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Cover Story

# Triggered delivery of sequestered siRNA to the heart

Heart failure after myocardial infarction (MI) is a major cause of mortality worldwide, due in large part to upregulation of matrix metalloproteases (MMPs) [1]. Within the infarction, MMPs, in particular MMP2, digest local tissue and promote heart failure. Thus, targeting MMP activity is a therapeutic approach, but current approaches, which include the use of small molecules and tissue inhibitors of MMP (TIMPs), are non-specific. To specifically target MMP2 at a genetic level, small interfering RNAs (siRNAs) are able to silence gene expression by binding to complementary messenger RNA MMP2 targets.

The work by Jason Burdick and his team in this issue describes a hydrogel that can be used for the delivery of siMMP2 [2]. A hydrogel was selected for siRNA delivery because it overcomes many limitations of systemic siRNA therapies, including poor serum stability and low local bioavailability in the heart [3]. Using a hydrogel permits the local and sustained presentation of siMMP2 to local infarct tissue. The hydrogel was engineered beyond simply releasing the siRNA over time to degrade in response to endogenous MMP activity, releasing siRNA on demand. This is advantageous because MMP activity may vary in time, location, and from patient to patient [1]. Thus, this approach represents a personalized approach to MI treatment.

The engineered hydrogel had to be injectable, capable of sequestering siRNA, and proteolytically degradable. To confer these properties, hyaluronic acid (HA) was modified with hydrazides and aldehydes, which endow shear-thinning and self-healing properties to the hydrogel after gelation, allowing it to be extruded from a syringe or catheter. To sequester siRNAs, HA was further modified with cyclodextrin, a hydrophobic macrocycle that can tightly bind cholesterol-modified siRNAs [4]. Sequestering siRNAs is important to limit their passive diffusion from the hydrogel. Finally, peptide sequences were engineered between the crosslinks in the hydrogel to enable degradability in response to MMP activity, so the hydrogel erodes in response to MMP in the infarct, to release siMMP2. *In vitro* rheological testing verified the hydrogels were injectable and photobleaching studies confirmed that cyclodextrin presentation significantly attenuated the diffusion of siRNA within the hydrogel by 15%, preventing their passive release. This resulted in the release of less than 20% of siRNA over two weeks. However, in the presence of MMP activity, the hydrogel could release 100% of siRNA within two days. Thus, a clear response to MMP activity was illustrated.

Hydrogels delivering siMMP2 were further tested *in vivo* by injecting the hydrogel directly into ischemic tissue after inducing acute MI. An important finding was that delivery of siMMP2 compared to a non-targeting control (siCTRL) significantly reduced hydrogel erosion by nearly 50% in the infarct by 28 days. This suggested that silencing of local MMP2 activity was actually preventing further degradation of the hydrogel, corroborating the effects of the siRNA. Ultimately, hydrogel delivering siMMP2 led to improved cardiac function, improving ejection fraction and stroke volume by 27 and 32%, respectively, compared to hydrogel delivering an siCTRL. The Burdick team postulated this effect occurred through two mechanisms: (i) by silencing of MMP2 activity, which is individually responsible for adverse remodeling and heart failure; and (ii) by increasing hydrogel volumes in the infarct tissue, which can bulk and stabilize the thinning infarct wall, which can improve function.

These results corroborate previous literature that illustrate therapeutic potential of targeting MMP2 as well as broad MMP activity after MI using biomaterials [5]. To translate this material system, further iteration is necessary. In particular, the hydrogel in question required multiple modification steps to synthesize, which may impede scalability and warrant the use of alternative polymers. Moreover, combining the effects of silencing MMP2 in addition to other MMPs, such as MMP9, may have a synergistic benefit. Finally, a better understanding of the *in vivo* delivery will facilitate the use of this material in pre-clinical large animal studies. The importance of this study is that it showed how to design on-demand delivery of sequestered siRNA, and such understanding will undoubtedly make the future hydrogel systems simpler and more efficient for translation to clinical trials.

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Kinam Park
*Purdue University*
*Biomedical Engineering and Pharmaceutics*
*West Lafayette, IN 47907, USA*
*E-mail address:* kpark@purdue.edu

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