More than 20 years after the introduction of stem cells as a potential tool for cardiovascular regenerative medicine (CRM), the possibility of modulating cardiac regeneration in humans is still considered the most promising alternative to overcome the limitations of existent treatments for cardiovascular failure. However, CRM has not yet showed clear improvements over standard therapies in terms of clinical outcomes. Therefore, there is a compelling need and willingness among clinicians and scientists to discuss progress and hurdles of CRM in an open forum. This has been the aim of the International Symposium on Cell Therapy and Cardiovascular Innovations (TECAM, http://www.cardiovascularcelltherapy.com) since its inception 14 years ago. The latest edition of the TECAM conference was held in Madrid last May 12th and 13th. During the meeting, recent breakthroughs, open questions, and future steps were debated by the main experts worldwide and are summarized in this article.

Cardiac Regeneration: A Complex yet Real Phenomenon

The opening session started with a keynote conference delivered by Dr Olaf Bergmann who updated his results about the turnover of cardiac cells throughout human life by means of elegant analysis of nuclear bomb test-derived 14C DNA integration. These recent results corroborate the capacity of adult human hearts to generate new cardiac cells that could counteract the loss of cardiomyocytes due to varying causes. One of the more heated debates of the conference was led by Dr Piero Anversa and Dr Bergmann, since their respective results regarding new cardiomyocyte generation rates differ from 1% to 25% per year. Despite those discrepancies in the specific numbers, to be clarified in future years, the most important message is the unquestionable evidence that supports the existence of a conserved mechanism of novel cardiomyocyte generation in humans. The open question remains: which are the best strategies to potentiate this phenomenon, especially in damaged hearts?

In line with that, Dr Maximiliam Buja and Dr Juan Carlos Izpisúa provided their perspectives on the biological basis of cardiac regeneration and repair, both in animals and in humans. The accumulated knowledge depicts a complex mechanism of natural cardiomyocyte renewal mediated by a combination of endogenous cardiac stem cells, circulating stem cells, and cardiomyocyte dedifferentiation. This natural regeneration phenomenon is limited during the adult life of most mammalians, including humans. To overcome this limitation, different types of exogenous stem cells have been administered into the myocardium, demonstrating moderate improvements in global heart function. However, the heterogeneity of these biological treatments has complicated the interpretation of most study outcomes, with scarce evidence on mechanisms of action. Direct differentiation of exogenous cells into novel cardiac tissue is increasingly seen as too complex a process with a large number of impediments, from the ineffective homing and engraftment of implanted cells to the low rates of cardiomyocyte differentiation. One attractive alternative therapeutic strategy involves the stimulation of endogenous repair mechanisms by means of the so-called paracrine effect. This has been the main goal of first-generation stem cell trials, and now also of novel noncellular regenerative products. New paradigms and strategies based on a better understanding of the fundamental biology of cardiac repair are being approached and were discussed in depth during the conference.

Cardiac Regenerative Medicine: Cell Versus Cells, Cells Again, Beyond Cells

Stem cell–based treatments are still the main strategy of CRM. However, the large number of different types of cells and delivery approaches has created a complex scenario in which several fundamental questions remain open. The “What’s New in Cardiovascular Regenerative Medicine?” session of the TECAM conference gave a glimpse of where the main discussions are (Figure 1). Dr Giulio Pompolio delivered an intriguing talk comparing the state-of-the-art of different cellular products that are currently under investigation, from first-generation cells (bone marrow–derived mononuclear cells [BM-MNC] and mesenchymal stem cells), to subsequent generations of cells (cardiac stem cells, embryonic stem cells), and pluripotent-induced stem cells. This varying scenario prevents an easy efficacy comparison between cell types, even for the same type of cells. To date, only skeletal muscle cells have been discarded because of their arrhythmogenic side effects. Other cell types seem to have similar effects, moderately positive when systematically compared, but with a high variability between patients. In fact, the combination of different cell...
types, as described by Dr. Joshua Hare, is being considered an interesting strategy that could further enhance the effectiveness of CRM by mixing the effects of the stimulation of endogenous regeneration and the direct differentiation of implanted cells.

Regarding other long-standing topics, such as the suitability of allogenic versus autologous sources, Dr. Annarosa Leri commented on the potential loss of functionality of stem cells associated with aging and comorbidities, which could hamper the benefits of autologous treatments and could explain the large variability in patient outcomes. Another recurrent proposal to increase stem cell efficacy is the repetitive delivery of cells. Just as only continued cardiovascular drug treatments can produce clinical benefits, maybe only repeated implantation of cells would allow reproducible positive clinical effects in all patients. In this sense, Dr. Birgit Assmus presented the results of the REPEAT clinical trial, whose aim is to compare single with repeated intracoronary infusions of autologous BM-MNC (NCT01693042) in 300 patients. REPEAT positive results at 2-year follow-up provide the rationale for repeated intracoronary applications of such regenerative products.

Moving into the latest achievements with second-generation cell types, the war between cardiac progenitor cell (CPC) believers and nonbelievers was brilliantly summarized by Dr. Mark A. Sussman. Recent discoveries in Dr. Sussman’s laboratory point to c-kit expression as a necessary but not sufficient marker to identify efficient cardiac stem cells. The enhancement of certain proteins, such as the G protein-coupled receptor kinase 2-derived inhibitory peptide, may promote survival and proliferation of injected CPC and ensure their effectiveness.

In terms of regenerative strategies that do not only include stem cells, Dr. Doris Taylor discussed the importance of using tissue engineering approaches to increase the efficacy of CRM. The analysis of decellularized extracellular matrix demonstrates the proteomic complexity and the relevance of this structure, and how decellularized extracellular matrix can affect the behavior of stem cells, boosting their capability to proliferate and mature. Dr. María Angeles Espinosa further discussed this source of bioengineered scaffolds by presenting their positive results with human hearts to obtain cadaveric decellularized extracellular matrix following Dr. Taylor’s methodology and with eventual clinical applications. Furthermore, even without cells and without keeping the 3-dimensional structure of the extracellular matrix, the pathways by which decellularized extracellular matrix–derived hydrogels can benefit postmyocardial infarction patients were presented by Dr. Karen L. Christman. Their results indicate that myocardial extracellular matrix alters the inflammatory response and metabolic enzyme expression, reduces cardiomyocyte apoptosis, enhances neovascularization, diminishes cardiac hypertrophy and fibrosis by upregulating cardiac transcription factors, increases progenitor cell recruitment, and improves global cardiac function and hemodynamics. The reproducibility of these results in humans is being evaluated in the VentriGel phase I trial (NCT02305602).

Despite the fact that the administration of hydrogels without cells may facilitate clinical procedures and regulatory barriers, the combination of both cells and biomaterials is becoming technically possible and could be superior to those components separately. This concept was illustrated by Dr. Philippe Menasché who presented preliminary results of the ESCORT trial (Transplantation of Human Embryonic Stem Cell-derived Progenitors in Severe Heart Failure), designed to assess the feasibility and safety of the transplantation of human embryonic stem cell–derived cardiac-committed CD15+/Is1- progenitor cells in patients with severe heart failure. The methodology to implant those selected hESCs (human embryonic stem cells) makes use of a fibrin patch, which is slid
into a pericardial pocket over the epicardial surface of the infarct area. In addition to this challenging study, Dr Menasché opened the discussion about stem cell–based regenerative therapies without the need of implanting cells. The new paradigm is that secreted extracellular vesicles, including exosomes and microparticles, may orchestrate the same paracrine therapeutic effects on endogenous repair pathways without the need of implanting whole cells. These vesicles could be used alone or as functionalized biomaterials. From the group of Dr Eduardo Marban, the talk of Dr Luis R. Borlado featured exosomes from cardiosphere-derived cells as a critical agent of these cells’ regenerative capacity. Cardiosphere-derived cell exosomes contain a distinctive complement of microRNAs, particularly miR-146a, which has been able to reproduce some (but not all) of the benefits of cardiosphere-derived cell exosomes. Furthermore, Dr Susmita Sahoo described her results showing how the positive effects of exosomes derived from human CD34+ peripheral blood–derived hematopoietic stem cells were lost when the miR-126 is absent.

The important role of exosomes in cardiac cell-to-cell communication has helped us to elucidate the mechanisms of this complex system. A significant breakthrough in this area was presented by Dr Pilar Sepúlveda as one of the winners of the Best Poster Communication. Dr Sepúlveda presented her findings, which establish that cardiomyocyte exosomes are key components of the cardioendothelial communication system, and are also able to modulate glucose transport. The other Best Poster Communication award-winning group was the one of Dr Antonio Carlos Campos de Carvalho who reported their results with embryonic stem cell–derived cardiomyocytes in a rodent model of dilated cardiomyopathy, demonstrating that their beneficial effects in terms of ventricular function are mediated through paracrine mechanisms.

Gene therapies are also being increasingly investigated in CRM, and they were represented during the conference. Dr Marc S. Penn discussed the results of the STOP-HF (Study to Evaluate the Safety and Efficacy of JVS-100 Administered to Adults With Ischemic Heart Failure) randomized phase II trial in which the safety and efficacy of a single administration of nonviral plasmid-encoding stromal cell–derived factor-1 was evaluated in patients with ischemic heart failure. Despite the fact that plasmid-encoding stromal cell–derived factor-1 failed to demonstrate previously reported efficacy results, its safety profile supports repetitive treatment, and its impact on left ventricular remodeling suggests its potential to improve outcomes in larger future trials. Also in the gene therapy field, Dr Domenico D’Amario presented a personalized gene therapy for patients affected by Duchenne cardiomyopathy. Preliminary results demonstrate the feasibility to genetically modify and expand cardiac stem cells from those patients for a personalized administration.

The Preclinical Research Dilemma: Lost in Translation?
The debate regarding preclinical research methodology and its translation to the clinical standard-of-care was intense. Dr John Martin advocated a fast evaluation in humans of novel products, limiting preclinical research to safety evaluation, arguing that we do not understand the mechanisms of action of most of the clinical treatments that are being applied in the daily practice yet. Dr Stefannie Dimmelayer emphatically stated that only thanks to preclinical research do we have now the possibility to propose regenerative treatments. Following this idea, Dr Steven Chamuleau described the different stages of preclinical research, from tempting approaches in small animal models to efficacy evaluation in large mammals, and honestly commented on irreproducible preclinical results. He advocated for the same rules and methodologies used in clinical research to be applied in preclinical research. Specifically, the public diffusion of trial objectives and methodology in an independent platform—similar to clinicaltrials.gov—would increase the credibility of positive results and would recognize all the efforts that end with negative but valuable results.

As an example of how this could be developed, Dr Roberto Bolli presented the Consortium for Preclinical Assessment of Cardioprotective Therapies (CAESAR), a consortium of core laboratories with extensive expertise in large animal models that makes these complex models available to the scientific community and enables preclinical research to be conducted with the same standards of rigor as clinical research. Dr Bolli’s final remark was that progress of cell therapy will be hindered, and translation into human therapies will be difficult, if preclinical research is not rigorously developed.

CRM: Beyond Left Ventricular Dysfunction
Although CRM has been mainly focused on the regeneration of cardiac damaged tissue after an ischemic event, the application of these novel technologies to other cardiovascular diseases is showing promising results. Dr Timothy J. Nelson presented his experience with stem cells in children with hypoplastic left ventricle, whereas Dr Emerson C. Perin discussed the rationale of the PACE trial (Patients with Intermittent Claudication Injected with Aldehyde Dehydrogenase Bright Cells), focused on peripheral artery disease with the purpose to find out if aldehyde dehydrogenase-bright bone marrow–derived stem cells have a beneficial angiogenic effect in patients having critical limb ischemia. Moving to the valvular heart disease scenario, Dr Amir Lerman presented impressive preclinical results with the manufacturing of tissue engineered aortic valves, both biological (decellularized from porcine valves) or synthetic, and also preliminary results of recellularization of those constructs. Moreover, he commented on the first exploratory clinical trial to evaluate the safety and potential bioactivity of stem cells in patients with coronary microvascular dysfunction. Finally, the extracardiac applications of regenerative therapies were addressed by Dr Lilach Lerman, with the use of mesenchymal stem cells in patients with ischemic kidney disease.

The Clinical Scenario: Learning From the Experience
A highlight of the meeting was the critical evaluation of main clinical trials and recent breakthroughs. Dr Ricardo Sanz-Ruiz presented the results of the TECAM randomized trial (NCT00984178), in which 3 different bone marrow–derived stem cell approaches after an acute myocardial
infarction (AMI) produced a significant reduction in infarct size, although they did not improve left ventricular ejection fraction or volumes compared with standard-of-care. Dr Timothy Henry discussed the results of the recently published ixCELL-DCM phase II trial (The Effect of Intracoronary Reinfusion of Bone Marrow-derived Mononuclear Cells (BM-MNC) on All Cause Mortality in Acute Myocardial Infarction; NCT01670981), designed to assess the efficacy, safety, and tolerability of ixmyeloce-l-T delivery in patients with end-stage heart failure. This product, a combination of bone marrow–derived CD90+ mesenchymal stem cells and CD45–CD14+–activated macrophages, showed a 37% reduction of cardiac events compared with placebo at 12-month follow-up. Moreover, Dr Andreas Zeiher summarized their experience with the currently ongoing BAMI phase III clinical trial (NCT01569178), whose aim is to demonstrate the real clinical benefit of autologous BM-MNC in post-AMI patients with reduced left ventricular ejection fraction (<45%). This trial, which is funded purely by academic grants (EU-FP7) and has faced long delays because of regulatory requirements, will lead the way for subsequent generations of regenerative products to be investigated in large clinical trials. Interestingly, Dr Peter-Paul Zwetsloot reflected on the use of the first developed model to predict the response to autologous BM-MNC after AMI based on the REPAIR-AMI trial (Intracoronary Progenitor Cells in Acute Myocardial Infarction) results. With the same type of cells, Dr Anthony Mathur presented the results of the REGENERATE-DCM trial (Bone Marrow Derived Adult Stem Cells for Dilated Cardiomyopathy; NCT01302171), demonstrating that intracoronary infusion of those cells after G-CSF (granulocyte-colony stimulating factor) administration resulted in left ventricular ejection fraction improvements in patients with dilated cardiomyopathy, which were maintained to 1 year. Dr Neil Howell moved the discussion to recent breakthroughs of left ventricular assist devices, and finally Dr Enca Martin-Rendon presented the latest evidences obtained from systematic reviews and meta-analyses with BM-MNC, showing that there is insufficient evidence of a beneficial effect after AMI and revascularization, but robust evidence of such a beneficial effect on reducing mortality in patients with heart failure.

Planning the future: the TACTICS Alliance
One of the main sessions of the conference, entitled “The Field in Perspective,” had the goal of critically analyzing the reasons for the lack of definitive clinical results with CRM (Figure 2). In this plenary session, Dr Thomas J. Povsic presented the key points of the regulatory process, outlined the challenges faced in the development of CRM products, and proposed novel approaches that would provide an international uniform approach. Dr Joost P.G. Sluijter reviewed the challenges of basic research from the perspective of the Cellular Biology of the Heart–European Society of Cardiology Working Group, underscoring the importance of performing preclinical research in models that resemble human confounding factors (such as age and sex), common cardiovascular comorbidities, and standard cardiovascular medications. Dr Emerson C. Perin advocated the need of a collaborative approach and presented their experience in the United States with the
Cardiovascular Cell Therapy Research Network, funded by the National Institutes of Health (NIH).

Finally, Dr Francisco Fernández-Avilés presented the ultimate goal of a worldwide-established scientific group of excellence consisting of >100 biologists, veterinarians, cardiologists, cardiovascular surgeons, bioengineers, statisticians, and experts in regulatory issues, the Transnational Alliance for regenerative Therapies in Cardiovascular Syndromes consortium (TACTICS, http://www.tacticsalliance.org). The final aim of the TACTICS is to define achievable and realistic goals, by combining basic discoveries and translational clinical efforts from dedicated CRM centers all around the world, to finally develop tailored regenerative treatments to effectively improve quality of life of patients having cardiovascular diseases. Dr Fernández-Avilés stated that, despite the fact that clinical translation of CRM is taking longer than expected, great advances on basic knowledge during the last 20 years ensure that the near future of cardiovascular medicine will include myocardial regeneration and remodeling prevention.

Closing Remarks

The conference came to an end with a keynote lecture by Dr James T. Willerson who reflected on the findings of CRM during the past decade and who strongly supported the need for continuing our efforts to move the field forward, and with the recognition of 2 researchers with the Third Madrid Cardiac Regeneration Awards. This year, Dr André Terzic and Dr Stefan Janssens were awarded with these prestigious prizes in the fields of basic and clinical research, respectively, recognizing their outstanding contributions in the field (Figure 2).

Looking forward, the 14th TECAM conference will be held next June 1st and 2nd, 2017, in Madrid, and will provide all investigators working in this field with an excellent opportunity to get closer to effective treatments that will definitely change the standard-of-care of cardiovascular diseases. Please visit http://www.cardiovascularcelltherapy.com for a selection of most relevant information.

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Disclosures

None.
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