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Nanotransporters for drug delivery

Tessa Lühmann and Lorenz Meinel

Soluble nanotransporters for drugs can be profiled for targeted delivery particularly to maximize the efficacy of highly potent drugs while minimizing off target effects. This article outlines on the use of biological carrier molecules with a focus on albumin, various drug linkers for site specific release of the drug payload from the nanotransporter and strategies to combine these in various ways to meet different drug delivery demands particularly the optimization of the payload per nanotransporter.

Address
Institute for Pharmacy and Food Chemistry, University of Würzburg, Am Hubland, DE-97074 Würzburg, Germany

Corresponding author: Meinel, Lorenz (lorenz.meinel@uni-wuerzburg.de)

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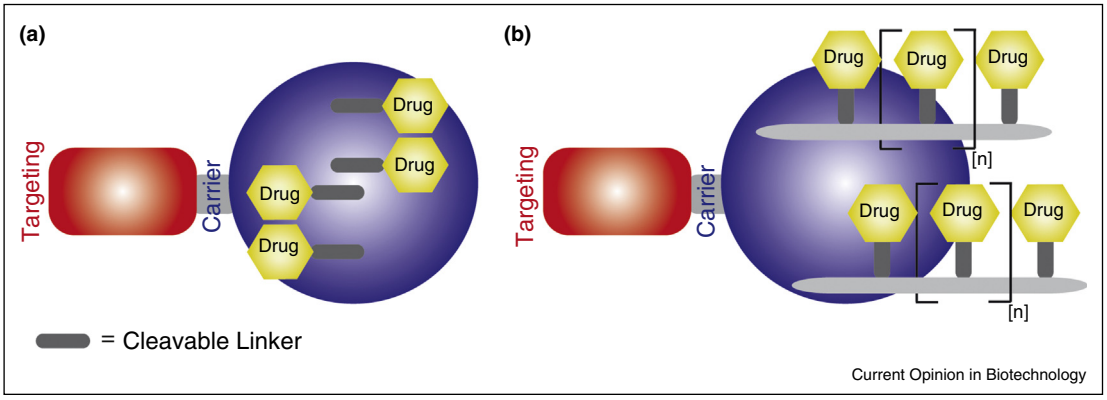
Introduction

Paul Ehrlich's vision of selectively delivering highly potent drugs primarily to the seat(s) of a disease has become reality. Particularly indications with limited alternative treatments (e.g. oncology, some rare diseases) benefit from the combination of a targeting moiety to cell surface antigens and concomitant delivery of a covalently connected cytotoxic drug providing that the resulting nanotransporters have adequate pharmacokinetic (PK) properties [2]. These drug nanotransporters expand the armentarium in fighting challenging diseases to very toxic drugs thereby inappropriate for untargeted, systemic use. Some of these nanotransporters integrate responsive linker technologies, such that the targeting moiety is separated from the drug in response to an extra-cellular or intracellular stimulus or in response to applied triggers. Learnings from the development of antibody–drug conjugates (ADC) have been extremely helpful in defining the necessary building blocks for nanotransporters and increased the understanding when tuning their properties. For example, heterogeneity in product quality outcome and clinical performance is a direct result of the availability of various potential conjugation sites on a carrier (i.e. the antibody or another macromolecule or polymer), genetic engineering and modern, bioorthogonal chemistries can help to overcome this obstacle thereby reducing the risk of development [3••]. Stability challenges of the nanotransporters are also related to the inherently instable drug linker, supposed to readily disintegrate at the site in need with premature cleavage during circulation potentially driving off target effects [4]. Lastly, validated targets for nanotransporter homing are few in number and extrapolated from existing therapeutic antibodies and their life cycle extension through cytotoxic drug decoration. However, the common denominator for valuable targets are a high target expression in the diseased tissue and low expression elsewhere. These building blocks — carrier, drug-linker, antigen selection — are addressed in the following sections (Figure 1). Future perspectives are delineated by outlining recent developments within each block while outlining the potential when combining these driven by the medical need.

Carrier systems

From a PK perspective, carriers derived from natural sources can be separated in those with intrinsic binding to the neonatal Fc Receptor (FcRn; such as albumin [5] and antibodies [6]) and those which do not. FcRn binding controls the fate of bound proteins in circulation with diminution of renal clearance [7] and by rescue from intracellular degradation [8]. FcRn binds antibodies and albumin — a 66.5 kDa protein — at acidic pH as found in endosomes, or the extracellular milieus in neoplastic or generally inflamed tissues [8]. Albumin concentrations in human plasma are typically around 0.6 mM and among other functions such as regulating the osmotic pressure, the protein evolved as multifunctional transporter for various drugs, nutrients, waste products, ions, bilirubin, or fatty acids among others. The binding site of albumin for the FcRn is known and serves as an insight to modulate the PK of the carrier as a function of albumin's decoration site [9]. Interference with the albumin's FcRn binding site through targeted decoration will likely impact the distribution of the carrier and its catabolism. The precise characterization of albumin detailed ridges and valleys through known binding affinities to various small molecules [10]. These insights might be particularly interesting for site specific decoration with linkers of known propensities to cleavage in plasma when exposed to certain micro-environmental conditions on the carrier surface, as has been reported for ADC [3••]. Albumin requires decoration for targeting of epitopes, whereas antibodies possess both properties, targeting and stabilization. An optimization of the number of bound molecules/targeting moieties is essential, such that the physical stability (aggregation) of the conjugates

Figure 1



Composition of the nanotransporter. **(a)** Individual drug-linker molecules are conjugated to the carrier. **(b)** The payload comprises series of connected drug linker conjugates.

is controlled [3••,11,12]. Alternative options include the use of synthetic polymers which has been elegantly reviewed before [13–15] and intriguing bioinspired polymers, emerging complementation to more controllable platforms [16], promising advanced compatibility with established bioconjugation chemistries.

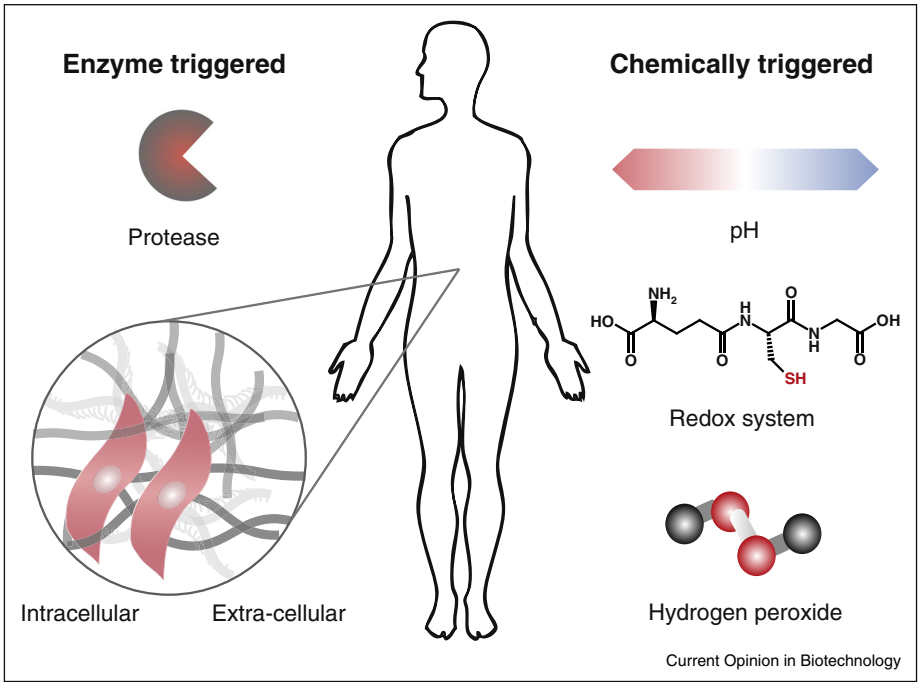
Cleavable linkers

Different types of linkers prone to cleavage by enzymes or responsive to variations in pH, redox potential or hydrogen peroxide levels are available for conjugation to attain (bio)-responsiveness of the nanotransporter in the target tissue or cellular compartments (Figure 2).

Enzyme triggered cleavage

Bio-responsible drug delivery systems devoted to enzymes with activity in intracellular compartments or present in the extracellular space can be modularly assembled dependant on the desired site of action of the target drug. Lysosomal delivery of, for example, ADCs is

Figure 2



Endogenous stimuli for bioresponsive drug delivery.