CELL THERAPIES: THE NEXT-GENERATION CLINICAL TRIALS

Reply to the Editor:

Innovative pursuits in the field of cell therapy through the last decade have accelerated our community's understanding and knowledge of this form of therapy. Starting with rapid translation from bench to bedside, the feasibility and safety of stem cell transplantation for ischemic cardiomyopathy have been demonstrated, but discrepancies between initial highly encouraging animal studies and clinical trials have remained. Intracardiac delivery of unselected bone marrow cells using a variety of different protocols yielded inconsistent results in first-generation clinical trials. However, advances in the field pointed toward the use of selected stem cells in the second generation of trials, which have demonstrated encouraging results. Our team initiated the first 2 randomized trials in North America comparing the transplantation of autologous bone marrow-derived CD133⁺ stem cells with placebo in patients presenting with an acute myocardial infarction treated by intracoronary stenting (Comparison of Intracoronary Selected CD 133⁺ Bone Marrow Stem Cells in Cardiac Recovery After Acute Myocardial Infarct and Left Ventricular Dysfunction [COMPARE-AMI], n = 38 patients)¹ and in patients with chronic ischemic cardiomyopathy undergoing coronary artery bypass grafting (Implantation of Autologous CD133⁺ Stem Cells in Patients Undergoing CABG [IMPACT-CABG], n = 40 patients).² To obtain approval for the use of the CliniMACS CD133⁺ Reagent System (Miltenyi Biotec, GmbH, Bergisch Gladbach, Germany) from Health Canada, and eventually the Food and Drug Administration, the primary safety end point for both trials was defined as freedom from major adverse cardiac events. For safety purposes, an upper limit of transplanted cells was set to 10 million. Within this first Canadian experience, we observed a dramatic improvement of cardiac functional recovery in some responders. This said, the underlying mechanisms underpinning the beneficial effects of cell therapy are still debated but also intensively explored.

We welcome the comments from Dr Christof Stamm on our recent publication reporting the safety and feasibility results of the IMPACT-CABG trial. As discussed in the editorial by Dr Philippe Menasché³ accompanying the publication of our article,¹ the phenotype and the functionality of the cells may be more strongly predictive of therapeutic success, especially in elderly patients with multiple comorbidities. We believe that these CD133⁺ cells may have the potential to serve as a platform for more advanced and tailored modes of cellular therapy. Indeed, we have investigated methods for improving the therapeutic

potential of stem cells by genetic modification to express therapeutic transgenes, such as Akt,⁴ vascular endothelial growth factor, and basic fibroblast growth factor.⁵ More recently, we have investigated ex vivo pharmacologic stimulation of cells to improve their engraftment, survival, and release of paracrine factors.⁶

In a pursuit to improve the clinical outcomes of this promising therapy, our team has already begun developing the technology for the next-generation IMPACT-CABG II trial, which incidentally addresses key lessons outlined in Dr Menasché's editorial.³ For this, we are identifying the phenotypic and transcriptomic profile of cells collected from our first CD133⁺ stem cell trials, which reveal gene sets associated with improved clinical outcomes targetable by a first of its kind precision pharmaco-optimization method (Nicolas Noiseux and Shant Der Sarkissian; US Patent and Trademark Office provisional: 62/350,258).

Because improved outcomes often rely on pursuing innovations and building on lessons learned from the past, we remain hopeful that our efforts to foster this new technology built on the IMPACT-CABG platform may harness the full potential of cellular cardiomyoplasty using CD133⁺ cells.

Terrence M. Yau, MD, MSc, FRCS(C)^{a,b}

Nicolas Noiseux, MD, FRCS(C), MSc, BSc^{c,d}

Shant Der Sarkissian, PhD^d

^aDivision of Cardiovascular Surgery

Peter Munk Cardiac Centre at the University Health Network

^bDepartment of Surgery

University of Toronto

Toronto, Ontario

^cDepartment of Surgery

University of Montréal

^dCentre Hospitalier de l'Université de Montréal

Pavillon Hôtel-Dieu and Centre de Recherche du CHUM
Montréal, Québec, Canada

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DO NOT THROW THE BABY WITH THE WATER BATH!

Reply to the Editor:

In his thoughtful letter, Dr Stamm discusses the neutral outcomes of the IMPACT-CD33 trial¹ in which autologous CD133⁺ bone marrow-derived hematopoietic cells were injected intramyocardially in patients with left ventricular dysfunction during a coronary artery bypass grafting procedure. The failure of these cell injections to significantly improve left ventricular function leads Dr Stamm to question the therapeutic usefulness of moving forward with this approach. Dr Stamm is highly knowledgeable in the field because this group first published a unblinded study² that yielded a positive signal in favor of the intramyocardial delivery of CD133⁺ cells but then honestly reported that this benefit no longer could be demonstrated in a subsequent trial conducted according to a more rigorous protocol design involving randomization and blinding.³ I basically agree with Dr Stamm's conclusion that Dr Noiseux and colleagues'¹ assumption that "the positive findings (of the IMPACT-CD133 trial) support a larger randomized, multicenter trial, with higher numbers of transplanted cells to demonstrate beneficial effects" is debatable because analysis of cell therapy trials has rather shown that increasing the number of patients has usually resulted in weakening the expected treatment effect.⁴ However, I think that, so far, this conclusion specifically should

be restricted to the use of these hematopoietic progenitor cells and cannot yet be generalized to the whole field of cardiac cell therapy. Many questions still remain to be solved, and it may be premature to conclude that we "should cut our losses and move on to testing more promising concepts"⁵ because some other cell types or their secreted biologics might, at the end, find a place in the armamentarium of techniques that can be offered to patients with ischemic heart disease.

Philippe Menasché, MD, PhD
Department of Cardiovascular Surgery
Hôpital Européen Georges Pompidou
Paris, France

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