Drug Delivery and Translational Research (2018) 8:865–867
https://doi.org/10.1007/s13346-018-0483-y

EDITORIAL

Cardiovascular delivery of drugs and biotherapeutics

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Published online: 22 January 2018

Cardiovascular diseases (CVD), i.e., diseases affecting the function of the heart and blood vessels, encompass coronary heart disease (CHD), cerebrovascular disease, peripheral arterial disease, rheumatic and congenital heart diseases, and venous thromboembolism. CVD account for more than 30% of all deaths worldwide and collectively remain a major healthcare issue with suboptimal treatment outcomes and significant clinical and economic burden [1]. Despite remarkable progress in diagnostics and the vast global effort focused on improving their clinical management, the morbidity and mortality associated with CVD have continued to grow over the decades [2], fueling interest toward the development of novel, more effective, and safer therapies. Therefore, a special issue of DDTR dedicated to new trends in CVD pharmacotherapy and novel experimental strategies designed to treat or prevent CVD through effective delivery of small-molecule and biologic drugs appears to be well-timed and important.

The issue includes five invited reviews critically discussing new developments in cardiovascular drug delivery and focusing on biological pathways that play important roles in the pathophysiology of CVD and thus represent potential targets, which can be accessed by properly designed delivery systems. As an example, angioplasty with stent placement used to treat obstructive vascular disease triggers acute local inflammation due to disruption of the protective endothelial layer and infiltration of inflammatory cells, primarily monocyte-derived macrophages, to the site of arterial injury, in turn leading to arterial renarrowing (restenosis). Similarly, acute inflammation driven mainly by monocytes and macrophages is a major contributing factor to the pathophysiology of myocardial infarction (MI). The key role played by inflammatory cells provides a strong rationale for applying drug targeting approaches as a way of improving outcomes in both conditions by favorably modulating the inflammation and tissue healing processes [3]. Such pathway-targeted pharmacotherapy is elegantly accomplished with cell-type specific delivery of small-molecule drugs, such as bisphosphonates or statins, formulated in biodegradable polymer-based or liposomal nanocarriers, nanosuspensions, or albumin complexes taking advantage of the phagocytic nature of the target cells. The development of appropriate delivery systems, studies elucidating their mode of action in the context of restenosis and MI therapy, results showing effectiveness of monocyte-targeted drug delivery in animal models of the disease and its recent evaluation in clinical trials, and the potential utility of these novel therapeutics for other CVD applications are reviewed by *Aizik* et al. [4].

Post-angioplasty restenosis continues to pose a need for new therapeutic approaches due to suboptimal effectiveness of existing treatment modalities in patients with complex lesions. An even greater therapeutic challenge is presented by a form of in-stent restenosis (ISR) currently lacking effective treatment options that develops in a growing number of "real-world" patients unsuccessfully treated with drug-eluting stents (DES)—combination devices, which in recent years have largely replaced bare-metal stents as a strategy for treating the symptoms and consequences of obstructive vascular disease and for mitigating ISR [5, 6]. This particularly stubborn variant of arterial reobstruction, termed DES-ISR, is still approached by repeat stenting ("stent sandwich" technique) in the absence of more effective treatment options. Generally recognized limitations of DES currently in clinical use include deterioration of their polymeric coating and the associated inflammatory response, as well as the non-selective mode of action of stent-eluted drugs, which together strongly increase the risk for stent thrombosis and neoatherosclerosis, both contributing to eventual stent failure [7–9]. Other deficiencies include drug release kinetics that

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cannot be adjusted to a distinct vulnerability period of blood vessel types other than coronaries or to the disease status of a treated blood vessel, and poor compatibility of traditionally designed DES with cell-type selective drugs evaluated as potentially safer alternatives to taxanes or mTOR inhibitors of the "limus" macrolide family. This has inspired a search for new stent designs capable of addressing the limitations of existing DES, and for other local delivery platforms not utilizing stents. The first approach is exemplified by stents covered with non-polymeric coatings and providing site-specific delivery of immunosuppressants, anti-inflammatory and antithrombotic drugs, and other active compounds as single agents or in combination. *Kommineni* et al. [10] review recent progress on advanced coating technologies for producing polymer-free DES and give an update on such stents currently under development or already approved for clinical use. The side effects of currently used DES and their poor performance in a subgroup of patients at high clinical and angiographic risk who often present with a particularly challenging, drug-resistant form of DES-ISR can potentially be addressed by acting on a set of molecular targets, which may not be readily accessible to small-molecule therapeutics. In this context, site-specific gene transfer using engineered viruses to block the restenotic cascade by interfering with early events in restenosis pathophysiology can offer a viable and effective alternative to traditional DES. Such gene delivery strategies, biological mechanisms targetable with therapeutic transgenes, considerations behind the choice of appropriate viral vectors, and their evaluation in a clinically relevant atherosclerotic pig model of restenosis are reviewed in the paper by *Hall* et al. [11].

The problems of vascular inflammation, thrombosis, and oxidative stress can potentially be approached by endothelium-selective delivery of small-molecule drugs and biotherapeutics acting as antioxidants or antithrombotic agents. Experimental strategies for targeting vascular endothelium whose proof-of-concept has been demonstrated in preclinical studies are based on endowing therapeutic cargoes with affinity toward specific endothelial epitopes, especially those upregulated in pathologic conditions. In their review paper, *Kiseleva* et al. [12] introduce principles and key elements of endothelium-selective delivery accomplished through exploiting target-dependent processes, discuss the roles of disease pathophysiology and formulation design as essential determinants of the pharmacokinetics and therapeutic performance of biologic and small-molecule drugs targeted to the injured vascular endothelium, and present evidence supporting the implementation of nanocarriers as a way to overcome obstacles to the successful translation of these therapies into the clinic. Finally, the topics of the prophylaxis and treatment of thromboembolic disorders, and risks associated with existing approaches for thrombosis management posing a need for new and safer anticoagulants and for non-toxic neutralizing agents capable of reversing excessive anticoagulant activity are presented in the paper by *Kalathottukaren* et al. [13]. This review summarizes recent progress on such antidotes for the potentially life-threatening bleeding complications in patients receiving long-term anticoagulation treatment.

An important aspect of targeting monocytes to prevent arterial restenosis is introduced in a research paper by *Grad* et al. [14] demonstrating differential effects of two liposomal bisphosphonates on monocyte subclasses and their correlation with the antirestenotic effect in a rat carotid injury model. In particular, the authors show that, unlike liposomal clodronate, alendronate formulated in liposomes exerts significant antirestenotic activity primarily through increasing the ratio of the anti-inflammatory/pro-inflammatory monocytes, emphasizing the distinct roles of the different monocyte populations. A research paper by *Battig* et al. [15] centers on a targeted cell delivery strategy for restoring functionally and structurally intact endothelium and for accelerating arterial healing after injury. The authors evaluate adenovirus-impregnated magnetic nanoparticles designed to both endow endothelial cells (EC) with magnetic responsiveness and capacity for magnetic guidance and to enhance their growth inhibitory effect on arterial smooth muscle cells (SMC) via overexpression of a therapeutically relevant transgene, inducible nitric oxide synthase. The paper introduces an in vitro SMC/EC co-culture methodology compatible with chemically labile effectors, such as enzymatically produced NO, as an approach for optimizing the process of EC functionalization with MNP-virus formulations for vascular targeted delivery. Focusing on nanocarrier-based drug delivery for enhancing regenerative repair of the elastic matrix in aortic aneurysms, *Camardo* et al. [16] have systematically studied the pro-elastogenic and antiproteolytic effects of doxycycline formulated in positively charged biodegradable nanoparticles. Using SMC cultures derived from arterial aneurysms, the authors show that these effects are mediated by inhibition of JNK2 kinase causing attenuation of elastolytic matrix metalloproteinases and an increase in elastic matrix deposition and crosslinking.

Collectively, the review papers and experimental studies presented in this theme issue cover a broad spectrum of established and novel strategies designed for the treatment and prevention of CVD, illustrating different facets of cardiovascular delivery of drugs and biotherapeutics. We hope that this compendium will be of value for researchers interested in the development and diverse applications of targeted delivery systems and nanomedicines.

Compliance with ethical standards

Competing interests MC and RJL declare that they have no conflict of interest. GG has a financial stake in Biorest Ltd.

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