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EDITORIAL

Interdisciplinary nanomedicine publications through interdisciplinary peer-review

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Nanomedicine aims to apply and further develop nanotechnology to solve problems in medicine, related to diagnosis, treatment and/or disease prevention at the cellular and molecular level (Feng, 2006; Feng and Chien, 2003). Nanomedicine by nature is interdisciplinary, with benefits being realised at the interface of science and engineering, physical science and engineering, chemical science and engineering, cellular and molecular biology, pharmacology and pharmaceutics, medical sciences and technology and combinations thereof. The difference in perspective between disciplines may be partly responsible for the lack of nomenclature or universally-accepted definition for various "nano" terms, which causes issues with respect to publication consistency, regulatory agencies, patent offices, industry and the business community (Rannard & Owen, 2009; Tinkle *et al.*, 2014; Bawa, 2013; Bawa, 2016). Regulatory agencies such as the US Food and Drug Administration (FDA; http://www.fda.gov/) and European Medicine Agency (EMA; http://www.ema.europa.eu/ema/) have generally failed to employ an interdisciplinary approach to regulate nanoscale technologies in the same manner as they apply to drugs because they do not fully appreciate the interdisciplinary nature or novel characteristics of many submissions that disclose nanomedicines (e.g., as a result of high-surface-area to-volume ratio, inherent reactivity due to a greater proportion of exposed surface atoms, unpredictable properties, or toxicity profiles as compared to bulk). Currently, these agencies instead rely upon established laws and regulations validated through experience with conventional small molecule medicines. Synthesis and characterization of molecular biomaterials forms the material basis for nanomedicines. Molecular biomaterials may include synthesized biocompatible polymers such as currently accepted biodegradable polymers including polylactic acid (PLA), polycaprolactone (PCL) and polylactic-co-glycolic acid (PLGA), or molecularly engineered macromolecules such as lipids, DNAs, RNAs, proteins and peptides. Such bio materials are either used to stabilise nanosized particles of drug or to form nano-carrier technologies for sustained, controlled or targeted release of diagnostic and therapeutic agents to enhance their biological effects and to reduce their side effects (Feng *et al.*, 2007; Owen, 2014; Bawa, 2016).

Similarly, patent offices also often fail to recognize that an interdisciplinary approach needs to be applied by patent examiners while reviewing nanotechnology-based patent applications, since the technologies reflected in these patent applications often involve a combination of disciplines. In fact, non-uniform or

improper patent prosecution is the major reason for the issuance of patents of dubious scope and breadth where the patent holder is uncertain of their validity or strength during litigation (Bawa, 2009).

Taken collectively, this can have a detrimental effect on commercialization activities and in turn delay the ultimate translation of novel nanomedicines. Ultimately, for a clinical scientist or physician the true value of a particular material lies in its clinical utility balanced against any potential adverse effects. Therefore, effective translation of nanomedicine candidates requires a "technological push" coupled to a "clinical pull", which is bridged by logical intermediary data that mechanistically demonstrate the efficacy and safety in biological systems.

Given this backdrop, there is a clear need for "true" interdisciplinarity during the generation of robust nanomedicine data but also during examining, discussing or analysing these data because interpretation by physical scientists is often different than by biological scientists. Physical scientists and life scientists also view the nanotechnology landscape with different perspectives (Khushf, 2011; Silva, 2006). For example, the physical scientist might be more inclined to observe intrinsic novel properties of nanoparticles like the specific wavelength of light emitted from a quantum dot due to variations in the quantum dot's size. Examples of properties of particular significance to a physical scientist but of limited interest to a pharmaceutical scientist include the increased wear resistance of a nanograined ceramic due to the Hall-Petch effect (Schiotz and Jacobsen, 2003) or quantum confinement where one photon can excite two or more excitons (electron-hole pairs) in semiconductor nanoparticles (Ellingson *et al.*, 2005). On the other hand, the pharmaceutical scientist is more likely to focus on the extrinsic novel properties of nanoparticles that arise because of the interactions with biological systems or nanodrug formulation/efficacy properties that improve bioavailability, reduce toxicity, lower required dose or enhance solubility (Bawa, 2016).

Materials can be miniaturized by many orders of magnitude from macroscopic to microscopic with few or no changes in physical or biological properties. However, as materials are miniaturized into nanoscale dimensions, *often* profound changes in optical, electrical, mechanical and conductive properties are observed, especially in inorganic materials. These changes emanate from the quantum mechanical nature of some materials at the nanoscale where classical macroscopic laws of physics do not operate. Electrical, optical, physical, magnetic, surface properties and reactivity may all be different at the nanoscale than in corresponding bulk materials. Ultimately, it is the difference in physical or biological properties of a material that is critical rather than any firm definition related to a sub-1000 nm or a sub-100 nm size or diameter. Moreover, it should be noted that many quantum effects are irrelevant when it comes to medicine, drug delivery, drug formulation or even many nano-enabled assays (Bawa, 2016). Although the sub-100 nm size range as proposed by the US National Nanotechnology Initiative (NNI; http://www.nano.gov) may be important to a nanophotonic company (i.e., a quantum dot's size dictates the color of light emitted), this arbitrary size limitation is not critical to a clinical scientist or a drug company from a formulation, delivery or efficacy perspective because the desired therapeutic property (e.g., V_{max}, pharmacokinetics or PK, area under the curve or AUC, zeta potential, etc.) may be achieved in a size range greater than 100 nm (Bawa, 2016). In fact, there are numerous FDA-approved and marketed nanomedicines where the particle size does not fit the sub-100 nanometer profile: Abraxane (~120nm), Myocet (~190nm), DepoCyt (10-20 micometer), Amphotec (~130nm), Epaxal (~150nm), DepoDur (10-20 μm), Inflexal (~150nm), Lipo-Dox (180nm), Oncaspar (50-200nm), etc. (Bawa, 2016).

Materials chemistry and colloid science have made a huge contribution to the fundamental science of nanomedicine and its success in scale-up and commercial/clinical translation. A wide array of nanoparticle carriers including inorganic and organic materials, self-assembled polymers, liposomes/lipid vesicles, drug-polymer conjugates and nanoprecipitates often stem from synthetic chemistry and the explorative, sometimes elegant, solutions to materials generation (Horn & Rieger, 2001). The production of solid drug nanoparticle technologies finds their origins in the processing of slurries, suspensions and liquids through techniques such as milling, homogenisation and solvent/antisolvent technologies (Pawar *et al*, 2014). Initially termed colloid science, the formation of sub-micron materials suspended within liquids, and the understanding of their stability and formation, has been critical to the creation of new nanotherapeutic and diagnostic options. Also, the considerable recent advances in microfabrication, electronics and cheap manufacturing are important within diagnostics. Above all though, the unmet clinical need that these technologies target is the main driving force that guides collective progress and, when coupled directly to the disease and patient-specific requirements, generates relevant options to improve outcomes or quantify disease state. It is clear that materials chemistry alone cannot judge the clinical importance of a target or the appropriateness of a particular solution. As a single discipline, it cannot optimise or scale-up the solution without a direct interaction with the relevant biology, pharmacology, safety, immunology and clinical perspective and input. It is also clear that many poorly informed technologies may be developed that may have no clinical or disease relevance but are, nevertheless, scientifically exciting. The overlap of the many disciplines is the true essence of nanomedicine and for materials chemistry and colloid science to

continue to impact future challenges, a greater integration is required. The temptation to go into the laboratory to generate a novel material structure without consideration of the overall needs of the target application has led to many technological advances but with limited translation to clinical applications (Venditto & Szoka, 2013). The integration of materials chemistry with clinical need, which is in itself coupled to biological and disease-relevant intelligence, should act as the main driver for chemical and colloidal science interventions in future nanomedicines. Such an approach will also act as a filter to prevent academic curiosities from being heralded as major breakthroughs, with effort and funding directed away from outputs with clinical relevance. As new materials are developed with a clear focus on unmet clinical needs, challenges exist to demonstrate a considered approach to risk, such as the inherent material toxicity, off-target effects, altered biological distribution of drugs/or clearance. These challenges can only be met through the collective working of expert scientists from a multitude of complimentary disciplines.

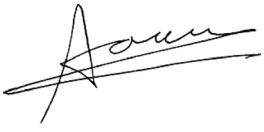
In this regard, some factors that determine ultimate medical performance may include size or size distribution, surface morphology and surface charge, drug loading, drug release profiles, cellular adhesion and internalization, or inhibition of the intracellular autophage (Zhao *et al.*, 2013). The advantages of nanocarrier systems in the delivery of bioactive molecules to diseased cells have been intensively investigated *in vitro* and *in vivo* in the past decade, although clinical trials seem to be in early phases with some results not as expected. Nanocarrier systems may protect bioactive molecules from enzymatic degradation and immune recognition. Also, nanocarrier systems can deliver a drug payload as a reservoir through mechanisms such as endocytosis, in which the nanocarrier sacrifices its surface energy to detach a small piece of the cell membrane and trigger internalisation. The delivery efficiency is much higher than when single molecules cross the cell membrane by the various other mechanisms such as facilitated diffusional transport, active transport and receptor-mediated transport. Nanocarrier systems can be further conjugated to a ligand to target a corresponding biomarker on the membrane of a relevant target cell. Such nanocarrier materials, if of appropriate size and surface functionality can escape excretion by the reticuloendothelial system and thus realize sustained delivery, prolonging the agent's half-life with a more desirable biodistribution. Moreover, well designed nanomedicines may get through the various biological drug barriers such as those within the gastrointestinal tract for oral delivery (Hatton *et al.*, 2015; McDonald *et al.*, 2014) and the blood-brain barrier for treatment of brain diseases (Nunes *et al.*, 2012), to give just two examples. Co-delivery of siRNA with bioactive molecules may overcome multidrug resistance of diseased cells and appropriately modified materials can inhibit the intracellular autophagy (Mei *et al.*, 2014). However, it should be noted that there is often inconsistency between results obtained *in vitro*, *in vivo* and in clinical trials and as for any medicine, the safety must be thoroughly investigated before clinical applications can be assessed.

A frequently pursued benefit for nanomedicine in drug delivery relates to their pharmacokinetic performance, with many applications aiming to improve bioavailability, distribution or residence time within the systemic circulation. The mechanisms that dictate pharmacokinetics are diverse and the complexity is underpinned by numerous molecular, cellular and physiological processes contributing to absorption, distribution, metabolism and elimination (ADME) (Owen *et al.*, 2006). A holistic approach to understanding ADME can be realised through the integration of mechanistic ADME data through the mathematical algorithms that underpin physiologically-based pharmacokinetic (PBPK) modelling. PBPK modelling is now almost routinely utilised to support regulatory submissions for conventional medicines in the US by the FDA (Center for Drug Evaluation and Research) and in Europe by the EMA (Committee for Medicinal Products for Human Use). The approach has also been successfully applied post-licensing for assessing pharmacogenetic variability (Siccardi *et al.*, 2012) and drug-drug interactions (Siccardi *et al.*, 2013). Many of the mechanisms that underpin ADME for nanomedicines may be different than for conventional medicines and the first PBPK models relating to nanomedicines are now beginning to emerge (Bachler *et al.*, 2014; Li *et al.*, 2014; Li *et al.*, 2010; Li *et al.*, 2012; McDonald *et al.*, 2014; Moss and Siccardi, 2014; Rajoli *et al.*, 2015; Yang *et al.*, 2010). Thus there is the need to mathematically integrate interdisciplinary knowledge to improve the performance of such modelling approaches.

It is clear that in order to effectively characterise, translate and apply advances in the area of nanomedicine, a holistic approach is required that by definition involves the integrated contribution of scientists from multiple disciplines.

The British Society for Nanomedicine (www.BritishSocietyNanomedicine.com) is a registered charity (charity number 1151497) that was established in 2012 with the aim of bringing people from different backgrounds together to move the nanomedicine field forward. Since then, feedback from many of the members of the society has been that there is often difficulty and inconsistency in the peer review system for existing nanomedicine journals. At the heart of this issue is that many investigators often feel that their predominantly materials-based manuscripts have been unfairly critiqued by life science reviewers or *vice versa*. It is on this

basis that the Society has elected to create the *Journal of Interdisciplinary Nanomedicine* in collaboration with Wiley. *The Journal of Interdisciplinary Nanomedicine (JOIN)* is an international, peer-reviewed academic journal that aims to provide a forum for dissemination of truly interdisciplinary nanomedicine research. The journal contains evidence-based research outputs with high-level contributions from at least two sciences, and is unique in its provision of peer-review by reviewers from multiple disciplines tasked to focus only on their specialist areas. Moreover, authors are requested during submission to indicate the primary and secondary discipline of their manuscript and the paper will be accordingly assigned two editors to facilitate an editorial process that effectively accounts for inter-disciplinarity. Multiple first and/or corresponding author status is encouraged so as to provide transparency and acknowledgment for contribution to interdisciplinary work. The Journal embraces submissions from all relevant fields as applied to early stage scientific developments and studies aimed at the progression of nanomedicines towards the clinic, which include physical science, life science, clinical science, intellectual property, regulatory issues and policy considerations. JOIN contains original research papers, editorials, review articles, technical notes, and letters to the editor about matters that may benefit the wider readership. Advances that are progressing to application through consolidation of multiple areas of expertise are especially encouraged. Core areas of particular interest include diagnostics, pharmacology, pharmaceutics, toxicology, clinical outcomes, new materials, drug delivery, targeted delivery, electronics and engineering.



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