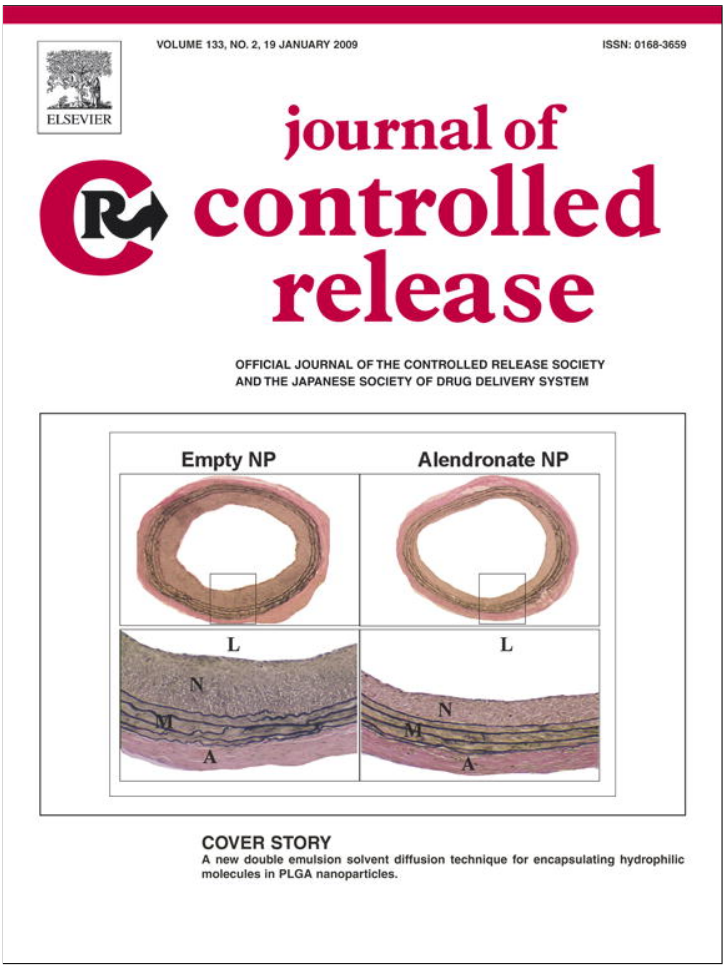

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Cover Story

A new method for preventing restenosis: A single IV injection of drug-loaded nanoparticles

Restenosis is re-obstruction of the coronary arteries following percutaneous coronary angioplasty. Currently, restenosis is effectively treated by local delivery of a drug (e.g., sirolimus or paclitaxel) from drug eluting stents (DESs) for a month or longer. Because of its unprecedented success in preventing restenosis, DES has become one of the most useful drug-biomedical combination products. Recent data, however, suggest that patients with an implanted DES still suffer from the late in-stent thrombosis, and this is partly due to the lack of endothelialization resulting from the release of a drug that acts on both smooth muscle cells (SMCs) and endothelial cells. The paper from Professor Golomb's laboratory in this issue [1] shows that alternative approach of treating restenosis is possible. Unlike conventional, local drug delivery from DES directly to SMCs, Professor Golomb prevented restenosis by controlling the circulating monocytes.

Professor Golomb and his co-workers were the first to hypothesize that partial and transient depletion of circulating monocytes could decrease macrophage recruitment in the arterial wall, and consequently result in attenuation of neointimal formation [2]. Monocyte inhibition has previously been achieved with a systemic injection of liposomes containing bisphosphonates (BPs) or nanosuspensions of macrophage inhibitors. The particulate encapsulation of BPs affects targeting of these normally bone-seeking agents to cells capable of effective phagocytosis, i.e., monocytes and macrophages [3]. The release rate is titrated such that the drug is protected in the circulation for a sufficient period of time to be taken up by monocytes, while still rapidly and sufficiently releasing the drug inside the cells. This approach has been successful in prevention of intimal hyperplasia and stenosis in animal models.

The work by Professor Golomb presents a major shift in paradigm in the treatment of restenosis, a presumed localized pathogenic process. The role of innate immunity in vascular injury and repair has been recently emphasized. Inflammation is considered to have a major role in linking early vascular injury to eventual growth of vascular neointima. Inhibition of systemic monocytes and macrophages suppress this inflammatory link. This leads to a new concept of "biological targeting," in comparison with physical targeting through localized delivery of a drug from DESs. The biological targeting exploits the body's own mechanism for recognizing injury. The paper by Professor Golomb's group [1] clearly shows that a single injection of alendronate-containing NPs at the time of angioplasty is capable of preventing restenosis, regardless of the procedure and the device(s) used. The use of a systemic treatment modality allows flexibility in choosing the type and number of stents to be deployed. It can also serve as an adjunct therapy in high-risk patients, and may even reduce the need of stenting altogether. The first generation liposomal systems are currently in Phase II clinical studies [4], and the prevention of late in-stent thrombosis is expected. The study by Professor Golomb in this issue [1] is highly significant, because controlling restenosis by a single injection of drug-loaded NPs allows DES-based delivery of a drug that can promote endothelial cell growth for ultimate prevention of late in-stent thrombosis. The unconventional approach of controlling restenosis described in this issue [1] is expected to allow development of a new generation of DES that can promote endothelialization for eliminating the late in-stent thrombosis.

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

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