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Carbon Nanotubes: a viable drug delivery platform for the treatment of cancer

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ABSTRACT

The development of new drug delivery platforms and specific vectorization processes for the treatment of diseases like cancer has become vitally important for the pharmaceutical industry. One of these new platforms are functionalized carbon nanotubes (f-CNTs), which are characterized by their high aspect ratio, high loading capacity, rich surface chemistry with functional groupsfor binding drugs and molecules. It has been demonstrated that functionalization processes of CNTs generate a marked decrease in toxicity, which makes them ideal candidates for clinical studies for their use as drug vectors.

INTRODUCTION

One of the revolutionary fields in nanotechnology is nanomedicine, which is principally based on the exploitation of the nanometric scale for biomedical uses. Nanomedicine focuses on the development of new platforms for the diagnosis and treatment of diseases. It poses two important challenges: (1) understand the effect of drugs from knowledge their interactions with biomedical systems at a molecular level, and (2)control with high precision these effects. The latter of these two challenges requires the development of drug delivery nanometric platforms, also known as nanoplatforms, nanostructures, nanocarriers or nanoparticles. The existing set of nanoparticles so far includes liposomes, smart polymers, dendrimers, viral nanoparticles, metal nanoparticles, polymeric nanoparticles, solid lipid nanocarriers, mesoporous silica nanoparticles, etc. In the figure 1 and figure 2 are shown some nanoplatforms compared to what we know. Liposomes are the platforms most studied and were the first to be accepted for commercialization by the FDA. Two examples are Doxil (doxorubicin HCl), commercialized by Ortho Biotech Products, and Vysudine (Verteporfin) from Novartis.

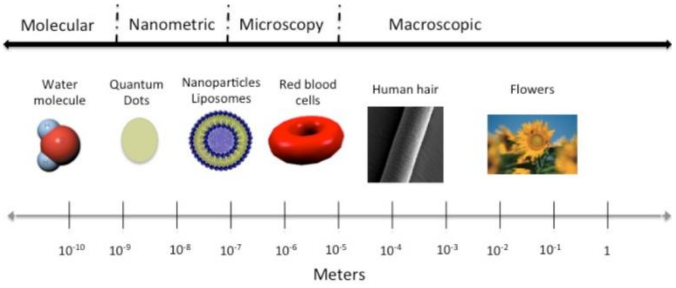

Fig. 1: Scale of the representative sizes know objects.

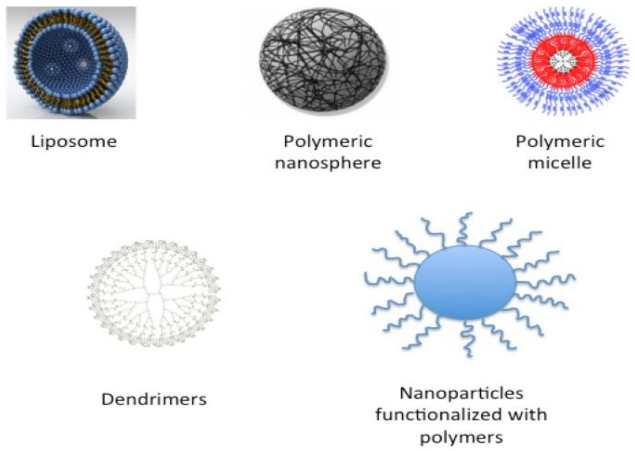

Fig. 2: Nanoparticles used for drug delivery in biological systems.

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Table 1: Pharmaceutical products commercially availableon a nanometric scale (Zolnik and Sadrieh, 2009).

Drug name	Generic name	Nanoplataform	Company	Indication	Route of administrations
Abelcet	Amphotericin B	Liposome	Enzon Pharmaceuticals	Antifungal	i.v.
Abraxane or nab-PTX	Paclitaxel	Albumin-bound particles	Abraxis oncology	Cancer	i.v.
AmbiSome	Amphotericin B	Liposome	Astellas Pharma US, Inc.	Antifungal	i.v.
AmBisome	Amphotericin B	Liposome	Gilead sciences	Antifungal	i.v.
Bind-014*	Docetaxel.	Polymeric	Bind Therapeutics	Cancer	i.v.
Caelyx	Doxorubicina	Liposome	Schering-Plough, S.A	Cancer	i.v.
CALAA-01*	siRNA	Rondel ™	Calando pharmaceuticals inc	Cancer	i.v.
Cynviloq™	Paclitaxel	Polymeric micelle	Sorrento Therapeutics	Cancer	i.v.y
DaunoXome	Daunorubicin citrate	Liposome	Diatos	Cancer	i.v.
DaunoXome,	Daunorubicin	liposome	Diatos,	Cancer	i.v.
Depocyt	Cytarabine	Liposome	Enzon Pharmaceuticals	Lymphomatous meningitis	i.t.
Doxil	Doxorubicin HCl	Liposome	Ortho Biotech Products, LP	Cancer	i.v.
Genexol-PM	Paclitacel	Polymeric micelle	Samyang Biopharmaceutic	cancer	i.v.
Invega Sustenna	Paliperidone palmitate	Nanocrystal	Janssen	Schizophrenia.	IM depot
Lipodox Lipodox 50	Doxorubicin	Liposome	Sun Pharma Global FZE	Cancer	i.v.
Lipoplatin+	Cisplatin	Liposome	Regulon	Cancer	i.v.
Myocet	doxorubicina	Lipoosome	Enxon Pharmaceuticals	Cancer	i.v.
Neulasta	Pegfilgrastim	Polymeric micelle	AMGEN	neutropenia,	Subcutaneous
Oncaspar	Pegaspargase	Polymeric micelle	Enzon Pharmaceuticals	Leukemia	IM or IV
Rapamune	Sirolimus	Nanocristal	Wyeth	Immunosuppressant	Oral
TriCor	Fenofibrate	Nanocristal	Abbott Laboratoires	Hypercholesterolemia and Hypertriglyceridemia	Oral
Triglide	Fenofibrate	Nanocristal	Sciele Pharma, Inc.	Hypercholesterolemia and Hypertriglyceridemia	Oral
Xeplion	Paliperidone	Nanocrystal	Janssen	schizophrenia.	IM depot

+ Clinical phase III, *Clinical phase I.

Other examples of nanoplatforms commercially available are reported in Table 1. Through the use of nanoplatforms for drug delivery, nanomedicine is getting close to what Paul Ehrlich meant in 1904 when he talked about a "magic bullet", because nanostructures are designed to confer therapeutic specificity, in a process known as drug vectorization.

Therapeutic specificity from the combination of three key elements: 1) a targeting ligand to disease to be counteracted, 2) a drug for the treatment of this disease, and 3)a carrier to deliver this drug in the specific place.

There are various reasons for drugs vectorization. One of these is the existence of drugs that are highly toxic to humans and their use is due to the risk-benefit ratio, such is the case with the majority of anti-cancer drugs. Through the technique of vectorization, adverse effects can be reduced or even completely eliminated by preferential delivering the drug to the site of interest, some examples are the efforts that have been made to reduce the systemic effects of doxorubicin (Lin *et al.,* 2012), morphine (Carvalho *et al.,* 2007), paclitaxel (Fetterly *et al.,* 2008) and cisplatin (Stathopoulos *et al.,* 2006). Another reason is the low bioavailability of many drugs due to their low aqueous solubility, limited absorption and distribution in the body. About 70% of new drugs exhibit poor aqueous solubility (Kawabata *et al.,* 2011), the vectorization process enable modify the interactions of the drug with water, becoming an insoluble drug in a viable option.

Finally, the costs associated to the development of new medicine (Adams and Brantner, 2006), significantly decrease if therapeutic effectiveness of the drug has already been proven.

Through vectorization processes a new medicine may be created with a new performance profile. Considering that currently there are many drugs whose patent protection has expired or is close to expire (Paul *et al.,* 2010), and the fact that it is getting more and more difficult to discover new drugs, vectorization looks to become an ever more attractive strategy.

CANCER AND NANOPLATFORMS FOR THE DELIVERY OF DRUGS

Therapeutic specificity

To achieve design particles with therapeutic specificity is important to understand the biochemistry of the disease process that is going to intervene. In this sense, it must be recognizing that in early stages the carcinogenic tumor passively feeds on the oxygen and nutrients by simple diffusion. When the tumor begins to grow and its size is greater than 2 mm^3, a hypoxic state is generated and this triggers a complex process known as angiogenesis. The angiogenesis is the formation of small blood vessels from those that already exist. This process consists of 5 stages: (1) activation of endothelial cells, (2) degradation of the support membrane, (3) migration of cells from the endothelium, (4) vessel formation and (5) angiogenic remodeling (Bergers and Benjamin, 2003).

The knowledge of angiogenesis process has provided two strategies to confer therapeutic specificity to the drug delivery nanostructures: passive and active specificity. The passive specificity, which takes advantage of an effect known as the

enhanced permeability and retention effect (EPR effect). Active specificity mostly relies on the functionalization of nanostructures with specific ligands for certain receptors that are over-expressed either within the tumor or in the surrounding vascular tissue (Lammers *et al.*, 2012).

Passive specificity

Passive specificity is based on the exploitation of EPR effect, a phenomenon that is expressed in almost all solid tumors, except in tumors with hypovascularity such as prostate and pancreatic cancer. EPR effect occurs as result of anatomical differences between a neoplastic and a normal tissue. In tumors, aside from the hypervascularization given by angiogenesis, tumor capillaries presents large gaps between the endothelial cells ranging from 100-780 nm, while in normal endothelium is 5-10 nm, furthermore, solid tumors lack of functional lymphatic drainage (Fang *et al.*, 2011).These factors favor accumulation of the nanostructures in the tumor microenviroment (Nakamura *et al.*, 2014). EPR effect was discovered by Matsumura and Maeda (Matsumura and Maeda, 1986) and has become one of the cornerstones in treatments utilizing drug delivery nanoplatforms. The main problem by this phenomenon is that almost all solid tumors presents a high interstitial fluid pressure, which substantially decreases the uniform distribution of the drug throughout the tumor, especially in its center. Bazak, 2014presents a more complete panorama about passive specificity.

Active specificity

The active specificity process is based on the binding of ligands to the surface of the nanoparticle. Ligands must be recognized by specific tumor cell receptors or the tumor endothelium. The main characteristic of these receptors is that they must to be uniformly over-expressed in the target cells. The most studied target receptors for carcinogenic cells are transferrin, folate, surface glycoprotein receptors, and the epidermal growth factor receptor (Xu *et al.*, 2013). When a tumor endothelium ligand is used, it is expected that the antineoplastic agent avoid the growth of new blood vessels and promote the death of the existing vessels. In this way, the tumor is killed through the suppression of oxygen and nutrients in its interior. The most studied receptors for tumor endothelium are the vascular endothelial growth factor, the αvβ3 integrin, the vascular cell adhesion molecule-1 (VCAM-1) and matrix metalloproteinases. Wang and Thanou, 2010 give a more extensive analysis of active specificity.

To date, a new generation of nanoparticles is emerging, which looks for targeting at subcellular level, this new challenge arises that the drug is released within specific cellular organelles as the attempts to the selective accumulation in the mitochondria, e.g. it was found that nanoparticles positively charged are preferentially located in mitochondria of human cervical cancer (HeLa) cells (Marrache and Dhar, 2012). Also, it has tried to develop nanoparticles targeted to the nucleus where the endoplasmic reticulum and the Golgi apparatus have been used as vias to reach nucleus (Reilly *et al.*, 2012). A comprehensive review for this new level of complexity of the nanoparticles is presented by Yameen, 2014.

General characteristics of nanoparticles with therapeutic specificity

Some physical properties of the nanoparticles crucially influence their interaction with biological systems and therefore their performance as drug-carriers. These properties affect the kinetic behavior and intratumoral penetration of the nanoparticles. The nanoparticles to achieve an accumulation process on tumor tissue, must maintaining in the systemic circulation for a long time, and must avoid being excreted from the body quickly or eliminated by the reticule endothelial system (RES). The nanoparticles, after being injected intravenously into the body, are distributed into multiple RES organs, mainly the liver (between 60% - 90%), spleen (2% - 10%), lungs (3% - 20%, even more), and bone marrow (1%) (Gastaldi et al, 2014). The clearance by RES begins with opsonization process, where a foreign particle is covering with non specific proteins to be recognized by phagocytic cells (Owens and Peppas, 2006).

The nanoparticle size affects its ability to reach the tumor and accumulate there. The extravasation to the tumor require that the nanoparticle was smaller than the fenestrations of neovascularization of the tumor (400-600nm) (Ernsting *et al.*, 2013). Several studies have shown the degree of influence of nanoparticles size on its penetration in tumor (Huo, 2013; Hrkach *et al.*, 2012). The size also affects the systematic distribution and the clearance of nanoparticles, smaller sizes favor excretion in the kidneys (5.5 nm cut off renal filtration) (Choi *et al.*, 2007) and larger sizes favor metabolism by the liver (50-100 nm cut off liver filtration), or are leakage at the inter-endothelial splenic cell slits(400-500 nm) (Moghimi *et al.*, 1991). Consequently, the size of the drug delivery nanoparticles must be between 10-100nm.

The surface charge particle is essential to avoid the opsonization process because it has been found that the proteins are adsorbed on the surface of the nanoparticles through electrostatic interactions, hence the neutral particles are less prone to opsonization (Li and Huang, 2008), while positive and negative nanoparticles, with zeta potential in the range of -10< ς-potential >10 mV) are strongly opzonizable (Xiao, 2011). Positive ones exhibits a greater effect. In addition, the nanoparticle charge also influences cellular uptake, since the cell membrane is dominated by a negative environment conferred by the presence of sulphated proteoglycans (Bernfild *et al.*, 1999). In the case of cancer cells, the negative charge density on the cell surface is increased due to the translocation of anionic molecules (such as phosphatidylserine) from the inner layer of membrane to the surface cell (Ran, 2002).Hence the positive nanoparticles are adsorbed on the cell membrane by electrostatic forces, and then they are internalized through pinocytosis, endocytosis or other process. (Löhr *et al.*, 2012). Since nanoparticles charge can promote processes that positively or negatively affect drug targeting delivery, the zeta potential of the nanoparticle must be optimized to enhance the

intratumoral accumulation of the drug. A major review is presented by Honary and coworker, 2013a and 2013b.

The modification of nanoparticle surface by hydrophilic polymers like polyethylene glycol (PEG), is a strategy extensively used in drug targeting, to prevent the opsonization and protect the nanoparticles from being cleared up by RES and reduce hematological toxicity when they are administrated for i.v. via. PEGylation can amend the pharmacokinetic behavior of nanoparticles because imparts to nanoparticle steric hindrance, a high hydrodynamic size due to capacity to entangle water molecules, and a softness surface (Termsarasab *et al.,* 2014, Rabanel *et al.*, 2014).

The effectiveness of PEGylation rely on long chain and coverage-density, these factors can also avoid nanoparticles reach the target tumor by inhibition of cellular uptake mechanisms or prevent binding with proteins targets (Rabanel *et al.,* 2014, Kim *et al.*, 2013). Recently, it has been observed that PEG-coating results in the generation of PEG specific IgM antibodies that enhance clearance under in vivo assays under repeated administration, effect known as the "accelerated blood clearance (ABC) phenomenon (Abu Lila *et al.*, 2013).

A new approach to improve the circulation time, it is the association of nanoparticles with circulatory cells, where the nanoparticles are attached to cell by adsorption, covalent binding or internalization. This strategy has been coined as cellular hitchhiking-based drug delivery (Anselmo and Mitragotri, 2014).
Another important aspect is the shape, because nanoparticles can take many forms such as spheres, needles, tubes, among others. An inadequate control of the size and shape can affect the toxicological response in the organism in negative way (Ernsting *et al.,* 2013, Toy et al, 2014). It has been observed that nanoparticle geometry is a pivotal factor in the interaction with macrophages, the elongated particles are less prone to internalization via phagocytosis (Mathaes *et al.*, 2014).

CARBON NANOTUBES AS NANOPLATFORMS FOR ANTINEOPLASTIC AGENT DELIVERY

Carbon nanotubes (CNTs) are an allotropic form of carbon like diamond, graphite and fullerenes. Their structure consists of a layer of graphite wrapped around itself(see Figure 3a). The way the layers are rolled up and the conformation of the original layer result in nanotubes of different diameters and internal geometry. NTCs are classified as simple-walled nanotubes (SWCNT) and multiple-walled nanotubes (MWCNT). CNTs have interesting properties mainly due to a structural conformation that gives them great versatility and potential for use in different applications (Kim *et al.,* 2014) despite the short time that has elapsed since their characterization by the Japanese scientist Iijima in 1991 (Iijima, 1991). They exhibit some features that not favor the biological interaction as their hydrophobic nature, which leads to they are prone to agglomerate and cause cell death (Peretz and Regev, 2012). Therefore the pristine-CNT surface modification is necessary to make them compatible in the biological environment

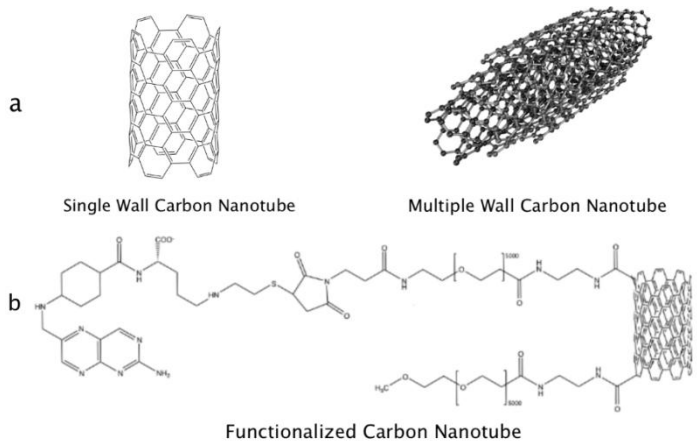

Fig. 3: Simple walled, multiple walled carbon nanotubes and carbon nanotubes functionalized by PEG and Folic Acid by covalented linkage like example of process of fucntionalization.

(Battigelli *et al.,* 2013), resulting a new type of NTC coined as functionalized nanotubes (f-NTC)(see Figure 3b). One of the most interesting applications for f-CNTs is their use in the treatment of diseases in areas as oncology, gene delivery, infectious diseases, and vaccines (Karimi, et al 2015). f-NTCs are currently considered a potential biomedical material to vectorization of drugs due to: (1) their ability to across the cellular membrane via passive diffusion in several types of cells, and also through energetically active routes (Kostarelos *et al.,* 2007, Lacerda *et al.,* 2013),(2) extremely high loading capacity due to ultrahigh surface area up to 2600 m2/g (Sun et al,2014), and also by their hollow monolithic structure; in fact, they are one of the nanoparticles with larger capacity of drug entrapment (Mody *et al.,* 2014), (3) rich surface chemistry which enables to simultaneously attach a wide range of molecules with different functions in nanomedicine, for example for targeting and imaging. Therefore f-CNTs represent a versatile structure compared with other nanoparticles,(4) f-NTCs exhibit an optical absorption from visible to NIR, allowing their use in photothermal therapy, which complements the chemotherapy (Wang *et al.,* 2013) and (5) f-CNT as any nanoparticles undergo the EPR effect resulting in an intratumoral accumulation.

On the other hand, one of the limitations of nanotubes is related to their toxicity. This will be discussed in the section below.

Toxicological aspects

Regarding this issue, it is necessary to distinguish the toxicity induced by occupational exposure of pristine-NTC and that induced by intentional administration of f-CNT in nanomedicine. Since the growing number of industrial applications of CNT, there are a significant number of workers who are exposed to handling of them, becoming an important occupational health problem. In these case, the major route of exposure for CNTs is the inhalation, leading to pulmonary accumulation and generating pathologic responses similar to those produced by the asbestos fibers (Stella, 2011): inflammation, fibrosis, oxidative stress, and mutagenesis. This effect has undoubtedly delayed the

use of f-NTC in nanomedicine. It has been found that the toxicity depends on the physicochemical properties of the CNTs, as size, surface properties and synthesis impurities, and pharmacological parameters (dose, administration via).

Pristine-NTCs exhibit small diameters and great lengths (approximate length up to 1 mm with diameters between 0.4 nm up to 100 nm). The needle-like shape enables NTC pierce the cell membrane, favors the indiscriminate adsorption by any cell type, facilitates their recognition and accumulation by RES and confers a similar behavior to asbestos fibers (Firme and Bandaru, 2010).Size reduction becomes an important tool to improve the safety profile as the biodistribution of f-NTC. With the advent of new technologies of production of CNT, it is possible to obtain homogeneous diameters, while the length control requires additional processes (Bouanis *et al.*, 2014). Various techniques such as mechanical fracture, selective oxidation and growth control have been implemented to shorten NTCs (Tserpes *et al.*, 2006, Kang *et al.*, 2006, Rauwald *et al.*, 2009). It has found that pristine-NTC> 10 µm produce granuloma, pristine-NTC <10 µm are retained by RES, whereas oxidized SWNTC < 300nm and oxidized MWCNT <500 nm are excreted via the kidneys and bile ducts (Kolosnjaj-Tabi et al., 2010, Jain *et al.*, 2011). The f-NTC diameter also affects its biodistribution, narrow diameters (9.2 nm) exhibit a higher tissue accumulation than wider diameters (39.5 nm) (Wang, 2014a).

Regarding impurities, transition metals (As, Fe and Ni) are used as primers in the synthesis of NTCs by chemical vapor deposition, remaining bonded to them as impurities, and may represent between 20% and 40% of their weight. The metal impurities may act as biocatalysts, thereby promoting the formation of oxidative species and generate cell death by apoptosis (Firme and Bandaru, 2010). Purification processes using strong acids such as HCl, H_2SO_4 and HNO_3, which act as oxidizing agents, can remove these metals and other impurities such as carbon graphite and thus can reduce the toxicological effect exerted by themselves. At the moment, there are new synthesis technologies, such as plasma and electric arc to achieve high-purity metallic CNTs, where impurities have been reduced to less than 5% weight. Pristine-NTCs have highly hydrophobic surfaces, which favors aggregation process resulting in a change in their size and surface area, and in turn increase the citotoxicity (Wick et al, 2007). Functionalization processes are mandatory to impart greater hydrophilicity in the NTC surface. The surface modification can be achieved from two approaches: covalent and non-covalent functionalization.

The non-covalent functionalization consists in the binding of amphiphilic macromolecules to NTC surface through physisorption by π- π stacking, hydrophobic interactions or macromolecules wrapping (see figure 4). It has been performed numerous studies with various surfactants of different nature (ionic and non-ionic) to evaluate its effect on the dispersibility and adsorption of drugs on NTC (Madni *et al.*, 2010, Oleszczuk and Xing, 2011).

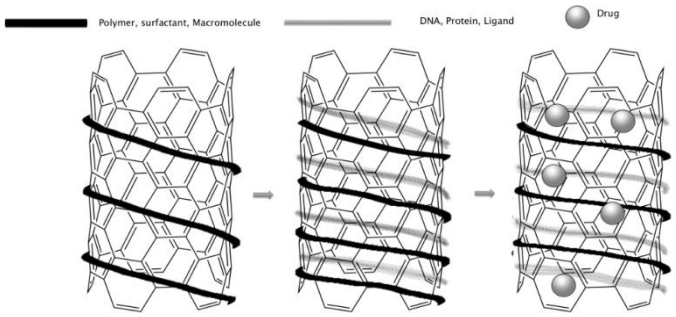

Fig. 4: No-covalent functionalization of Carbon Nanotubes.

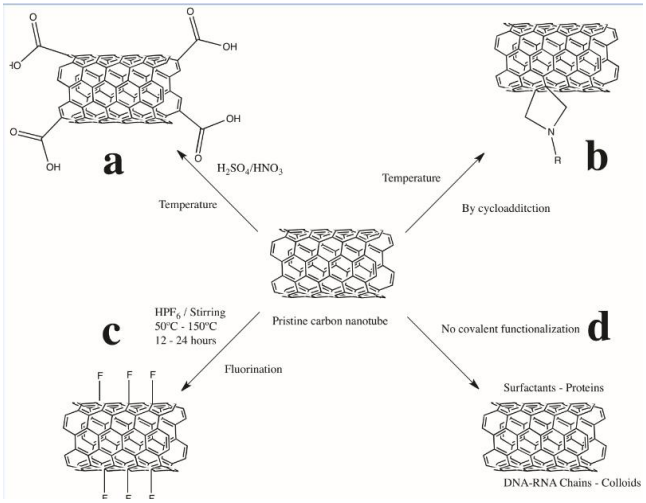

Fig. 5: Functionalization of carbon nanotubes, (a) by oxidation, (b) Cycloaddition, (c) Fluorination, and (d) no covalent functionalization.

Also the non-covalent functionalization has been used in gene therapy to transport proteins, DNA and RNA (Krajcik *et al.*, 2008, Wu *et al.*, 2008, Lee and Mijovic, 2009). However, the main disadvantage of this method is that there are several factors at biological level that can affect the stability of interaction NTC-functionalizing agent, such as pH, temperature of the body. Another inconvenience of non-covalent functionalization is the toxic effects associate to solvents used to generate CNTs dispersion, such as THF, dichlorobenzene and dimethylsulfoxide, which remain as traces (Madni *et al.*, 2010). Covalent functionalization is based on the binding of the modifier agent by forming of a covalent linkage. There are two subcategories: a direct method where molecules are tethered on NTC sidewall through addition reactions, such as cycloaddition, halogenation, etc (Chehimi, et al 2013), and an indirect method whose initial step is the formation of oxygenated groups on the NTC defect sites such as the opened tips, which act as sites for anchoring an wide range of molecules by amidation or esterification. The generation of active sites (oxygen functional groups such as carboxylic, ketone, alcohol, and ester) is achieved by oxidation with strong acids such as H_2SO_4 and HNO_3.The oxidation process also leads to shorten CNTs and removes impurities such as amorphous carbon and residual metal (Likodimos *et al.*, 2014). Figure 5 shows some of mechanisms of functionalization of NTCs.

Table 2: Vectorization of antineoplastic drugsin f-NTC.

Antineoplastic agent	NTC Type	Funcionalizant agent/ Ligand	Bioassays; cell line/animal model	Ref
Paclitaxel	SWNTC	Hydroxyl and carboxyl functional groups	MCF-7 and SK-BR-3 breast cancer cells/Nude mice	Wang et al ., 2014
Gliotoxin	SWCNT	Chitooligosaccharide/ Lysozyme, p53 and Folic acid	cervical cancer (HeLa) cells and Breast Cancer (MCF-7) cells/No in vivo assays.	Bhatnagar *et al.*, 2014
Doxorubicin	MWCN	d-α-tocopheryl polyethylene glycol 1000 succinate	MCF-7 cell/Balb/c mice	Mehra *et al.*, 2014
Doxorubicin	SWCNT	Chitosan/Hyaluronan	HeLa cells and fibroblasts. Not in vivo	Mo *et al.*, 2015
Doxorubicin	Iron- SWCNT	PVP/Endoglin/CD105 monoclonal antibodies	T1-Luc2 cancerous cells/ Balbc mice	Al Faraj, *et al.*, 2015
Cisplatin	SWCNT	phospholipids	C26 colon carcinoma cells and in vivo in BALB/c mice	Kazemi-Beydokhti, *et al.*, 2014,

The mere fact of introducing oxygen functional groups in the NTC surface can improve the biocompatibility. It has been observed oxidized MWNTC (<500 nm) inducing minimal hepatic accumulation and inflammation response after a single administration, because they are more easily cleared from the body via renal excretion, compared with pristine-MWNTC, which are retained in lungs and liver (Jain *et al.*, 2011). The cytotoxicity of oxidized MWCNTs decreases as a function of functionalization density according studies in vitro using macrophages (Singh *et al.*, 2012). A growing body of literature indicates that if the nature of the functionalizing agent favors the aqueous dispersion without forming tangling/bundling of CNTs, it can be expected that f-NTC not lead to an inflammatory response in vivo studies (Ali-Boucetta *et al.*, 2013). In this same line of reasoning, it has been found that increasing the degree of functionalization improves the cytotoxic profile, because the f-NTCs interact with biological system as individualized nanoparticle, leading to the rapid urinary excretion and low tissue retention (Al-Jamal *et al.*, 2012). One of the functionalizing agent most used is PEG, due toits high biocompatibility and versatility to bind ligands, drugs and other molecules, among other reasons as mentioned above. It has observed that chain length, coverage-density, conformation adopted by PEG affect the adsorption of corona protein and the activation of the complement system, varying the biological stealth and blood circulation times of f-NTC(Sacchetti *et al.*, 2013).f-NTC are facing the same obstacles that other vectors in nanomedicine, because it is recognized that there is not still enough research to know the complexity of the complement system (Farrera *et al.*, 2015), and to achieve design nanoparticles with high biological stealth and low RES clearance. Table 2 shows some studies of f-NTC as anticancer drug delivery system, reported during 2014. Different type of agents and ligands are been evaluated both biological compatibility and antitumor efficacy by in vitro and in vivo studies.

Biodegradation de NTC

A recent focus of research is the biotransformation of NTCs. Studies in vitro have shown the biodegradation of the oxidized-NTC by peroxidase enzymes such as horseradich peroxidase (HRP), human myeloperoxidase (MPO) and eosinophil peroxidase (EPO) under the presence of low concentration of $H_2O_2$and generating CO_2 as final product (Russier *et al.*, 2011; Zhao *et al.*, 2011,Andon et al, 2013, Kotchey *et al.*, 2013, Kagan *et al.*, 2010). The degradation of carboxilated MWNTC is a slower process that SWCNT and occurs layer-by-layer (Zhao *et al.*, 2011) (see figure 6).

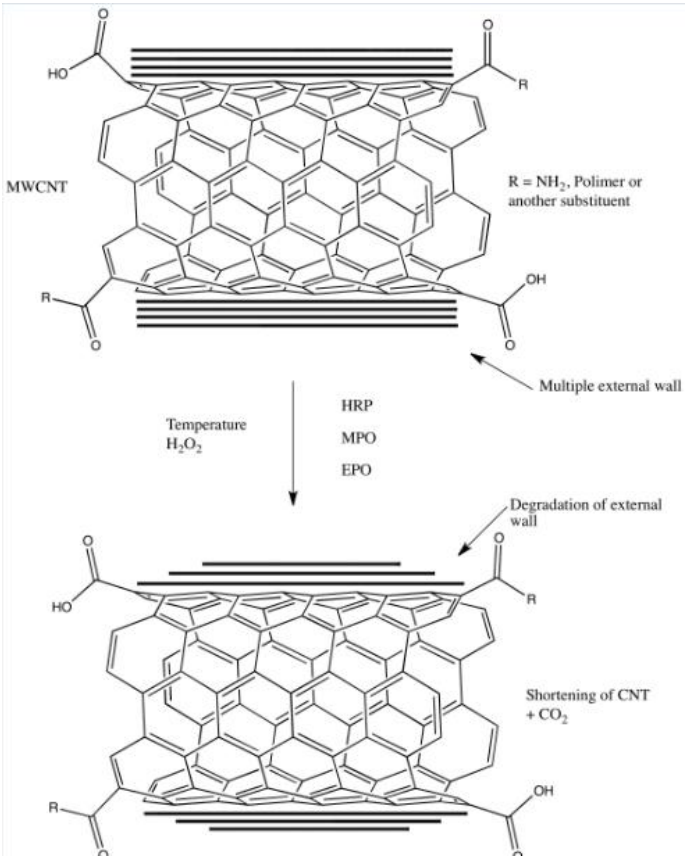

Fig. 6: General scheme of functionalized carbon nanotubes biodegradation process.

The fact that this result is observed in the oxidized-NTC, is attributed to carboxylate groups facilitate the orientation of NTC near the heme site of peroxidases (Allen *et al.*, 2009, Kagan *et al.*, 2010). The proposed mechanism also involve a role of Cl^-, which is became into hypochlorous acid (HClO) by MPO and EPO. HClO synergizes the oxidizing ability of these enzimes (Vlasova *et al.*, 2011). Studies at level cellular and in vivo, demonstrated that MPO (enzyme present in neutrophils) and EPO (in

eosinophils) in addition to its bactericidal function, protection against parasites and ability to oxidatively modify organic xenobiotics, are able to oxidatively degrade NTCs (Andón *et al.,* 2013, Vlasova *et al.,* 2012, Shvedova *et al.,* 2012; Shvedova *et al.,* 2012).

These results indicate that exists an alternative pathway (different from urinary or fecal excretion) to remove short and oxidized-NTCs and prevent their accumulation in organs such as lungs (see figure 7). The outcomeof in vitro studies have been controversial by a recent study, where it is demonstrated by different analytical methods that HRP degradation of different types of NTCsis slow, with half-lives of 80 years (Flores-Cervantes *et al.,* 2014). This has encouraged other researchers since the NTC biotransformation has large impacts on both environmental and human health. Recent studies have reported of biodegradation of SWNTC by superoxide/peroxynitrite oxidative pathway of activated macrophages (Kagan. 2014) and manganese peroxidase (Zhang *et al.,* 2014)

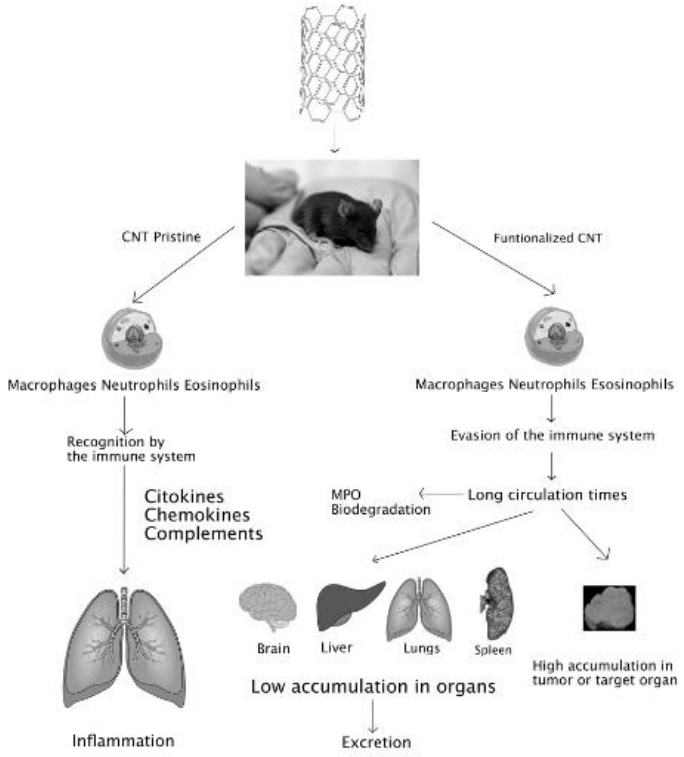

Fig. 7: Path follows the pristine and functionalized CNT in the body.

Drug vectorization in nanotubes

The binding of the drug to the f-NTC is accomplished with the same methods used to tether functionalizing agents on NTC surface, i.e. by covalent bond or physisorption.

Drug vectorization by covalent bond is achieved using spacer agents as ethylenediamine, cisteamine, diaminotriethylene glycol, etc to link the drug directly to the NTC (Wu *et al.,* 2009, Bhirde *et al.,* 2009, Samori 2010), or the drug can be link to functionalizing agent by esterification (Chen *et al.,* 2012, Marega *et al.,* 2011).

The vectorization by physisorptionis the most used because ithas two advantages, the first one is that the structure of the drug does not change and the second one is that the capacity of load of NTC is fully taken advantage. Various studies have been carried out indicating that there are a variety of possible forms in which drugs can be encapsulated, such as within the inner cavity of f-NTCs (Muzi *et al.,* 2015), or hydrophobic interactions, hydrogen bridges and π-π interactions on f-NTC surface (Mehra *et al.,* 2014, Li *et al.,* 2011).An approach to understanding these interactions is achieved through adsorption isotherms, such as isotherms of Langmuir, Freundlich, Sips and Polanyi-Manes Model.

CONCLUSIONS

NTCs present several properties that make them one of vectors more appropriate for use in chemotherapy, such as: high capacity, needle-like shape and versatile surface to attach different molecules.

It has been observed that the inflammatory response and cell death caused by the NTCs are related to their size, metal impurities and tendency to form agglomerates. Short f-NTCs show a different behavior than pristine-CNTs, the former are less retained by RES organ, are more rapidly removed by the renal excretion and are biodegraded. Therefore the functionalization of NTC has generated great expectations in nanomedicine. However, because the studies so far have high disparity between the characteristics of f-NTCs used and the conditions of the experiment, is not exactly known how the functionalization affects the kinetics that follow the f-CNTsat biological level and the biodistribution.

Also, it is necessary to overcome difficulties associated with interactions between f-NTCs and immune system, to achieve modular blood circulation time and promote the accumulation in target organ.

NTC biotransformation is a recent field of research and more experimental evidences are needed to reach a consensus on the metabolic pathways involved as the kinetics of biodegradation, using appropriate methods.

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