Journal of Controlled Release 262 (2017) 357

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Cover Story

Enhanced intrapericardial drug delivery by PLGA nanoparticles

Pharmacological therapy is the cornerstone of cardiovascular disease treatment, including heart failure, cardiac arrhythmias, and coronary artery disease. Many clinically-used drugs, however, are limited by non-specific distribution and dose-limiting extra-cardiac toxicities when administered systemically. Local, catheter-based strategies (e.g., intra-coronary delivery) are limited to transient, local effects, such as coronary vasodilation or thrombolysis. Intramyocardial delivery is inherently linked to myocardial trauma and associated morbidity, as well as limited retention [1].

The paper by Professors Elvin Blanco and Miguel Valderrabano highlights a novel local drug delivery approach to the heart [2]. Nanoparticles administered in the fluid-filled pericardial sac were used as a reservoir for sustained therapeutic targeting of the myocardium. The use of the pericardial space for sustained drug delivery is enabled by the safety, convenience, and reproducibility of pericardial access, a technique currently used clinically. Moreover, the drug clearance rates from the pericardial sac are comparatively lower as compared with other administration sites [3]. The authors hypothesized that sustained drug delivery from nanoparticles administered intrapericardially, combined with low clearance from the pericardium, would result in prolonged, local drug delivery to the myocardium. To test this, the authors fabricated fluorescently-tagged poly(lactic-co-glycolic acid) (PLGA) nanoparticles encapsulating a fluorophore, BODIPY, administered them intrapericardially to rabbits, and evaluated the kinetics of retention and distribution of both in the myocardium at different time points.

The authors present a few interesting observations. First, long-term presence of nanoparticles was observed on the epicardial surface of hearts at prolonged time points after intrapericardial administration, due principally to confinement within a compartment with low clearance. Small molecular weight drugs can undergo clearance by epicardial vasculature and lymphatics following pericardial delivery [4]. However, the relatively large size of the nanoparticles (~190 nm) resulted in delayed clearance and long-term retention within the pericardial sac. Second, another consequence of the relatively large size of nanoparticles was limited diffusion of nanoparticles into the myocardium, which resulted in their confinement to epicardial layers. Despite the limited diffusion into the myocardium, nanoparticles had a half-life of ~2.5 days in the heart. Third, the fluorophore released from nanoparticles was found in different regions of the heart over a sustained period of time, displaying a half-life of ~7 days in the heart. Penetration of fluorophore was seen at considerable distances within the myocardium, and a transmyocardial gradient was observed in all regions of the heart. It is noted that higher drug accumulation was observed in the atria compared to the ventricles, due in large part to the distinct architecture and decreased epicardial vasculature found in the atria.

The study by the Blanco and Valderrabano team is one of the first to demonstrate the potential of exploiting the pericardial space for local drug delivery to the heart. They demonstrate that pericardial delivery can result in prolonged presence of nanoparticles in the heart, with significant myocardial penetration and sustained accumulation of the released fluorophore. Since each drug is different and the drugs treating cardiovascular diseases are different from a fluorophore, it is difficult to generalize the finding, but it certainly provides a potential for improved local drug delivery. Nanoparticle-based intrapericardial delivery converts the pericardial space into a local drug-eluting post immediately adjacent to the heart. This in turn enhances pharmacokinetics by increasing the cardiac bioavailability of drugs, allowing administration of a lower dose for the same therapeutic effect, and thus, significantly improved patient outcomes and reduced adverse side effects in several heart diseases. Another point to note in this study is that nanoparticles can serve as a useful tool for local drug delivery when used properly.

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http://dx.doi.org/10.1016/j.jconrel.2017.09.008