Author response: new therapies for reducing post-myocardial left ventricular remodeling

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The need for advancing therapeutic strategies with respect to post myocardial infarction (MI) remodeling and the subsequent prevention to progressive left ventricular (LV) failure was well articulated in the editorial by Kloner and colleagues (1). Specifically, the editorialists identified the need to focus our attention on how localized delivery of stem cells and other strategies can favorably alter the structure and function of the MI region. In this commentary, reference was made to our study regarding the use of a localized delivery strategy by which a recombinant tissue inhibitor of the matrix metalloproteinases (rTIMP-3) was encapsulated in a degradable hydrogel biomaterial and injected directly into the MI region of pigs (2). In this study, we developed a method by which rTIMP-3 would continuously elute into the MI region with no detectable release into adjacent viable myocardium or the systemic circulation. The key findings were that rTIMP-3 release into the newly formed MI region attenuated key indices of adverse LV remodeling and failure, which included a reduction in LV dilation and pulmonary capillary wedge pressure. At the cellular/molecular level, rTIMP-3 release into the MI region reduced indices of inflammation, such as cytokine expression and macrophage polarization. This was the first study to demonstrate that localized release of a recombinant TIMP could alter the natural history of post-MI remodeling. These findings provide additional evidence that targeting the MMP system in the post-MI context is a relevant therapeutic target.

In this past study, we delivered the rTIMP-3/hydrogel construct at the time of MI induction by a direct myocardial injection technique and coronary ligation, respectively. Our initial titration/kinetic studies identified that local rTIMP-3 concentrations did not reach steady-state until approximately 72 h post injection, which was actually a desirable feature as this avoided interference with the initial wound healing response. However, as identified by Kloner and colleagues, this direct myocardial injection approach in the acute MI period cannot be translated to clinical application. As the authors discussed, there is however the potential to develop a hydrogel formulation that can be injected through a catheter. Thus, future studies using an imaging/electrophysiological catheter guided approach to perform the targeted injections would be an important translational step. We also envision the possibility of myocardial injections through minimally invasive/thoracoscopic cardiac procedure (such as a sub-xiphoid approach) (3) or as an adjunct to cardiac surgical procedures such as coronary revascularization. However, these delivery methods would likely occur at much later periods post-MI, in which the structure and composition of the MI region is much different to that which was examined in our past study. Thus, as identified by Kloner and colleagues, the results from our initial study warrant future studies that examine the effects of local MMP inhibition at later post-MI time points as well as exploring less invasive delivery methods. Another critical consideration is that our study was performed utilizing a permanent occlusion, whereas the majority of patients incurring an MI with an acute coronary syndrome arise from ischemia-reperfusion (IR) injury. Indeed the pathophysiology of an MI associated with IR

injury may be much different in terms of the magnitude and duration of inflammation and MMP activation. Based upon the favorable results achieved with our initial study, we hope to pursue this important line of inquiry in the near future.

We wish to take one exception to the commentary by Kloner and colleagues and that is in regards to potential differences in the initial myocardial injury sustained in the coronary ligation model, and whether and to what degree the rTIMP-3/hydrogel injections may have altered the magnitude of this initial myocardial injury. Due to a lack of significant collateral circulation in the porcine heart, and ligating at very specific and anatomically consistent sites (Figure 1E) (2), the initial myocardial injury was consistent across the randomly assigned treatment groups. In addition, we measured plasma troponin levels at 24 h post coronary ligation, and these were equivalent across the treatment groups (Figure 2) (2). However, it is certainly possible that with sustained release of rTIMP-3 into the MI region, an attenuation of continued myocyte loss either through necrosis, apoptosis, or autophagy may have occurred. Thus, the suggestion by Kloner and colleagues to assess the degree of myocardial injury at earlier time points to address this possibility is a valid one. It is now recognized that TIMPs impart a number of biological effects over and above MMP inhibition, and this includes altering cell growth and viability (4). Moreover, there is growing evidence that the different TIMPs, all of different gene products, impart different effects on cell growth, viability, differentiation, and inflammation. Thus, whether and to what degree other recombinant TIMPs would impart similar effects on post-MI remodeling to that achieved with rTIMP-3 remains an open and important question.

Targeting MMP activity through the use of small molecule inhibitors achieved significant enthusiasm based upon the uniform findings from multiple laboratories using different post-MI models, thus identifying a beneficial effect of these compounds (5). For example, using the pig MI model, we have demonstrated previously that systemic administration of a pharmacological MMP inhibitor attenuated adverse LV remodeling and progression to failure (6). Of note, the effects obtained with this orally delivered pharmacological MMP inhibitor were very similar to those achieved in our recent rTIMP-3 local delivery studies. The pharmacological MMP inhibitor used in these pre-clinical studies was advanced to clinical study (7), but concerns regarding systemic toxicity, variability in the dosing regimen, and other experimental design issues yielded an equivocal study. These observations coupled with our recent findings regarding the effectiveness of a localized delivery approach suggest that systemic delivery of molecules that target the MMP system may not be necessary. Thus, an intriguing and exciting possibility would be to "re-purpose" these MMP inhibitors for localized myocardial delivery. This would therefore allow for precise, sustained, and controlled release of these molecules into the MI region and obviate the concerns regarding non-specific systemic effects. We hope that our initial study regarding localized delivery will form the catalyst for these future studies.

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