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Editorial

Killing two birds or more with one stone



As we discover more about diseases, it becomes clear that they are vastly complex, dynamic, and versatile. This indicates that it may be infeasible to find a single drug that tackles all moving molecular targets with high efficacy and specificity. Delivery of therapeutic and diagnostic modalities on a nano-scale platform (nanomedicine) is a promising approach to effective and safe therapy via targeted delivery (selective accumulation) and subsequent controlled release (activation). These are obvious design goals that can easily be integrated into drug delivery systems with aims of incremental improvement. Another substantial strategy that has not gained the notoriety as targeted delivery and controlled release is co-delivery of multiple modalities, which may be specific to nanomedicine.

There are a plethora of therapeutic agents that target several pathological pathways, and they often have distinct pharmacokinetic (PK) properties. When a potential combination of drugs is identified, a PK discrepancy can undermine the therapeutic benefits. In addition to the difficulty of normalizing PK properties, a simple drug mixture (cocktail) is unable to kinetically control (ordered) drug release. When multiple, synergistically working drugs are formulated within the same carrier, however, they are ensured to be delivered to the same target, followed by ordered release if desired. This will comprehensively result in synergistically improved therapeutic effects and minimally required doses of each drug (minimized adverse side effects). Simultaneously tackling multiple molecular targets may overcome drug resistance or significantly reduce the possibility of its development.

Despite many foreseeable advantages, several considerations of the multi-modal nanomedicine need to be underscored. There are many combination candidates of therapeutic agents identified based on separate biological evaluations, and they should be carefully reviewed for their potential adverse and attenuating effects on each other. Not all therapeutic combinations may not be co-deliverable and may necessitate a pre-modification or formulation. Evaluating separate and combination effects of co-delivered therapeutic agents can be tricky, particularly if their target pathways overlap. One of the most significant concerns in moving forward with multi-modal nanomedicine is administrative approval on safety concerns when multiple therapeutic agents are used.

A collection of illustrative examples of co-delivery and multi-modal therapeutics for synergistic therapy is presented in this theme issue (Table 1). Prospects and concerns about multi-modal nanomedicine, which are briefly mentioned above, are delineated throughout the issue. It starts with a review by Kemp et al. which

succinctly discuss the principles of co-delivery of multi-modal therapeutics with broad examples. Hu et al. specifically describe overcoming the current clinical limitations when multiple chemotherapeutic drugs are administered via several combination modes. Nastiuk and Krolewski introduce cancerous pathways that are potentially good targets of multi-modal gene therapy. Teo et al. combine chemotherapy and gene therapy in order to effectively manipulate key pathways in cancer. He et al. and Gilmore et al. pay attention to delivery of proteins as biologically active macromolecules along with chemotherapeutics. Northrup et al. discuss enhancement of antigen-specific immunotherapy by co-delivery of small molecule drugs, antigens, and nucleic acids. Kim et al. combine a physical therapeutic modality (photothermal therapy) and gene therapy. Lastly, Jang et al. re-cap the status and prospective of multi-modal therapy using nanomedicine. Publications on this topic rapidly grow nowadays and expand the small selected collection of this theme issue. The purpose of this issue is to provide the readers of *Advanced Drug Delivery Reviews* with awareness of the need, challenge, and opportunity in developing interdisciplinary nanomedicine for effective, safe, and versatile therapy for diseases.

	Therapeutic modality			
	Chemotherapeutics	Nucleic acids (RNA/DNA)	Peptides/proteins	Photosensitizers /nanomaterials
Kemp et al.				
Hu et al.				
Nastiuk and Krolewski				
Teo et al.				
He et al.				
Gilmore et al.				
Northrup et al.				
Kim et al.				
Jang et al.				

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