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Reply to the Editor:

I thank Dr Vincenzo Pitini for his comments and concerns regarding our recently published article.¹ The salient questions regarding the optimal cell type, dose, purity, method of injection, and final fate of the cells are all important and need to be addressed. However, this article was the first randomized study to address some of the more basic issues related to the use of cell therapy in an adjunctive fashion to revascularization. Because there is a chance of overlap between collateral vessels and regions of cell injection that were not directly revascularized, we wanted to see whether there was a difference over and above revascularization. This was found to be true. To address the other questions I will go in order. First, cell type along with purity was thought to be very important. The basic and

preclinical models using various fractions of blood or bone marrow, adipose, myoblasts, umbilical cord, or amniotic cells have all shown promise of cardiac differentiation. However, myoblasts, blood, and bone marrow have been used clinically showing early promising results; only myoblasts have problems related to ventricular arrhythmias. Both blood and bone marrow have been used as a relatively pure formulation of CD 34+, AC 133+, mesenchymal cells, or a mixed population based on density gradients. Neither has truly shown a benefit over the other thus far. Therefore, no one really knows the optimal cell type or purity yet. As to the dose of cells, according to the work of Stamm and colleagues² on AC 133+, there has been no dose-response curve.² Currently, at the University of Pittsburgh, we have a Food and Drug Administration-approved Phase I prospective randomized blinded trial for 3 arms of low, medium, and high doses of CD 34+ and 1 placebo arm for coronary artery bypass grafting and cells for patients with ejection fractions of less than 40%. This may help lead to more answers at least for this cell type. However, dosing trials will be needed for each different cell type used and each clinical indication desired. The method of injection is also a variable related to success of delivery and possible retention of cells in the tissue. We have been using a modified needle with side holes injected on an angle and left in the tissue for a short period of time to decrease leakage. This has been successful, but the use of biodegradable gels is promising but not yet clinically applicable. We have also started partnering with industry to develop an automated cell injection sys-

tem to help increase the reliability of cell delivery in terms of accurate doses. Finally, the fate of the cells has led to many proposed mechanisms from differentiation, to fusion, to a paracrine response. We do not have the answers yet in humans, but we do have a Food and Drug Administration-approved trial for the CD 34+ cells injected into the hearts of patients with a ventricular assist device implanted as a bridge to transplant. Half of the heart is injected with cells, and the other half is injected with a placebo. The heart is explanted at the time of transplantation, and the tissue is analyzed for cellular changes. Again, the issue arises because the cells cannot be marked and tracked once in vivo. Overall, the early clinical trials are promising, but there is a lot of research that still needs to be performed to help understand the clinical improvements seen in our and many other patients.

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