



## Cover Story

## New biomedical polymer targeting E-selectin to reduce atherosclerosis



Atherosclerosis is a prevalent, chronic inflammatory disease of the arteries and the primary cause of ischemic heart disease, heart failure, and stroke. Despite the large availability of anti-inflammatory drugs, most of the drugs have significant adverse effects due to the lack of specificity to atherosclerotic lesions. In this issue, Professor Jonathan Leor from Tel-Aviv University and Professor Ayelet David from Ben-Gurion University of the Negev present a simple yet highly elegant approach to inhibit vascular inflammation by blocking E-selectin on the inner surface of inflamed blood vessels in atherosclerotic lesions [1]. E-selectin is a cytokine-inducible cell adhesion molecule expressed on the surface of inflamed vasculature and mediates leukocyte trafficking from the blood into the inflamed tissues. Poly(N-(2-hydroxypropyl)methacrylamide) (PHPMA), a water-soluble polymer, was grafted with the high affinity E-selectin binding peptide (P-Esbp). As expected, P-Esbp was shown to target the inner lining of blood vessels on the surface of atherosclerotic lesions in ApoE<sup>-/-</sup> mice. More importantly, however, it also increases the stability of atherosclerotic plaques, and prevents adverse cardiac remodeling and dysfunction [1]. It was further demonstrated that the treatment increases the number of M2 macrophages in the spleen and decreases the total leukocyte count in the circulation, suggesting less systemic inflammation.

The favorable effect on cardiac function by P-Esbp is surprising and needs further investigation. Nevertheless, the strategy of using a polymer without a conventional drug (or an active pharmaceutical ingredient) is exciting and offers several advantages: easy construction of a polymer with strong adherence to E-selectin; selective targeting of blood vessels in atherosclerotic lesions without affecting the healthy tissues; and the absence of side effects as the polymer lacks a drug. Moreover, since E-selectin is an early marker of endothelial activation and dysfunction, the polymer can inhibit atherosclerotic lesions at an early-stage, thus attenuating plaque progression. Tumor cells utilize the leukocytes traffic mechanism and promote their own extravasation from tumor blood vessels, eventually forming metastases. This E-selectin-targeted “drug-free” therapeutic polymer was shown previously by the authors to inhibit the formation of metastases *in vivo* in several types of cancer [2], supporting the strategy presented in this issue.

Although the Leor-David team has shown promising therapeutic results in mice, there are challenges that must be addressed before clinical testing. First, E-selectin plays a fundamental role in leukocytes

trafficking, and thus, attenuating or blocking leukocyte trafficking could affect the infiltration of other immune helper cells (T lymphocytes). This may impact the healing process. In addition, accelerated development of atherosclerosis induced in the Apo E<sup>-/-</sup> mice creates lesions that may vary from those found in humans, and thus adjustments in P-Esbp regimen (dosing and timing) are necessary for translation into the clinic. More importantly, many of the selectin inhibitors have not held up to the high expectations, in some cases due to the compensation for selectin functions by other selectins (P-selectin, in particular) or suboptimal pharmacokinetic properties of the compounds [3], and this is yet to be addressed. These issues, however, apply to all new drugs or drug delivery systems, and thus, they are not unique to P-Esbp.

An important finding by the Leor-David team is that PHPMA grafted only with E-selectin binding peptide has the ability to target endothelial cells on the surface of atherosclerotic vessels and stabilize arterial lesions, as well as prevent cardiac remodeling and improve cardiac function. While this work is still in progress, the P-Esbp approach reinvigorates the research on “drug-free” macromolecular therapeutics. Since P-Esbp becomes effective without entering cells, its simplicity, as compared with other polymeric systems which have to enter the cells, offers great promise for the management of atherosclerosis.

## References

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