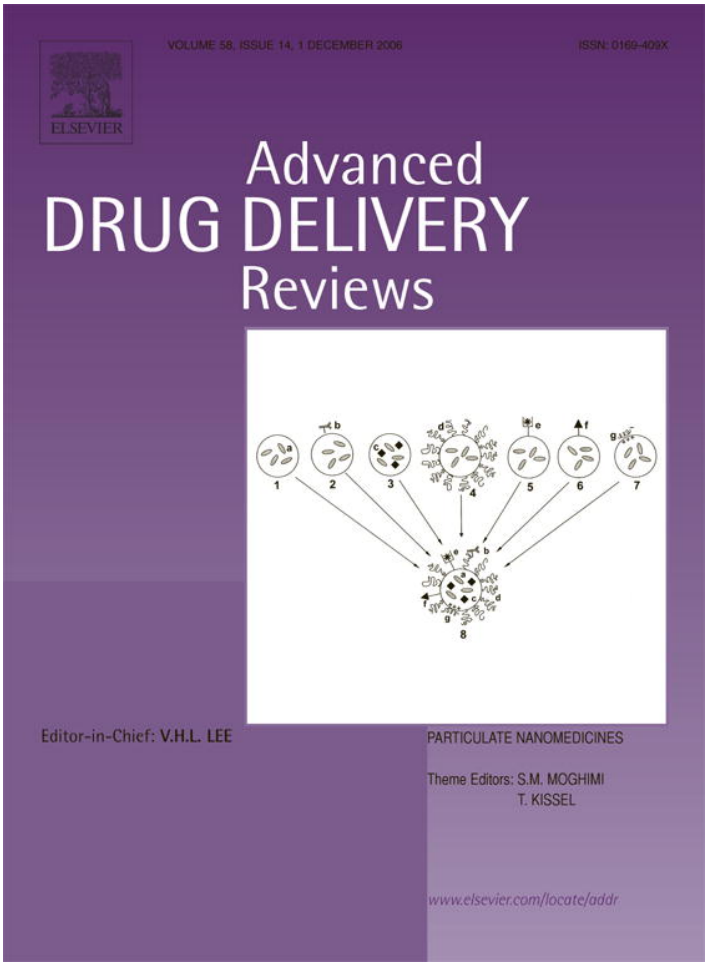

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Carbon nanotubes as nanomedicines: From toxicology to pharmacology ☆

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Abstract

Various biomedical applications of carbon nanotubes have been proposed in the last few years leading to the emergence of a new field in diagnostics and therapeutics. Most of these applications will involve the administration or implantation of carbon nanotubes and their matrices into patients. The toxicological and pharmacological profile of such carbon nanotube systems developed as nanomedicines will have to be determined prior to any clinical studies undertaken. This review brings together all the toxicological and pharmacological *in vivo* studies that have been carried out using carbon nanotubes, to offer the first summary of the state-of-the-art in the pharmaceutical development of carbon nanotubes on the road to becoming viable and effective nanomedicines.

Keywords: Toxicology; Biodistribution; Pharmacokinetics; Cancer nanotechnology

Contents

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1. Introduction

1.1. Nanomedicine: hopes and promises

The last few years have witnessed the discovery, development and, in some cases, large-scale manufacturing and production of novel materials that lie within the nanometer scale. Such novel nanomaterials consist of inorganic or organic matter and in most cases have never been studied in the context of a pharmaceutical. In contrast, some of the most promising and exciting applications of such nanomaterials involve their biomedical utilisation. Use of nanomaterials, nanoparticles and nanocomposites for biomedical purposes constitutes a burgeoning new field called nanomedicine.

The lack of confidence that sometimes is associated with nanomedicines is due to the use of extremely promising and powerful technologies but at the same time potentially harmful ones. This is not unfamiliar territory to fields such as oncology, whereby very powerful technologies (such as nuclear technology) are utilised for the treatment or eradication of diseased tissues, but at the cost of healthy ones with the associated severe side effects. In order to identify if the same is true for nanomedicines, systematic studies must be undertaken to assess their toxicological and pharmacological profiles. Such toxicological and pharmacological characterisation is already part of the process of pharmaceutical development and approval, so nanomedicines should not be considered more harmful than any of the cytotoxic drug molecules being developed.

Administration of nanomedicines as components of therapeutic or diagnostic agents, involves a multi-scale, multi-step process from the initial administration to trespassing the tissue endothelium and into the interstitial space of tissues, through the cell membrane into intracellular compartments and even through the perinuclear membrane into the nucleus of cells (Fig. 1). Nanomedicines will have to go through these barriers following administration before reaching their target or being eliminated.

The development of drug delivery systems to date has indicated that each one of the parameters described in Fig. 1 can have a determinant role in the *in vivo* fate of any material administered, irrespective of the level of complexity or sophistication of the design features on them. The same will hold for all types of novel, 'smart' nanomedicines that are currently under early-stage and will soon be in preclinical development. Any attempt that will ignore or underestimate such parameters will find it difficult to succeed in the preclinical studies and consequently attract the attention of pharmaceutical companies and clinicians that eventually need to be involved in the clinical development of nanomedicines.

In the present paper we are attempting to offer a concise and focused review of the state-of-the-art in the early exploratory exercise of carbon nanotubes (CNT) as nanomedicines that have involved *in vivo* studies. Most studies of this kind using CNT have to this date concentrated on the safety and toxicological burden and response to the nanomaterials. However, elucidation of the pharmacological profiling of CNT has been initiated and it will gradually become apparent what their limitations, opportunities and mechanisms involved are, as more laboratories investigate the pharmacological profile of their nanotubes.

2. Carbon nanotubes (CNT)

Carbon nanotubes (CNT) consist exclusively of carbon atoms arranged in a series of condensed benzene rings rolled-up into a tubular structure. This novel nanomaterial belongs to the family of fullerenes, the third allotropic form of carbon along with graphite and diamond. CNT can be classified in two general categories, based on their structure: single-

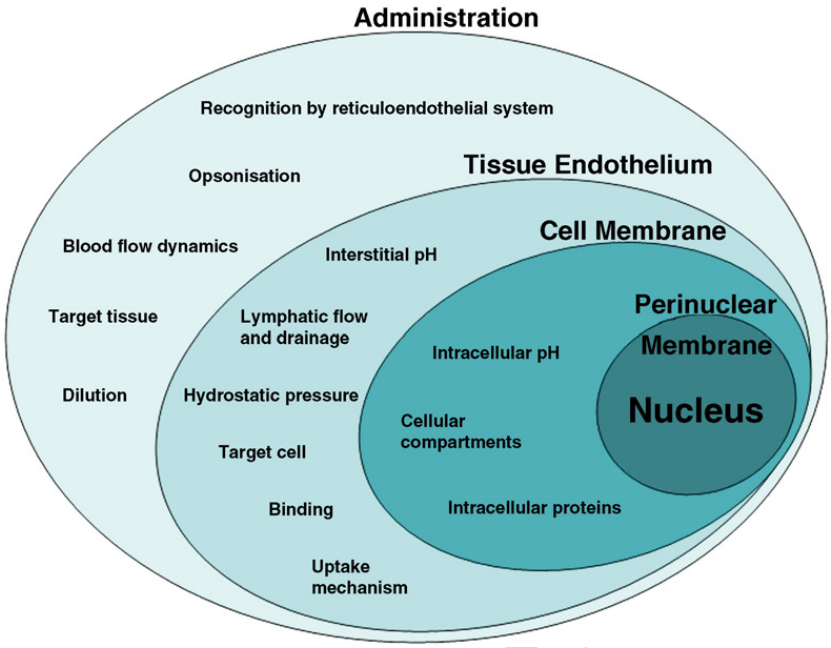

Fig. 1. *In vivo* barriers and critical parameters affecting the fate of nanomedicines.

walled (SWNT), which consist of one layer of cylinder graphene and multi-walled (MWNT), which contain several concentric graphene sheets. CNT have nanometric dimensions: SWNT have diameters from 0.4 to 2.0 nm and lengths in the range of 20–1000 nm, while MWNT are bigger objects with diameters in the range of 1.4–100 nm and lengths from 1 to several μm.

2.1. Physicochemical properties of CNT — a good candidate for nanomedicines

CNT have very interesting physicochemical properties such as: ordered structure with high aspect ratio, ultralight weight, high mechanical strength, high electrical conductivity, high thermal conductivity, metallic or semi-metallic behaviour and high surface area. The combination of these characteristics make CNT a unique material with the potential for diverse applications, including biomedical [1]. There is an increasing interest in exploring all of these properties that CNT possess for applications ranging from sensors for the detection of genetic or other molecular abnormalities, to substrates for the growth of cells for tissue regeneration, and as delivery systems for a variety of diagnostic or therapeutic agents.

2.2. Rational delivery system engineering: what can we do with CNT?

In the last 30 years numerous nanoscale and microscale systems have been developed in order to find efficient carrier systems for drugs, antigens and genes that will facilitate their transport into specific tissues, cell populations and intracellular compartments by minimizing deleterious side effects. Very recently, studies that our groups have pioneered reported that CNT hold potential to becoming a viable component of delivery systems. These studies have shown the translocation of SWNT and MWNT loaded with peptides, proteins, nucleic acids and drugs into mammalian cells [2–6]. Moderate biological effects have been achieved in these studies, but more importantly, they have proven the principle that CNT can offer advantages in terms of their pharmacological utilisation. Moreover, further engineering of the CNT structures will certainly offer new possibilities for diagnostic and therapeutic applications.

2.3. Limitations

Pristine CNT (as prepared, non-functionalised) are inherently hydrophobic, therefore the main obstacle in

the utilisation of CNT in biology and medicinal chemistry is their lack of solubility in most solvents compatible with the biological milieu (aqueous based). To overcome this problem the modification of the surface of CNT (functionalisation) with different molecules is achieved by adsorption, electrostatic interaction or covalent bonding of different molecules and chemistries that render them more hydrophilic. Through such modifications, the water solubility of CNT is improved and their biocompatibility profile completely transformed. Moreover, the bundling/aggregation of individual tubes through van der Waals forces is also reduced by the functionalisation of their surface. However, severe limitations persist as the production of structurally and chemically reproducible batches of CNT with identical characteristics, high quality control and minimal impurities is still a challenge to the pharmaceutical and clinical application of these nanomaterials.

3. *In vivo* studies using CNT

3.1. Toxicity of CNTin vivo

Generally, the harmful effects of nanoparticles arise from the combination of various factors, two of which are particularly important: (a) the high surface area and (b) the intrinsic toxicity of the surface [7]. In contrast with conventional particles of larger mean diameter, nanoparticles under 100 nm can potentially be more toxic to the lung (portal of entry), can redistribute from their site of deposition, can escape from the normal phagocytic defences and can modify the structure of proteins. Therefore, nanoparticles can activate inflammatory and immunological responses and may affect the normal tissue function [7]. CNT, in the context of toxicology, can be classified as 'nanoparticles' due to their nanoscale dimensions, therefore unexpected toxicological effects upon contact with biological systems may be induced. The nanometer-scale dimensions of CNT make quantities of milligrams possess a large number of cylindrical, fibre-like particles, with a concurrent very high total surface area. This total surface area will also depend on their degree of bundling and aggregation of nanotubes in solution. Concerning the intrinsic toxicity of CNT, *in vitro* studies had indicated that SWNT functionalised by a covalent method with phenyl-SO_3H or phenyl-$(COOH)_2$ groups produced less cytotoxic effects than aqueous dispersions of pristine SWNT stabilised with a surfactant — 1% of Pluronic F108 [8]. Moreover, in the same study, the cytotoxicity of covalently modified SWNT has been reported to be further decreased with the increase in the degree of sidewall functionalisation [8]. However, the intrinsic toxicity of CNT does not only depend on the degree of surface functionalisation and the different toxicity of functional groups. Batches of pristine CNT (non-purified and/or non-functionalised) readily after synthesis contain impurities such as amorphous carbon and metallic nanoparticles (catalysts: Co, Fe, Ni and Mo), which can also be the source of severe toxic effects have been reported in studies using pristine CNT.

Donaldson et al. has shown that the structural characteristics of nanomaterials, such as the fibre-shape, the length and the aggregation status of the CNT, can also influence their local deposition in the lungs and the immunological response following exposure to CNT [9]. Another important factor is the bioavailability of CNT in the body. The mechanism of CNT metabolism, degradation or dissolution, clearance and bioaccumulation require attention and study in order to obtain a clearer idea of the limitations of such nanomaterials as components of pharmaceuticals. In the case of fullerenes, non-funtionalised C_{60} were found to have a widespread distribution in tissues and long-term accumulation in the liver [10,11] following intravenous administration, while water-soluble C_{60} were widely distributed in all tissues, retained in the kidneys, bone, spleen and liver and excreted through the urine [12,13] or feces [14]. Because of their similar graphitic backbone nature, previous studies with fullerenes indicate that striking differences between water-soluble and unmodified CNT should be anticipated.

So far the vast majority of reports published on the administration of CNT are primarily concerned with the toxicology of CNT, addressing the possible negative side-effects of this nanomaterial on human health and environment, and particularly from the point of view of public health and safety for CNT production plant workers. As large-scale manufacturing gradually becomes routine for the production of CNT, handling and exposure (dermal and pulmonary) of workers to CNT brings exposure-risk issues to the surface. Maynard et al. have studied the release of particles from unrefined SWNT material into the air and the potential routes of exposure of the workers in a

Table 1
In vivo studies performed with CNT

	CNT	Amount	Model	Exposure conditions/ administration	Exposure duration	Toxicity	Mechanism of toxicity	Ref.
Toxicology	CNT	Soot with high content of CNT	Human volunteers Albino rabbits	Patch test (filter paper saturated with water suspension of soot). Ocular instillation (Modified Draize rabbit eye test)	96 h 24, 48 and 72 h (0.2 ml of water suspension of soot).	No association with skin irritation or allergene risks	Dermatological trials have not shown signs of health hazard.	[16]
	Pristine Arc-CNT	25 mg	Male Dunkin Hartley guinea pigs	Intratracheal instillation (suspension in sterile saline with Tween)	4 weeks (single dose of 0.5 ml)	Not induce any abnormalities of pulmonary function or measurable inflamation	Working with CNT is unlikely to be associated with any health risks.	[17]
	Pristine-laser SWNT	1 and 5 mg/kg	Male Crl:CD® (SD)IGS BR Rats	Intratracheal instillation (suspension in PBS with 1% Tween 80)	24 h, 1 week, 1 and 3 months	Exposure to the high dose produced mortality within 24 h post-instillation. Pulmonary inflammation with non-dose-dependent granulomas.	Mechanical blockage of upper airways. Foreign tissue body reaction.	[20]
	Raw and purified HiPco CNT, Arc-CNT	0.1 and 0.5 mg/ mouse	Male mice $B6C3F_1$	Intratracheal instillation (dispersion in heat-inactivated mouse serum)	7 and 90 days (single bolus of 50 μl)	Induced dose-dependent epithelioid granulomas. Mortality was observed with the high dose.	Intrinsic toxicity (surface chemistry, fibrous structure). Biopersistence	[19]
	Pristine HiPco and laser-ablation-SWNT	Particles in the air (aerosol)	Human volunteers	Inhalation exposure (filter samples) Dermal exposure (cotton gloves)	30 min 11–16 h	Nanotube concentrations from 0.7 to 53 $\mu g/m^3$ (HiPco material produced visible large clumps on the filter) Deposition on individual gloves from 0.2 to 6 mg (visible contamination)	Propensity to unprocessed SWNT forms an aerosol during handling.	[15]
	Hat stacked carbon nanofibers	Not specified	Male Wistar rats	Clusters were implanted in the subcutaneous tissue (thoracic region)	1 and 4 weeks (2 bilateral implants/ rat)	Normal process of inflammation for foreign bodies, without severe inflammatory response was observed. No acute toxicity in the subcutaneous tissue. No inhibition of wound healing.	Water solubility and characteristic structure composed (were phagocytosed and delaminated)	[22]
	MWNT	0.5, 2 and 5 mg/rat	Female Sprague–Dawley rats	Intratracheal instillation (suspension in sterile 0.9% saline with 1% Tween 80)	1 and 2 months (single bolus of 500 μl/rat)	Not ground MWNT accumulate in the airways. Ground MWNT were cleared more rapidly. Both MWNT have induced inflammatory (more marked for ground MWNT) and fibrotic reactions. Also both have caused pulmonary lesions at 2 months.	Length appears to modulate clearance kinetics. Biopersistence. Intrinsically toxic to the lung.	[24]

	MWNTox (220 and 825 nm)	Clusters of 0.1 mg	Male Wistar rats	Clusters were implanted in the subcutaneous tissue (thoracic region)	1 and 4 weeks (2 bilateral implants/rat)	Granulomatous inflammation. Inflammatory response around 220 nm was slighter than 825 nm MWNTox.	Length: macrophage could envelop the 220 nm more readily than MWNTox. Amount implanted.	[23]
	Metal-free HiPco SWNT	0–40 μg/mouse	Female C57BL/6 mice	Pharyngeal aspiration (suspension in PBS)	1, 3, 7, 28 and 60 days (single bolus of 50 μl)	Rapid progressive fibrosis and granulomas. Dose-dependent increase in expiratory time. Increased pulmonary resistance.	Delivery and deposition of SWNT in aggregates or dispersed structures. Exposure to respirable SWNT particles can be a risk to developing some lung lesions.	[21]
	CVD-and Arc-MWNT from Huczko's lab and commercial sources	15 mg	Guinea pigs	Intratracheal instillation (suspension in sterile saline with SDS)	90 days (single bolus of 0.5 ml)	Organizing pneumonitis with focal non-specific desquamative interstitial pneumonia-like reaction. Increase of lung resistance. Pulmonary lesions.	Time of exposure and material characteristics.	[18]
	Purified open SWNT and MWNT	50 μg/ml	Wistar–Kyoto rats	Intravenous administration (suspension in 0.9% saline solution)	(single dose of 0.5 ml)	Accelerated time and the rate of development of carotid artery thrombosis.	Ability to activate platelets.	[25]
Pharmacology	^{125}I-SWNT (OH)	1.5 μg/mouse	Male KM mice	Intraperitoneal injection, subcutaneous injection, stomach intubation and intravenous injection	Time points from 1 h up to 18 days (single dose of 100 μl)	Distribute in the entire body quickly except for the brain. Accumulate in the bone. Excreted via urine.	Biological behaviour attributed to their compact structure and good biocompatibility.	[28]
	[^{111}In] DTPA-CNT	60 and 400 μg/mouse	Female BALB/c mice	Intravenous administration (in PBS)	30 min, 3 and 24 h (single dose of 200 μl)	Not retained in any of the reticuloendothelial system organs. Rapidly cleared from systemic blood circulation via renal excretion. No accumulation was observed. Without any toxic side effects or mortality.	Water-soluble CNT. Biocompatibility. Improved toxicity profile compared with non-functionalised CNT. Low interaction with blood proteins.	[29]
Therapeutics	Mono-and bis-derivatized B cell epitope SWNT	Not specified	Female BALB/c mice	Intraperitoneal administration (in Freund's emulsion with ovalbumin)	2 weeks (single dose)	Elicited strong anti-peptide antibody responses with no detectable cross-reactivity to the CNT.	Suggest that CNT do not possess intrinsic immuno genicity.	[30]
	Open–ended CNT	5 mg/kg	Male Wistar rats	Intra-small intestinal administration	Time points from 1 to 6 h (single dose)	CNT gave maximum serum levels of erythropoietin. CNT improve bioavailability of erythropoietin.	Attributed to their size and structure (high adsorption area).	[31]

small-scale production facility. They have found that handling of unrefined material produces airborne particle concentrations of 53 μg/m^3 and glove deposits of 0.2–6 mg per hand [15].

Huczko et al. have analysed the toxicity of purified, pristine CNT material suspended in a saline solution using the surfactant Tween by dermatological tests on human volunteers and rabbits [16]. Also, they examined the effects of a CNT dispersion using a saline solution with Tween or SDS (sodium dodecyl sulphate) by pulmonary function tests and bronchoalveolar lavage examinations in guinea pigs [17,18]. No association was found between working with a soot containing CNT and risk of skin irritation or allergy. However, it was shown that the duration of exposure to CNT plays a critical role in the degree of respiratory distress caused and the induction of pathologies in lung tissues.

Lam et al. have also investigated the pulmonary toxicity of SWNT in mice and considered that chronic inhalation exposure of SWNT is a serious occupational health hazard [19]. Histophathological studies of lungs 7 and 90 days after a single intratracheal instillation of a SWNT dispersion have shown that in a dose-dependent manner, SWNT containing different types and amounts of residual catalytic metals induced epithelial granulomas and interstitial inflammation at 7 days, which persist and develop to peribronchial inflammation and necrosis at 90 days. In this study the pristine SWNT were suspended in heat-inactivated mouse serum by shearing and sonication.

Warheit at al. reported the acute pulmonary toxicity effects of SWNT in rats. The SWNT used were dispersed in PBS (phosphate buffer saline) with the aid of 1% Tween 80 and exposure by intratracheal instillation at 5 mg/kg resulted in a 15% mortality rate. The authors considered the agglomeration of SWNT in the major airways as the primary cause of death, excluding the role of any inherent toxicity of the SWNT. However, a dose independent foreign tissue body reaction was verified by the formation of multifocal granulomas centered around SWNT aggregates [20].

Very recently, Shvedova et al. exposed mice to pharyngeal aspiration of purified pristine SWNT (free of metal contaminants) in order to extend the understanding of the dose-dependence and time-course of pulmonary responses. The suspension of purified SWNT in PBS produced acute inflammation, progressive fibrosis and formation of granulomas. Furthermore, an increase in the protein levels was verified, namely lactate dehydrogenase and γ-glutamyl transferase activities in BAL (bronchioalveolar lavage) fluid and the effect on normal pulmonary function was persistent, while bacterial clearance was decreased [21].

Yokoyama et al. have evaluated the biocompatibility of hat-stacked carbon nanofibers implanted in the subcutaneous tissue of rats. Around the carbon nanofibers they have observed granulomatous inflammatory changes after 1 week and fibrous connective tissue after 4 weeks. However, the lack of necrosis or invasion of neutrophils (severe inflammatory response) led the authors to conclude that the wound healing capacity of the tissue was not inhibited and that the carbon nanofibers are not acutely toxic in the subcutaneous tissue of rats [22].

Lastly, two very recent studies illustrated that the length of CNT modulates the immune response, clearance kinetics and bioavailability regardless of whether CNT were functionalised or not [23,24]. Radomsky et al.[25] have shown that platelets were easily targeted and activated by carbon nanotubes with consequent *in vivo* acceleration of the rate and time for the development of carotid artery thrombosis. A summary of all studies reported in the literature so far using *in vivo* investigations of CNT is presented in Table 1. This is hoped to serve as a guide to laboratories designing *in vivo* studies to assess the tissue tolerance and toxicity of their carbon nanotubes. Moreover, it indicates that most investigations to date that have looked at the interaction between CNT and the tissues of live organisms have predominantly been examining the toxicological burden and response of these materials rather than assessing any therapeutic aim. This will gradually change as more confidence and knowledge is gained on how to handle CNT for biomedical applications.

3.2. Pharmacology of CNTin vivo

The biodistribution and pharmacokinetics of nanoparticles rely to a large extent on their physicochemical characteristics such as size, shape, aggregation, chemical composition, surface functionalisation and solubility [26,27]. Fig. 2 schematically represents those physicochemical parameters that play a determinant role in the pharmacological and toxicological profile obtained (left column) and the more specific

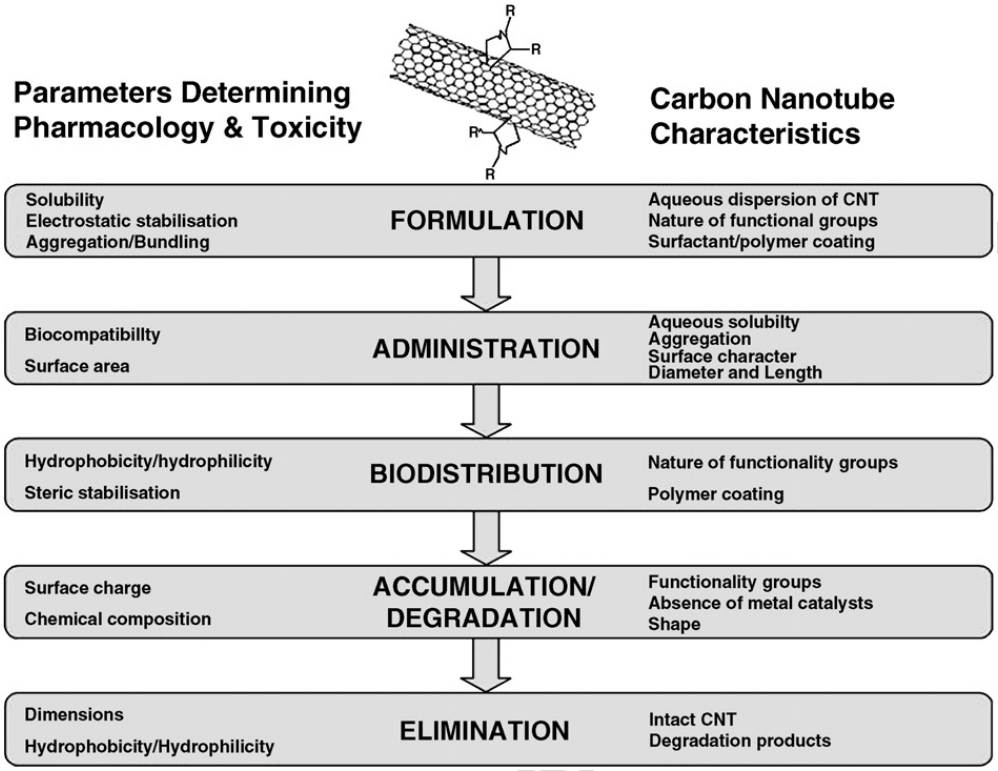

Fig. 2. Parameters determining the pharmacological and toxicity profile of CNT and the CNT characteristics that can be used to control them.

CNT characteristics (right column) critical at each stage of their development as nanomedicines.

To our knowledge, only two studies have been reported so far concerning the biodistribution of CNT. Both studies were performed with water-soluble CNT, which are biocompatible with the body fluids. None of the studies report toxic side effects or mortality. Wang et al. [28] have used ^{125}Iodine-labeled multiple hydroxylated SWNT (^{125}I-SWNT-OH), functionalised by oxidation of the nanotubes, and radiotraced their distribution in mice after administration by, primarily, intraperitoneal (i.p.) administration. Other routes of administration were compared to i.p. such as subcutaneous, oral (by stomach intubation) and intravenous. This study reported that the CNT biodistribution was not significantly influenced by the administration route and that the ^{125}I-SWNT-OH distribute quickly throughout the whole body. The preferred organs for accumulation were the stomach, kidneys and bone. Most importantly from the safety point of view, 94% of the nanotubes were excreted into the urine and 6% in the feces as observed in this study. No tissue damage or distress was reported.

Another study, focusing on the intravenous route of administration and using functionalised SWNT and MWNT following a different surface chemistry (i.e. via the 1, 3-dipolar cycloaddition reaction) compared to the SWNT used in the study by Wang et al., was performed in our laboratories. The CNT were functionalised with the chelating molecule diethylentriaminepentaacetic (DTPA) and radiolabeled with ^{111}Indium ([^{111}In] DTPA-CNT) [29]. In this study, the effect on biodistribution and blood circulation half-lives of different degrees of surface functionalisation with DTPA was also studied, using 100% and 60% surface functionalisation with DTPA (the remaining 40% functional group were amino functions). The biodistribution profiles obtained were found very similar for both types of functionalised [^{111}In] DTPA-SWNT which showed an affinity for kidneys, muscle, skin, bone and blood 30 min after administration. However, all types of nanotubes were found to be rapidly cleared from all tissues and a maximum blood circulation half-life of 3.5 h was determined. The excretion of DTPA-CNT, both SWNT and MWNT functionalised with 100% DTPA were found to be excreted through the

renal route into the bladder and urine following intravenous administration. Moreover, both types of DTPA-CNT were observed intact in the excreted urine by transmission electron microscopy.

Even though more studies need to be carried out by more laboratories using different kinds of nanotubes, the implications from these two initial studies are encouraging since no acute toxicity or adverse reaction to the administration of functionalised CNT was reported, contrary to the quite severe tissue deposition and inflammatory response observed after administration of pristine CNT. The future application of CNT for the construction of novel nanomedicines, as indicated from both studies above, is important not only to reveal the biodistribution of these nanostructures but also to show the importance of the organic functionalisation on the surface of CNT, which transform non-functionalised CNT (insoluble in most solvents) into water-soluble and biocompatible CNT with an improved toxicity profile.

3.3. Therapeutics with CNTin vivo

Clinical applications of CNT are offering a great number of opportunities provided we are able to take advantage of the characteristics nanotubes offer. To date two *in vivo* studies have been published which demonstrate the potential of CNT in helping improve the characteristics of known therapeutics.

Our groups have developed a CNT-based vaccine delivery system, which *in vivo* has elicited strong anti-peptide antibody responses in mice. Covalent conjugation to CNT of the neutralizing B cell epitope from the foot-and-mouth disease virus has shown that the appropriate peptide conformation to be recognised by antibodies is maintained. Moreover, no antibodies were produced against the CNT backbone alone, suggesting that the nanotubes do not possess intrinsic immunogenicity [30]. Combination of all the described features of the vaccine system with the fact that the capacity of the anti-peptide antibodies to neutralise FMDV have been enhanced has indicated that CNT can have a valuable role in the construction of novel and effective vaccines.

A recent study from Venkatesan et al. has shown that among a group of different types of nanoparticles, CNT were the delivery systems offering the best improved bioavailability of erythropoietin (EPO). The formulation comprised CNT (adsorbent), erythropoietin (protein drug), casein (intestinal enzyme inhibitor) and Labrasol (absorption enhancer) and was evaluated in rats by intra-small intestinal administration [31]. This study proposed that the above CNT-based carrier system can offer a successful oral alternative administration of EPO, which has not been possible so far because of the denaturation of erythropoietin by the gastric environment conditions and enzymes.

Since more *in vitro* proof-of-principle studies generate promising biomedical applications for CNT, one can expect that the *in vivo* development of such systems will follow. Such *in vitro* studies include the work by Kam et al. showing selective cancer cell killing obtained by hyperthermia due to the thermal conductivity of CNT internalised into those cells [32]. Also from our laboratories, the work developed regarding the use of CNT as gene therapy vectors [2,33] and drug delivery systems [5,34] have shown that these engineered structures can effectively transport the genes and drugs inside mammalian cells. In fact, the CNT-transported genetic material have conserved the ability to express proteins and while the CNT-mediated delivery of amphotericin B leads to therapeutic efficacy by offering improvements in the currently problematic and cumbersome formulation of this drug in aqueous solutions. The pharmacological and therapeutic profiling of such CNT-based systems will generate more *in vivo* studies as the field of carbon nanomedicines comes of age.

4. Conclusions

The development of nanomedicines depends on extremely promising and novel materials of only a limited existing knowledge of their toxicological and pharmacological profiles. CNT are such materials that have been poised to revolutionalise a variety of biomedical applications. The *in vivo* toxicological and pharmacological studies undertaken so far indicate that funtionalised carbon nanotubes can be developed as nanomedicines, contrary to non-funtionalised, pristine carbon nanotubes. Functionalisation renders the surface of carbon nanotubes water-soluble, compatible with biological fluids and leads to their rapid excretion through the renal route, minimising unwanted tissue accumulation. The door of opportunity for the development of carbon nanotubes as diagnostic and

therapeutic nanomedicines has opened, and systematic study of their therapeutic efficacy is anticipated.

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