



Cover story

Perivascular administration: The outside-in concept



Perivascular administration has attracted increasing attention since intimal hyperplasia was identified as the main cause for coronary and peripheral bypass graft occlusion. For preventing the graft occlusion, a local treatment using a sustained drug delivery system would be ideal, as the vessels are readily exposed to the vascular surgeons [1]. However, neither local nor oral formulations have been developed, not to mention clinically available products, to prevent the advance of this pathological condition. A drug delivery system that would meet the needs of this pathology will help those undergoing bypass surgeries greatly.

The paper by Doctor Florence Delie and her coworkers in this issue is a collaborative effort between the Geneva-Lausanne School of Pharmacy and the Vascular Surgery Department of Lausanne's University Hospital [2]. They investigated the optimal release kinetics necessary to decrease the development of intimal hyperplasia in a murine model. Based on the time course of the evolution of the pathology, three different atorvastatin releasing profiles were tested *in vivo*: short-term release over 3 days (fast), sustained release over 45 days (sustained) and a combination of both (biphasic). Poly(D,L-lactic-co-glycolic acid) microparticles were used to sustain the release of atorvastatin, a compound known to inhibit human smooth muscle cell proliferation *in vitro*. A cross-linked hyaluronic acid gel, also used for fast release, ensured ease of application and retention of the formulation at the site of action. The biodistribution of atorvastatin over adjacent and distal organs was investigated. An *ex vivo* test was set up to ensure permeability of atorvastatin through human saphenous veins, the graft of choice for bypass interventions.

The study by the Delie team draws significant conclusions. First, the biphasic releasing system, combining fast and sustained release of atorvastatin, was demonstrated to be optimal. *In vivo*, after four weeks, this biphasic formulation reduced by 68% the occurrence of intimal hyperplasia compared with the untreated control group. Fast or sustained release formulations did not provide such an efficacy. This observation indicates that there may be a synergistic effect: an initial bolus release of atorvastatin is necessary to prevent smooth muscle cell proliferation at the very early stage of the pathology, and the sustained release inhibits later events such as smooth muscle cell migration from the media to the subintimal level. Second, the endothelium was not affected

by the presence of high local concentrations of atorvastatin. This is essential to insure the anti-thrombotic effect of the intact endothelium. Third, local perivascular administration limits the exposure of vital organs to toxic concentrations of atorvastatin. Hepatotoxicity and severe myopathy are commonly reported side effects after oral atorvastatin intake. In this study the concentrations of atorvastatin found in these tissues were very low. Finally, the permeation of atorvastatin through human saphenous veins was validated, paving the way for pre-clinical tests over bigger animals, such as pigs.

The work by the Delie group indicates that, as expected, treating intimal hyperplasia is more complex than just delivering a compound at the target site. Indeed, an efficient approach should also include the right release profile matching the evolution of the pathological process, an issue often underestimated in the literature. It is not just the long-term release of small quantities of a drug, but the release of a therapeutically effective drug in a pulsatile manner at the right times. Most *in vitro* drug release studies simply measuring the drug release kinetics without monitoring the drug efficacy will not be able to find the optimal drug release kinetics. Thus, development of clinically useful drug delivery systems requires new experimental set-ups that would monitor the drug efficacy as a function of drug release kinetics at the preclinical level to increase the success rate of clinical applications.

References

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