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When Pharma Meets Nano or The Emerging Era of Nano-Pharmaceuticals

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Pharmaceutical formulations that contain nano-sized drugs are perceived as "Nano-pharmaceuticals" or "Nano-theranostics" (i.e. billionth meter compounds potentially useful for diagnostics and therapeutics). The pharmaceutics/theranostics loaded into nanoparticles (NPs) can offer significant benefit for the patient compared to the conventional formulated drugs (i.e. drugs in their bulk-/free-form). Nevertheless, if the NPs are: (i) inappropriately prepared (e.g. inadequate surface properties); (ii) inaccurately dosed for *in vivo* delivery; (iii) environmentally uncontrolled/unmanaged and so, allow accidental or involuntary contact (e.g. skin exposure, inhalation, ingestion during the NPs production or use), they might then cause serious illnesses/health hazards like cardio-vascular diseases, neurological disorders [1-3] as well as other effects similar to that reported with asbestos such as mesothelioma and other lung-related conditions (e.g. granuloma formation, interstitial inflammation, lung cancers) [3-5].

In fact, it is important to know not only about the effect of NPs in a given body (e.g. human) but also have a clear picture about how this body is answering to the intrusion of NPs. This shall facilitate and strengthener our data interpretations about the efficacy and safety of the entity (e.g. drug compound) they contain. For instance, while an increasing number of studies are highlighting the biodistribution of NPs, little is known about their specific fate (e.g. spatial and functional bio-persistence due to heterogeneous particle size issue?). In other words, the exact *in vivo* mechanisms of their relative deposition and clearance (e.g. phagocytosis by macrophages, excretion systems, and/or endocytosis by epithelial and endothelial cells?) remain unclear.

Therefore, there is still a lot to do for better understanding the healthy and safety issues related to the development and use of NPs (e.g. toxicity/dangers, fate: biodistribution and bioavailability/clearance) as well as for enhancing the public prevention/awareness (e.g. by sparing information and stimulating individual´s consciousness).

NPs, ideally between 5-200 nm, is a large family of various nano-polymers (e.g. different shapes and surface properties) that includes, but not limited to, lipid-based nano-molecules (e.g. liposomes, solid lipid NPs (SLN) and nanostructured lipid carriers (NLC)) [6], carbon nanotubes (e.g. single-walled or multi-walled-CNTs) [7,8], fullerenes (i.e. C_{60}) other than CNTs [9,10], quantum dots (e.g. semi-conductor QDs) [11-13], diamondoids (e.g. adamantine, memantine) [14,15], gold NPs (AuNPs) [16] and silver NPs (AgNPs) [17].

A number of emerging studies showed that NP therapeutic formulations (e.g. encapsulation of natural, semi-synthetic, synthetic compounds such as anti-cancer drugs, polyphenols, bio-therapeutics like peptides, proteins, nucleic acids) present several advantages. Indeed, the features of nano-theranostics are relatively broad in terms of efficacy and safety, and include: (i) enhanced solubility and dissolution rate; (ii) enhanced local or systemic bioavailability; (iii) improved dose proportionality; (iv) reduced adverse effects (i.e. usually safer and less toxic, often because of minimal applied concentration); (v) enhanced controlled-site targeting; (vi) progressive release of the loaded drug into blood, targeted tissues such as tumors as well as specific individual cell; (vii) suitability for administration by all routes (e.g. oral, trans-dermal/topical, intravenous); (viii) stability against possible enzymatic-, cellular-, thermal- and/or photo-degradation(s); (ix) relatively high bio-compatibility; (x) possibility of sterile filtration due to decreased particle size range.

Besides, the fluorinations of NPs, not only with radio-isotopes or fluorescent dies, which are respectively toxic or unstable, but preferentially with Carbon-Fluorine (C-F) or other label-free/green methods, may further overcome several limitations (e.g. toxicity, safety, security, efficacy) [18]. Several techniques are available to characterize NPs such as transmission electron microscopy (TEM), scanning electron microscopy (SEM), high-pressure liquid chromatography (HPLC), spectroscopy-derived techniques (Carbon-Fluorine spectroscopy (CFS) *aka* Spectro-Fluor™, X-ray diffraction (XRD), Raman, near-infrared (NIR) spectroscopy) [13,18,19]. Further, it is possible to: (i) excite and deliver NPs at a specific location (e.g. tumor site) with technologies such as fluorescent resonance energy transfer (FRET) [20]; (ii) localize NPs in tissues with technologies such as regular energy fluorescence [11,12], clinical molecular imaging such as positron emission tomography (PET) [14] or CFS [18]. Constant technological innovation shall permit the achievement of milestones/breakthrough discoveries regarding the spatio-temporal, physico-chemical and functional characterizations of NPs.

Nowadays, several nano-pharmaceuticals are successfully marketed. Different patented techniques are commercialized to prepare nano-pharmaceuticals such as milling, homogenization and precipitation. In all cases, particular attention shall be given on purity (e.g. minimization of immunogenicity), size (e.g. ability to reach any tiny locations in the body with minimal toxicity such as ultra-passing blood-brain barrier), shape (e.g. minimization of aggregation and blood flow-related problems), and "functionalization" of NPs (e.g. possible requirement to modify the surface properties such as polarity to ensure water-solubility and enhance NPs bio-availability - This can be achieved by specific coating; other modifications can be done to control the binding and release of the loaded theranostic at a targeted location – This can be done by adding a functional moiety at the surface of NPs).

However, one should keep in mind that a given NP (e.g. especially inert, apolar and hydrophobic such as carbon nanotubes, gold and silver NPs), even pure enough, might cause harmful health effects and naturally be or become a double-edged sword if appropriate precautions are not fully taken during the design, the development

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process, the storage and the testing. Indeed, improper NPs can cause inflammatory-state diseases through the recruitment of specific immune cells (e.g. macrophages), liberation of pro-inflammatory mediators (e.g. interleukins, chemokines, cytokines), and generation of reactive oxygen species (ROS) which subsequently could cause lipid hyper-peroxidation of normal/healthy cells and tissue burden [21]. The potential deleterious health effects (e.g. cytotoxicity, inflammogenicity, fibrogenicity, tissue burden) of NPs are relative and may depend on, but not limited to:

(i) their physical-chemical characteristics (e.g. surface properties such as their carried charge densities in contact with the cell membranes and/or their chemical reactivity; flexibility or rigidity); (ii) their size (e.g. < 4 nm or > 20 nm); (iii) their shape (e.g. spherical, fiber-like); (iv) the mode of administration (e. oral, topical, intraveinous) (iv) their administrated/inhalated dose; (v) their accumulated dose (i.e. risk of overload); (vi) the body micro-environment they reached (i.e. biodistribution/deposition); (vii) their exposure time at a specific location (i.e. bioavailability/bio-persistence/clearance capacity); (viii) their biocompatibility; (ix) their interactions with the body´s microenvironment; (x) the body´s heath status and its relative capacities to deal with NPs, which could be tissue-specific.

For instance, while AuNP is quite interesting for applications in oncology (e.g. cancer treatment) [22] and gerontology (e.g. treatment of Alzheimer´s disease) [23] - in particular because of its ability to be thermally excited -, it remains however limited by its inert character and its natural hydrophobicity, which both lower its biodistribution and enhance the body immune-induced toxicity [24,25]. Indeed, highest cytotoxicity has been observed when AuNPs were smaller than 4 nm both in cancerous and healthy cells [26]. Interestingly, PEG-modified gold nanorods were cleared at a high rate clearance (77%) within five hours following *in vivo* administration [27]. Conversely, it was reported that nano-diamonds (NDs) exhibited the lowest toxicity compared to that of other carbon nanomaterials mostly because of their effective removal by macrophages [28] (i.e. phagocytosis) and excretory systems/clearance mechanisms [29].

Overall, chronic administration/application/inhalation of one or a combination of these parameters such as high concentration, smallest, polycationic, highly flexible, branched nanofiber-like NPs at a specific body location, is more likely to cause higher cytotoxicity/low biocompatibility compared to that single or combined criteria such as acute contact, low dose, large, poorly cationic, rigid, globular-like NPs at the same specific body location (Menaa et al., data not shown).

Hence, to minimize the cytoxicity and possible associated poor clinical outcomes induced by remaining NPs, there is a need to ensure their high functionalization (e.g. surface modification) in a pre-administration setting as well as an efficient NPs bio-filtration in a post-administration setting. Fortunately, the US Environmental Protection Agency (EPA) is highly considering the inclusion of toxicology aspects for manufactured NPs [30].

Eventually, the future of nano-theranostic applications is bright and brings hope for more successful and safer treatments both to the patients and health care professionals. Nevertheless, more studies that aim to clearly assessing the *in vivo* biodistribution, the metabolism (i.e. bioavailability) and toxicity of each type of NPs, which shall be possibly homogeneous, are definitively required in addition to the entity (e.g. drug compound) they might contain. I also think that an international common policy agreement (i.e. including with developing countries) to validate the commercialization of nano-theranostics (e.g. including e-business) is requested. In these regards, may I already suggest the name of "nanopharmacokinetics" and "nanopharmacovigilance" for nano-drugs, by analogy to "pharmaco-kinetics" and "pharmaco-vigilance" which are respectively attributed to bulk-drugs formulation?

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