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Current Opinion in Biotechnology

Nanotubes in biological applications

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Researchers over the last few years have recognized carbon nanotubes (CNTs) as promising materials for a number of biological applications. CNTs are increasingly being explored as potent drug carriers for cancer treatment, for biosensing, and as scaffolds for stem cell culture. Moreover, the integration of CNTs with proteins has led to the development of functional nanocomposites with antimicrobial properties. This review aims at understanding the critical role of CNTs in biological applications with a particular emphasis on more recent studies.

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Current Opinion in Biotechnology 2014, **28**:25–32

This review comes from a themed issue on **Nanobiotechnology**

Edited by **Jonathan S Dordick** and **Kelvin H Lee**

For a complete overview see the Issue and the Editorial

Available online 22nd November 2013

0958-1669/$ – see front matter,

http://dx.doi.org/10.1016/j.copbio.2013.10.012

Introduction

Carbon nanotubes (CNTs), by virtue of their unparalleled electrical, mechanical, and optical properties, have emerged as ideal candidates for bioimaging, biosensing, and biomedical applications [1]. Moreover, the development of techniques for the facile functionalization of nanotubes (Table 1) has further expanded the range of potential applications [2]. For instance, nanotubes are not only being used to develop functional nanocomposites, but are also serving as potent vehicles for delivering a variety of drugs *in vivo*. This review focuses on the key biological applications of CNTs, with special emphasis on reports published within the last three years (Figure 1).

Nanotubes in drug delivery/cancer therapy

On the basis of extensive research during the past decade, nanomaterials, particularly CNTs, have emerged as potent drug delivery vehicles [4•]. CNTs are taken up passively into tumors without the assistance of antibodies or other large molecules, and this enhanced permeability and retention (EPR) effect has been exploited for the successful delivery of various anti-cancer drugs [4•,5]. The ease of functionalization of CNTs provides opportunities for the attachment of multiple drugs [6].

P-glycoprotein is overexpressed in multi-drug resistant (MDR) mammalian cells and is responsible for the increased efflux of anti-cancer drugs out of the cells. To overcome the challenge posed by MDR cells, Li and colleagues [7] loaded single-walled CNTs with doxorubicin (DOX), a popular anticancer drug, and functionalized them with an antibody to P-glycoprotein. The resulting nanotubes specifically recognized MDR K562 leukemia cells, and exhibited effective loading and controlled release of DOX, thereby exhibiting 2.4-fold higher cytotoxicity towards these cells as compared to free DOX [7].

Liu and colleagues [8••] used π–π stacking to load DOX onto single-walled nanotubes (SWNTs) functionalized with branched PEG and studied their biodistribution and pharmacokinetics. Their results clearly demonstrated an increase in the circulation half-life from 0.21 hours for free DOX to 2.22 hours for SWNT-DOX (Figure 2(a)). The branched PEG reduced the clearance by macrophages and repeated passage of these drug conjugates though tumor vessels caused increased tumor uptake (Figure 2(b)). Another advantage of the physical stacking of drugs onto nanotubes is that it does not compromise the drug chemistry. Lay and coworkers [9] extended this advantage to paclitaxel (PTX), another potent anticancer drug, but devoid of an extended π structure; hence, the formation of noncovalent CNT–drug conjugates may be more general than once believed.

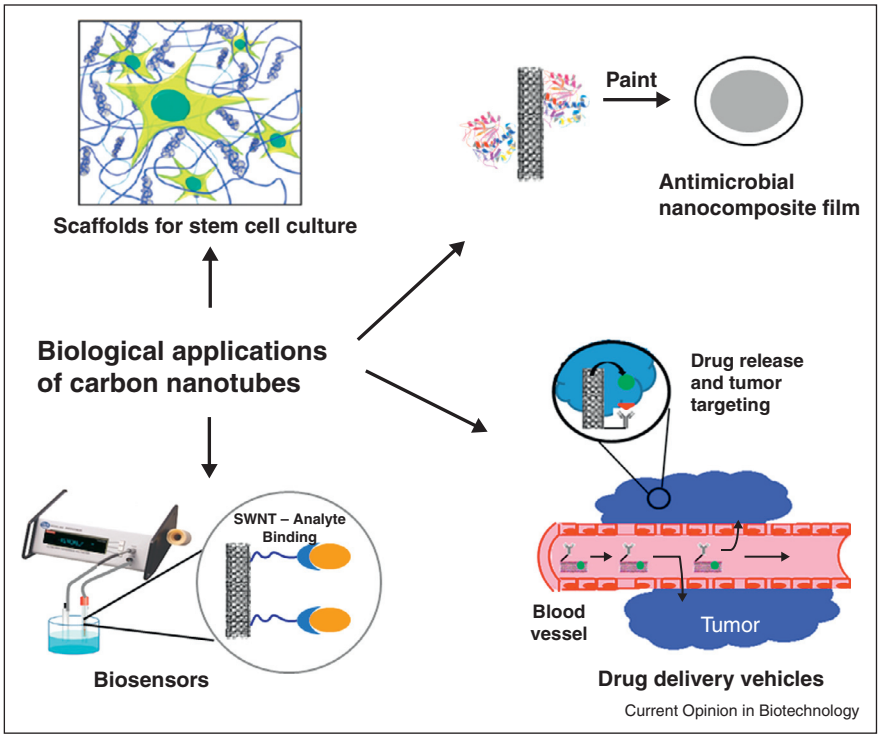
Despite these developments, a major limitation of CNTs as drug carriers *in vivo* has been the underlying concern about their toxicity. Karchemski *et al.* [10•] addressed this concern by combining the efficient cell uptake of CNTs with the high drug loading capacity of liposomes in a synergistic fashion. One of the concerns about liposomal delivery is the rapid systemic clearance of the liposome *via* macrophages, which limits the therapeutic effectiveness of the loaded drug [10•].

Table 1

Summary of reviewed functionalization chemistries

Types of association	Advantages	Disadvantages	Molecules attached	Potential applications	References
Non-covalent attachment	Higher loading than covalent approaches	Weaker binding and higher leaching than covalent approaches	Paclitaxel	*In vivo* drug delivery for cancer therapeutics	[9]
	Chemistry of attached molecule is unaltered	Limited to molecules with affinity for nanotube surface	DNA	Detection of protein-protein interactions	[21•]
			Doxorubicin	*In vivo* drug delivery for cancer therapeutics	[8••]
			M13 phage	Tumor detection	[23••]
Covalent attachment (EDC-NHS chemistry)	Exhibits stronger/longer term binding	Loading is limited to the number of available functional sites on nanotube surface	Lysostaphin	Antimicrobial nanocomposite films	[45]
			AcT (perhydrolase)		[44••]
			Protoporphyrin IX		[50•]
	Works for molecules which do not have a high affinity for the nanotube surface	Alters structure of molecule attached which might prove detrimental for the desired application	RNA aptamer	Glycoprotein detection	[26]
			Drug loaded liposomes	*In vivo* drug delivery for cancer therapeutics	[10•]

Figure 1



Key biological applications of carbon nanotubes. Biological applications of nanotubes discussed in this review namely the use of nanotubes as biosensors (inspired by [26]), scaffolds for tissue engineering (to be reprinted with permission from [3]), vehicles for drug delivery in cancer therapeutics (inspired by [4•]) and formation of antimicrobial surfaces.