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Reply to the Editor:

We appreciate the interest of Sim and colleagues in our article describing the implantation of single, isolated skeletal muscle fibers into the heart. We agree that many important questions need to be answered before further clinical trials of myoblast transplantation into the heart.

A major issue is the mechanism by which skeletal myoblast transplantation can improve cardiac function. Sim and colleagues' suggestion that the improvement in myocardial function is directly related to the number of myoblasts implanted has not been firmly established. We consider the quality of cells implanted to be as important as, or perhaps even more important than, cell number.¹ In addition, only one recent study with donor cardiac myocytes has attempted to adequately quantify graft cell survival with quantitative real-time polymerase chain reaction, and no direct correlation between numbers of surviving donor-derived cells and functional improvement was made in that study.²

It should be noted that the issues regarding the adverse effects of prolonged in vitro culture on skeletal myoblasts are far from theoretical, as suggested by Sim and colleagues. There is clear evidence for the susceptibility to infection, as well as altered immunogenicity and adverse effects on myogenicity.³ With respect to

the risk of coronary embolism after cell transplantation, we have reported that infusion of more than 2 million myoblasts in a volume of 1 mL into the coronary circulation of the rat heart results in embolization, with edema and cardiac arrest.⁴

Sim and colleagues suggest that the functional benefit of myoblast transplantation is due, at least in an ischemic heart failure model, to the formation of new muscle ("neomyogenesis") with "phenotypic features similar to skeletal and cardiac muscle." This statement is not clear, and such a mechanism would require extensive functional, electrophysiological, and molecular characterization.

The relevance of the discordant human-to-pig xenogenic model cited by Sim and colleagues is not clear, and it is unlikely that a significant degree of myoblast survival would be seen after grafting with only transient immunosuppression—although the protocol for this is not detailed. We find interpretation of the staining in the figure difficult. With respect to labeling, the promoter driving reporter *lacZ* expression is not stated; thus one cannot be absolutely certain as to the identity of the stained cells in the presented figure. The varied distribution of the X-gal stain is difficult to explain, and counterstaining with skeletal myosin-specific antibody, as reported in our own data, would be informative; an additional nuclear marker would confirm the specificity of the stain.

The key findings in our study are that myogenic precursor cells derived from the parent fibers appeared to survive, proliferate, and differentiate within the cardiac microenvironment. Further, this treatment improved cardiac function in ischemic and dilated cardiomyopathy models to a degree that was far beyond what one might expect for the amount of new muscle formed. We have proposed at least two possible causes for this remarkable effect. One is a paracrine effect resulting in neovascularization, as shown in our article; the other is the endogenous protection afforded to the resident satellite cells by the parent fiber. This latter effect may be important in enhancing graft cell survival in the most hazardous acute phase after grafting and may also deliver satellite cells that have some important qualitative differences. We consider the skeletal muscle fiber system to be

promising, although further studies are needed to investigate the effects that we have proposed.

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Large cell neuroendocrine carcinoma of the lung: What we have to do

To the Editor:

I read with interest the excellent article of Takei and colleagues¹ about large cell neuroendocrine carcinoma (LCNC) of the lung. This series represents the largest ever published in English language literature.

The family of neuroendocrine tumors of the lung has recently been the object of study by several pathologists and surgeons. The recent World Health Organization classification criteria² consider neuroendocrine tumors of the lung as a distinct subset of neoplasm with specific morphologic, ultrastructural, immunohistochemical, and molecular characteristics. Travis and associates³ distinguish between typical and atypical carcinoid, LCNC, and small cell neuroendocrine carcinoma of the lung. Of these tumors, LCNCs appear to have an intermediate biologic behavior between atypical carcinoid and small cell carcinoma.³ LCNCs have a tendency to spread