Chapter 52

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 realized 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 and 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 small molecule drugs because they do not fully appreciate the interdisciplinary nature or novel characteristics of many submissions that disclose nanomedicines (e.g., those that arise 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 drugs. 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 biomaterials are used either to stabilize nanosized particles of drug or to form nanocarrier 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, all of 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 analyzing 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. Other 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 (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). Moreover, there are numerous approved and marketed nanomedicines where the particle size does not fit the NNI sub-100 nanometer profile: Abraxane (~120 nm), Myocet (~190 nm), DepoCyt (10–20 μm), Amphotec (~130 nm), Epaxal (~150 nm), DepoDur (10–20 μm), Inflexal (~150 nm), Lipo-Dox (180 nm), Oncaspar (50–200 nm), 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 and 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, homogenization and solvent/anti-solvent 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 micro-fabrication, 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 optimize 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 clearly 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 and 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 nano-medicines. 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.

Some factors that determine ultimate medical performance may include drug 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). Often, these factors can be controlled or advantageously manipulated via nano-formulations. 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 internalization. The delivery efficiency is much higher in this manner than when single molecules cross the cell membrane by various other mechanisms like 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 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 is an active area of research. This approach 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 realized through the integration of mechanistic ADME data through the mathematical algorithms that underpin physiologically based pharmacokinetic (PBPK) modeling. PBPK modeling is now almost routinely utilized to support regulatory submissions for conventional drugs 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 modeling approaches.

It is clear that in order to effectively characterize, 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 (http://www.britishsocietynanomedicine.org/) 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* (http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2058-3273) 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 interdisciplinarity. 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.

Disclosures and Conflict of Interest

The authors declare that they have no conflict of interest. They did not utilize any writing assistance in the production of this chapter nor did they receive any payment for its preparation.

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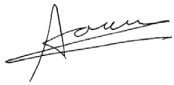

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About the Authors

Andrew Owen is a professor in the Department of Molecular and Clinical Pharmacology at the University of Liverpool, UK. He is also affiliated to the MRC Centre for Drug Safety Science and the Wolfson Centre for Personalised Medicine. He is Chair of the British Society for Nanomedicine, a fellow of the Society of Biology, and a member of the steering committee for the Academy of Pharmaceutical Sciences Nanomedicines Focus Group. His research focuses on understanding the mechanisms that underpin inter-patient variability in pharmacokinetics and pharmacodynamics for drugs used in the management of infectious diseases, predominantly HIV infection. In recent years a major emphasis has been to employ knowledge of these mechanisms to accelerate the translation of nanomedicine candidates to clinical applications. Central to this ambition is the utilization of interdisciplinary knowledge to understand and progress pharmacological benefits.

Steve Rannard is a professor in the Department of Chemistry at the University of Liverpool and vice-Chair of the British Society for Nanomedicine. He spent 16 years in global industry prior to taking a Royal Society Industry Fellowship and latterly an academic post at Liverpool. He is the academic lead for Nanomedicine within the newly developed Materials Innovation Factory at Liverpool, Director of the Liverpool Radiomaterials Laboratory, has co-founded three start-up companies (IOTA NanoSolutions Ltd, Hydra Polymers Ltd and Tandem Nano Ltd) and is an editor-in-chief for the *Journal of Interdisciplinary Nanomedicine*. Whilst in industry, he was the first recipient of the joint RSC/Macro Group UK Young Researcher of the Year Medal (1998), RSC Industrial Lecturer at both Strathclyde University (2001) and the University of Sussex (2002), visiting Lecturer at the University of Sussex (1999–2001) and visiting Professor at the University of Liverpool (2003–2007). His current research aims to focus materials science onto the unmet needs of medicine to achieve patient benefits. Through the development of new and scalable nanoparticle synthesis techniques, new

platform technologies for solid drug nanoparticle formulation (stabilized by excipients that are used in conventional medicines), branched polymer nanoparticles and nanoemulsions, candidate nanotherapies have been generated and scaled for human trials. Prof. Rannard has received collaborative grant income from various funding sources, including the Medical Research Council, Engineering and Physical Sciences Research Council, European Commission, US National Institutes of Health, the Clinton Health Access Initiative, Fight for Sight, and the British Society for Antimicrobial Chemotherapy. His research has generated multiple peer-reviewed manuscripts and been protected in 50+ patent families with >100 nationally granted patent applications.

Raj Bawa is president of Bawa Biotech LLC, a biotech/pharma consultancy and patent law firm he founded in 2002 and based in Ashburn, VA, USA. He is an inventor, entrepreneur, professor and registered patent agent licensed to practice before the U.S. Patent & Trademark Office. Trained as a biochemist and microbiologist, he has been an active researcher for over two decades. Since 1999, he has held various adjunct faculty positions at Rensselaer Polytechnic Institute in Troy, NY, where he currently is an adjunct professor of biological sciences and from where he received his PhD degree (biophysics/biochemistry). Since 2004, Dr. Bawa has been an adjunct professor of natural and applied sciences at NVCC in Annandale, VA. He is scientific advisor to Teva Pharmaceutical Industries, Ltd. He has previously served as the principal investigator of National Cancer Institute/SBIRs and reviewer for both the NIH and NSF. In the 1990s, Dr. Bawa held various positions at the US Patent & Trademark Office, including primary examiner (6 years). He is a life member of Sigma Xi, founding director of the American Society for Nanomedicine, co-chair of the Nanotech Committee of the American Bar Association and serves on the Global Advisory Council of the World Future Society. He has authored over 100 publications, co-edited three texts, and serves on the editorial boards of 17 peer-reviewed journals, including serving as special associate editor of *Nanomedicine* (Elsevier) and an editor-in-chief of *Interdisciplinary Nanomedicine* (Wiley). Some of Dr. Bawa's awards include the Innovations Prize from the

Institution of Mechanical Engineers, London, UK (2008); Appreciation Award from the Undersecretary of Commerce, Washington, DC (2001); the Key Award from Rensselaer's Office of Alumni Relations (2005); and Lifetime Achievement Award from the American Society for Nanomedicine (2014).

Si-Shen Feng obtained his 6-year diploma from Peking University (China), an MS in mathematics and mechanics from Tsinghua University and his PhD in bioengineering from Columbia University (USA). Dr. Feng is currently a Chair Professor at the Second Military Medical University in China and an Adjunct Professor at NUS in Singapore. He is a pioneer in chemotherapeutic engineering, cancer nanotechnology and nanomedicine. He has previously served as an associate editor of *Biomaterials* (2008–2014) and currently serves as an associate editor of *Nanomedicine* (2008). He also serves on the editorial boards of *Nanomedicine: Nanotechnology*, *Biology & Medicine* and the *International Journal of Nanomedicine*. His research interests include viscoelastic fluid mechanics, cellular and molecular biology, molecular biomaterials, tissue engineering, chemotherapeutic engineering, cancer nanotechnology, pharmaceutical nanotechnology and nanomedicine. He is also interested in translational medicine and has founded a nanomedicine company, Suzhou NanoStar Pharm, Inc., in China.

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