

General Overview of the 14th International Symposium on Stem Cell Therapy and Cardiovascular Innovations Working Progress of a Global Initiative in 2017

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Regenerative therapies with cardiac and vascular applications represent one of the most promising options in the fight against cardiovascular failure. Since 2004, the International Symposium on Cell Therapy and Cardiovascular Innovations (TECAM, www.cardiovascularcelltherapy.com) has been held in Spain on a yearly basis to gather the most important research groups of clinicians and scientists worldwide and to discuss the progress and hurdles of Cardiovascular Regenerative Medicine (CRM) in an open forum. The latest edition of the TECAM conference took place in Madrid on June the 15th and the 16th. Recent breakthroughs and future steps were debated during the meeting, with a special focus on the most recent achievements of the Transnational AllianCe for regenerative Therapies In Cardiovascular Syndromes (TACTICS, www.tacticsalliance.org) group and are summarized in this article.

Opening Lectures on Emerging Technologies

The opening session started with a keynote conference delivered by Dr Michael Laflamme, who reflected on the difficulties for obtaining real cardiac regeneration with old types of stem cells. He therefore focused his talk on pluripotent stem cells, the one cell type that has demonstrated robust differentiation into cardiomyocytes. After presenting the important functional benefits of human embryonic stem cell (ESC)-derived cardiomyocytes in murine models and recognizing safety concerns (ie, ventricular arrhythmias) in primates and swine models of myocardial scar, he concluded that large-scale re-muscularization is possible using this type of human-derived cells. In the second talk, Dr Juan Carlos Izpisua presented the latest approaches to manipulate the genome in cells that do not divide. After describing how CRISPR/Cas9 can be used to induce double-strand breaks and nonhomologous end joining-based repair on the DNA, he explained the Homology Independent Targeted Integration technology that has been designed by his group. This novel tool for gene editing has been used to correct mutations in nondividing cells such as neurons and cardiomyocytes, with impressive results in murine

models of retinitis pigmentosa and progeroid syndromes. In the last talk, Dr Joseph Wu commented on the use of induced pluripotent stem cell (iPSC) platforms for elucidating disease mechanisms, for precision medicine (ie, developing human iPSC-derived cardiomyocytes from a specific patient to predict chemotherapy-induced cardiomyopathy) and for performing clinical trials in a dish (ie, to identify eventual responders).

Update on Preclinical and Clinical Breakthroughs in the Field of Cardiac Regenerative Medicine

The “What’s New in Cardiovascular Regenerative Medicine?” session presented the latest achievements of the field in 2 parts, one dedicated to preclinical research and another one focused on clinical trials. In the former, Dr Stefanie Dimmeler summarized the role and the regulation of fibroblasts in the ischemic myocardium and the ways we are investigating to modulate the function of these cells to promote myocardial repair (ie, inhibition of PAD4 [peptidylarginine deiminase 4] or micro-RNA). In the last part of her talk, she commented on the contribution of the endothelial-to-mesenchymal transition to neovascularization and fibrosis. Dr Mark Sussman gave an outstanding lecture on strategies to potentiate and to empower the survival, the proliferation and the regenerative/repairative capacity of stem cells, and also on the use of gene therapy to overcome existing limitations of stem cell-based therapies. Dr Yuji Shiba presented the results of his group on generating cardiomyocytes from human ESC/iPSC and on the allogeneic use of these cells in primates. Once transplanted into a major histocompatibility complex-matched model, allogeneic iPSC-derived cardiomyocytes engrafted and survived at 12 weeks without tumor formation, improved contractile function, and electrically coupled with host cardiomyocytes. Dr Roberto Bolli delivered a disruptive lecture on how repetitive cardiac stem cell administration may overcome the low engraftment rates. By presenting 2 studies in murine models of old myocardial infarction, he concluded that repeated administrations of cells showed cumulative paracrine beneficial effects and were markedly more effective than a single administration

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in terms of new cardiomyocytes formation, cardiac function, capillary density, fibrosis, and inflammation modulation. Dr Paolo Madeddu summarized the role of adventitial pericytes in myocardial repair and showed that their transplantation in murine and swine models is feasible, safe, and immunologically acceptable, inducing proangiogenic and antifibrotic benefits. Dr Steven Chamuleau commented on preclinical experiences with cardiac stem cell for ischemic heart disease, reflecting on the appropriateness of preclinical models, on the importance of the translational axis and on strategies to improve the quality of preclinical research (ie, assessing reproducibility of experiments, reducing publication bias, encouraging prospective registration, and performing preclinical meta-analyses).

The clinical part of the session was opened by Dr Timothy Henry, who presented the results of the ix-CELL DCM trial (Ixmyelocel-T for Patients With Ischaemic Heart Failure). In patients with class III/IV heart failure (HF) caused by ischemic cardiomyopathy, transendocardial injections of autologous, bone marrow–derived mesenchymal stem cells (MSC), and M2-like macrophages reduced mortality, cardiac hospitalizations, and serious adverse events at 12 months, with no changes in left ventricular ejection fraction (LVEF) or LV volumes, New York Heart Association (NYHA) class, or 6-minute walk test. Dr Andre Terzic referred to another novel cell type, autologous cardiopoietic MSC, which were studied in the CHART-1 trial (Congestive Heart Failure Cardiopoietic Regenerative Therapy Trial). The injection of these cells in patients with advanced ischemic HF did not show an improvement of all-cause mortality, HF events, or functional benefits. However, patients with baseline LV end-diastolic volume of 200 to 370 mL and those treated with ≤ 19 injections showed a significant reduction in mortality and HF readmissions. About the suitability of allogeneic versus autologous sources, Dr Joshua Hare commented on the results of the POSEIDON-DCM trial (Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis in Dilated Cardiomyopathy), in which both autologous and allogeneic bone marrow–derived MSC showed safety and exerted beneficial effects in patients with nonischemic dilated cardiomyopathy. However, better results were obtained with allogeneic MSC in terms of LVEF, 6-minute walk test, MLHFQ (Minnesota Living With Heart Failure Questionnaire) scores, endothelial function, major adverse cardiac events, and tumor necrosis factor- α reduction. By presenting the BOOST-2 trial (Randomised-Controlled Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration Trial-2), Dr Kai Wollert demonstrated that bone marrow mononuclear cells did not improve LVEF at 6 months as assessed by magnetic resonance imaging in patients with ST-segment–elevation myocardial infarction (STEMI) and moderately reduced LVEF. Low and high doses were equally ineffective, and no significant impact was observed on any secondary end point either. Moving into the field of tissue engineering, Dr Thomas Povsic presented the results of the PRESERVATION trial (Prevention of Remodeling of the Ventricle and Congestive Heart Failure After Acute Myocardial Infarction), the first-in-man trial with intracoronary injection of an inert bioabsorbable cardiac matrix after STEMI. This approach did not prevent LV remodeling or the occurrence of HF, and secondary end points (ie, NYHA class and functional capacity) did not show clinical

differences between matrix and saline-treated patients. Dr Mariann Gyöngyösi draw the attention of the audience to her latest individual patient data-based meta-analysis of intramyocardial cell-based trials in patients with HF. After pooling data from 8 different trials, she confirmed that stem cells decreased LV end-diastolic volume and infarct size, increased LVEF and reduced mortality, cardiac and cerebrovascular events although some important trials were not included and a large heterogeneity was observed. Finally, Dr Douglas Losordo joined with Dr Thomas Povsic to offer to the audience their insights after treating >700 refractory angina patients with CD34⁺ cells. They concluded that these cells resulted in clinically and statistically significant durable improvements in exercise capacity and in angina frequency, reducing major adverse cardiac events and even mortality rates.

Acute Myocardial Infarction, End Points, and Pluripotent Stem Cells: The 2017 Debates

One of the most interesting sessions was dedicated to debate 3 hot topics: the need of regenerative therapies in STEMI, the best end points for future clinical trials, and the readiness for using iPSC/ESC in the clinical scenario, all of them presented with pros and cons by key opinion leaders. In the first debate, the negative vision was delivered by Dr Jens Kastrup, who recognized that the effect of cells after STEMI is small and not significant. The second point of his talk was that cells may have been delivered earlier after STEMI. Finally, he underscored the low mortality rates of STEMI with the current standard-of-care, which would force us to include 20 000 to 40 000 patients to show meaningful differences with regenerative therapies, concluding to fully stop stem cell research in this setting. Dr Andreas Zeiher defended the opposite message, indicating that we still face patients with low post-STEMI LVEF and high long-term mortality and major adverse cardiac event rates. These specific subpopulations may benefit from regenerative therapies and should be our target like in the case of the ongoing BAMI trial (The Effect of Intracoronary Reinfusion of Bone Marrow-Derived Mononuclear Cells on all Cause-Mortality in Acute Myocardial Infarction). During the second debate, Dr Filippo Crea elegantly showed why surrogate end points have frequently failed in predicting clinical outcomes with several examples of drug clinical trials (ie, detrimental off target effects, underestimation of side effects, wrong pathophysiological premises, or wrong study population) to finally advocate for mortality and hard clinical end points. Conversely, Dr Bernard Gersh reflected on the difficulties of developing large-size clinical trials with hard end points nowadays. He suggested to rigorously scrutiny previous large trials when designing new ones, to properly select surrogate end points, and offered some considerations on the limitations of quality of life as an end point. The last debate was opened by Dr Philippe Menasché, who summarized currently ongoing clinical trials with ESC-derived stem cells, indicated the advantages of using cardiac-committed cells in comparison with extracardiac lineages (ie, better engraftment, superior functional benefits, and higher paracrine potency). On the other hand, Dr Roberto Bolli described the good results of adult stem cells in patients with HF and highlighted the problems

with ESC and iPSC: ethical and regulatory issues, risk of tumor formation and genetic abnormalities, need for long-term immunosuppression, unclear long-term engraftment, and heterogeneous phenotypes and maturity. These, together with the lack of preclinical evidence of greater therapeutic efficacy, the absence of any clinical data, and the greater cost-effectiveness, were the reasons he argued to continue researching with adult multipotent stem cells.

New Approaches and Novel Cardiac Regenerative Products

Other breakthroughs, mainly related to new allogeneic cell products, were presented in the last session of the first day. In the basic research field, recent discoveries in Dr Doris Taylor laboratory pointed at comorbidities and cardiovascular risk factors as important predictors of bone marrow mononuclear cell numbers and quality (ie, age, sex, hyperlipidemia, hypertension, smoking, glucose, and creatinine levels), in a biorepository analysis of the TIME (Timing In Myocardial infarction Evaluation) and Late TIME trials based on the GRACE (Global Registry of Acute Coronary Events) score. Dr Eduardo Marbán presented a detailed description of novel applications of allogeneic cardiosphere-derived cells, such as HF with preserved ejection fraction (Regress-HFpEF), pulmonary hypertension (ALPHA), and duchenne muscular dystrophy (HOPE), summarizing some preliminary and promising results of those trials. Dr Jens Kastrup moved then to allogeneic adipose-derived stem cells to update the audience on the progress of the SCIENCE trial (Stem Cell Therapy in Ischemic Non-Treatable Cardiac Disease), in which these cells are being injected in patients with advanced ischemic HF. Specifically, he revised the design of the trial and commented on the regulatory process that had to be followed before starting such as a multicenter European trial. Finally, Dr Emerson Perin presented the results of the phase II trial with allogeneic MSC in patients with ischemic and nonischemic

HF before further discussing the phase III trial (DREAM-HF [Efficacy and Safety of Allogeneic Mesenchymal Precursor Cells (Rexlemestrol-L) for the Treatment of Heart Failure]). About the design issues, he explained how the trial had undergone a transformation from a 1700- to a 600-patient trial and gave an update on the recruitment status in the United States.

Recent Contributions Presented by Young Investigators

Friday sessions started with the presentation of the 2 winner works of the Best Poster Communication Award. Dr Ana Rico reported the results of an elegant murine experiment to analyze the effect of extracellular vesicles from bone marrow-derived MSC in a model of doxorubicin-induced cardiotoxicity. These vesicles were able to incorporate into murine cardiomyocytes and to reduce their damage after doxorubicin exposure. Dr Claudia Báez-Díaz presented her study on the effect of the intracoronary administration of porcine cardiac stem cell on myocardial recovery in a swine STEMI model: cardiac stem cell increased the myocardial salvage index and reduced myocardial edema and LV end-diastolic volume.

In the following session, Dr Saranya Wyles described the educational pathways in The Center for Regenerative Medicine (Mayo Clinic) and the principles that are followed to build the next-generation workforce throughout medical school training. Dr Reem Al-Daccak reviewed the pros and cons of allogenicity, explaining the cellular and humoral responses that allogeneic cells may provoke and several available tools of immunologic selection and modulation for a successful stem cell-based repair. Dr Elena Sommariva presented the role of cardiac MSC in the pathogenesis of arrhythmogenic cardiomyopathy. She also demonstrated that MSC phenotype is dependent on PKP2 deficiency and described the adipogenic mechanisms of these cells. In the last talk of this session, Dr Lior Zangi reported a new technology based on the generation of chemically modified mRNA to manipulate the

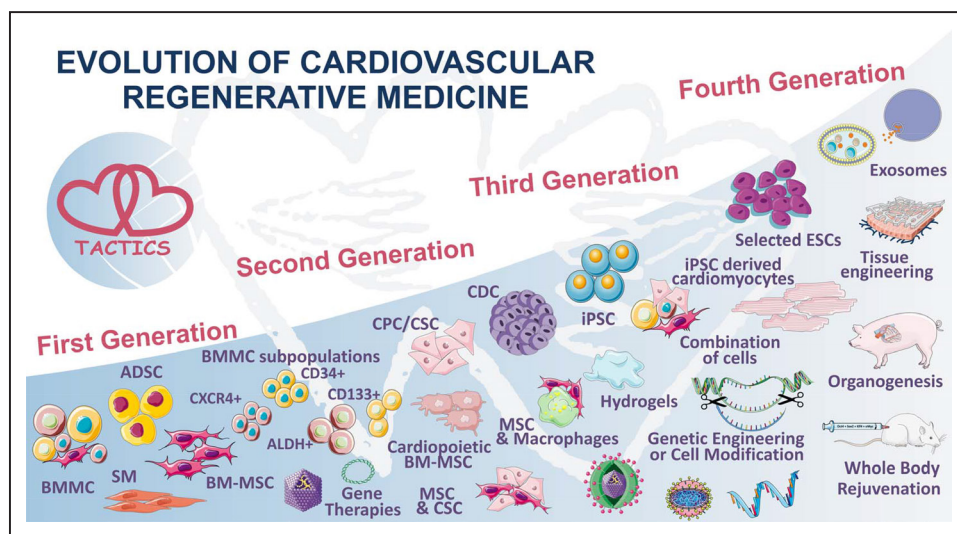


Figure 1. Schematic illustration of the evolution of Cardiovascular Regenerative Medicine according to the different products under evaluation. ADSC indicates adipose tissue-derived stem cells; BMMC, bone marrow mononuclear cells; BM-MSC, bone marrow-derived mesenchymal stem cells; CDC, cardiosphere-derived cells; CPC, cardiac progenitor cells; CSC, cardiac stem cells; ESC, embryonic stem cells; iPSC, induced pluripotent stem cells; MSC, mesenchymal stem cells; and SM, skeletal myoblasts.



Figure 2. Pictures during the meeting.

A, “What’s New in Cardiovascular Regenerative Medicine” session, **(B)** Keynote lectures, **(C)** Dr Doris Taylor, and **(D)** Dr Jens Kastrup, recipients of the Fourth Madrid Cardiac Regeneration Awards in the fields of basic and clinical research, respectively.

gene program of the adult mammalian heart with the final aim of reactivating adult cardiomyocytes proliferation.

Milestones, Predictions, and Next Steps of International Alliances

One of the main sessions of the conference, entitled “The field after the TACTICS enterprise”, had the goal of sharing with the audience the last achievements of the TACTICS task force and its roadmap for the next year. Dr Lina Badimon announced 2 important milestones of TACTICS in Europe: the publication of the Global Position Paper on Cardiovascular Regenerative Medicine in the *European Heart Journal* and the preparation of a new Working Group on Cardiovascular Regenerative and Reparative Medicine inside the European Society of Cardiology (ESC). Dr Eduardo Marbán presented some data on allogeneic cells, cardiosphere-derived cells, exosomes, and mRNA that will be critical to identify next-generation therapeutics. Dr Anthony DeMaria closed this session with a brilliant lecture emphasizing unanswered questions such as the ideal type of regenerative product (Figure 1), the optimal dosage, and the best delivery route and tracking technology for each condition. He finalized with some take-home messages: (1) cell therapy is not ready for clinical application, but (2) is ready for phase III pivotal clinical trials; (3) clinical trials must be meticulously designed and performed; and (4) concomitant basic research must continue and guide further clinical evaluations.

Closing Remarks

The 2017 conference came to an end with 2 master lectures. Dr Valentín Fuster delivered a comprehensive review of the main priorities of CRM by following the chapters of the Global Position Paper and by further commenting on other crucial aspects such as repetitive treatments, cell-free products, tissue engineering approaches, and in situ cell reprogramming (Figure 1). Dr Bernard Gersh envisioned the future management of chronic HF by developing new pharmacological molecules, untangling the molecular web of this condition, improving surgical approaches, optimizing cell and gene therapy, creating neo-organs, and probably by expanding nanotechnology.

The conference was closed with the recognition of 2 researchers with the Fourth Madrid Cardiac Regeneration

Awards. Dr Doris Taylor and Dr Jens Kastrup were awarded with these prestigious prizes in the fields of basic and clinical research, respectively, recognizing their outstanding contributions in the field (Figure 2).

Finally, the closing remarks of Dr Fernández-Avilés were rather optimistic. Although fundamentals of cardiac repair are not yet completely understood and some negligible outcomes from current cell therapy trials are being reported (especially in the STEMI setting), new evidences in the fields of HF and refractory angina and with new cell types are encouraging. Furthermore, the creation of truly cooperative and international networks (ie, TACTICS) and of a ESC Working Group on CRM will undoubtedly move the field forward, preventing further erosion of the field and increasing its credibility with pertinent, collaborative, and well-designed preclinical and clinical trials.

In 2018, the 15th edition of the International Symposium on Cell Therapy and Cardiovascular Innovations will be held on May the 10 and the 11 in Madrid. Once again, it will provide all CRM scientists with an excellent opportunity to leverage basic discoveries, translational efforts, and clinical investigation tracks with the final objective of developing effective treatments that will definitely change the standard-of-care of cardiovascular diseases.

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Disclosures

None.

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