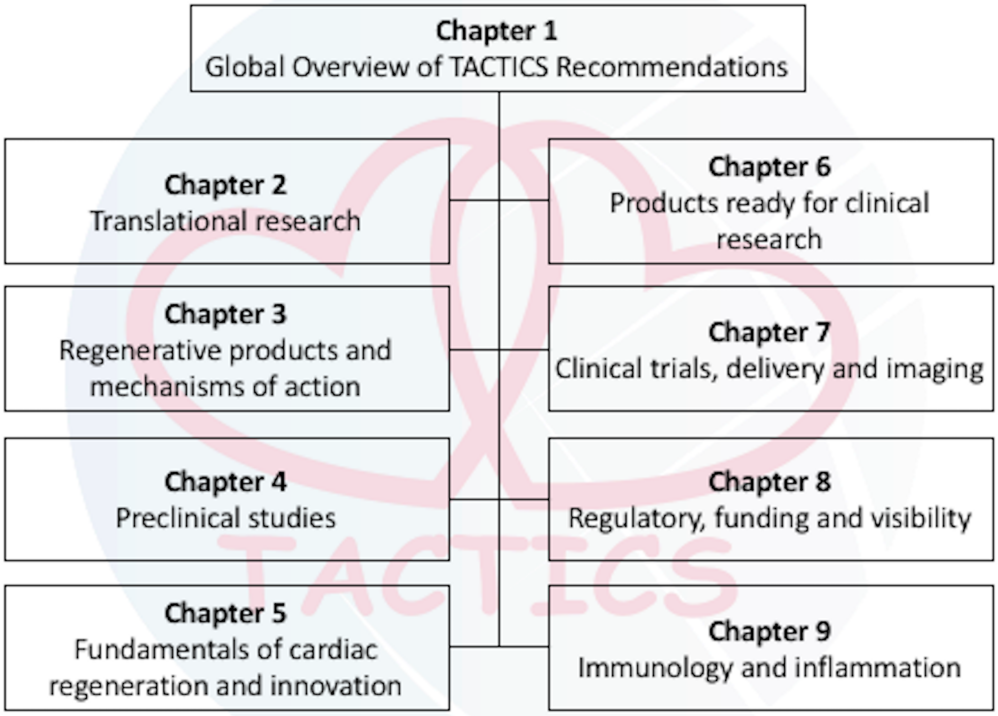
FIGURE LEGEND

Figure 1. Schematic representation of all manuscripts included in this Review Series. TACTICS: Transnational Alliance for Regenerative Therapies in Cardiovascular Syndromes.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