Chapter 44

Nanomedicine: Shadow and Substance

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44.1 Perspective: A View from Outside the Box

Nanotherapeutics and nanopharmaceuticals encompass small-scale technologies and system approaches that could achieve and facilitate earlier and more precise individual diagnosis, improved targeted therapies (eliminating side effects) and enhanced therapeutic monitoring [1, 2]. It is the global consensus that these technological developments are enabling instruments for
personalized and targeted medicine that could address the grand challenges of chronic diseases in an aging population [3, 4]. It is therefore, expected that these approaches could enhance quality of life, support a healthier more independent aging population, and be instrumental in improved cost effectiveness in health care. In April 2006, *Nature Materials* estimated that 130 nanotech-based drugs and delivery systems were being developed worldwide [5]. Today, this list extends to a few hundred companies with many potential products in preclinical and some in early phase human trials. Indeed, the global research into targeting of drugs, biologics and diagnostic agents via intravenous and interstitial routes of administration with multifunctional nanoparticulate entities and nanoconstructs, is at the forefront of translational nanomedicine research. However, the biological performance of many potential nanotherapeutics still requires optimization, and today the complex nature of such entities makes nanomedicine research and development challenging [2]. Sadly, there are too many promises with enabling technologies and multifunctional systems that are rarely delivered and eventually replaced by new promises [3, 6, 7]. It is essential to identify and translate realistic opportunities offered by understanding the pathophysiological processes for the design and engineering of efficient and safe nanomedicines that can truly enhance benefit-to-risk ratio [8]. This is in contrast to the overwhelming increase in the practice of empirical approaches that tend to find exaggerated *in vivo* biomedical applications for a broad range of emerging and poorly characterized multifunctional/hybrid entities and often non-biodegradable nanomaterials (e.g., carbon nanotubes, quantum dots, graphene oxide, certain metallic nanoparticles) [9–11], which have raised toxicity and safety concerns [1, 3, 6, 12–15]. After all, nanotechnology should address the needs of clinical therapeutics, pathology, and safety challenges, while concomitantly considering pharmaceutical viability and manufacturing issues. Therefore, it is imperative that nanotherapeutics must be structurally simple with attributes that will allow for production of an affordable, viable (e.g., considering scaling up and GMP) and clinically acceptable pharmaceutical formulation that pays careful attention to purity, drug loading capacity, drug release profile, stability, reproducibility, etc. Most of these requirements hardly fit with many emerging and poorly
mastered nanomaterials [9–11]. For the most advanced but simpler nanotherapeutics (e.g., liposomes and certain classes of polymeric nanoconstructs), we are still in need of establishing a better understanding of the interdependency of nanoparticle size, shape, and surface characteristics to interfacial forces, disease stage, controlled drug release, excretion, and possible adverse effects. Nevertheless, it is too early to suggest that nanotechnology could be a real game changer, at least within the pharmaceutical and therapeutics arena. Current evidence is more in favor of nanotechnology changing the life cycle of select, limited therapies [1]. Materials scientists and the nanotechnology community rarely address these issues; their focus is purely based in extolling the virtues of their own favorite nanosystem for demonstrating the proof-of-concept and often in models irrelevant to the human disease in question [9–11]. In many attempts a slight selectivity in organ uptake (and an acute pharmacological effect) of a “fancy” nanomaterial is heralded as “targeting” and “therapeutic success” even when less than 1% of the administered dose reaches the desired site. Clearly, this poses a question concerning the fate of unaccounted material.

Unfortunately, political forces, together with market directions, are predominantly shaping the future of nanomedicine:

Example 1: One example is cancer, where massive investments have been made for the development of anti-cancer nanomedicine, which has been rationalized on the basis of the enhanced permeability and retention effect seen in experimental animal models [6]. The majority of these developments, however, have led to disappointing therapeutic efficacy and incremental clinical success [6, 16]. In spite of these setbacks, there is an increasing number of forced efforts to combat cancer with a variety of alternative nanomaterials of different functionalities, but the same principles and perceptions still operate. Here, anti-cancer nanomedicine research and development has become the victim of narrative fallacy and epistemic arrogance [17, 18]. This is defined as vulnerability to over-interpretation and over-estimation of what we know, leading to underestimation of uncertainty. Cancer is a

complex heterogeneous disease [19]; engineering of effective and safe anti-cancer nanomedicines requires a far better understanding of integrated pathophysiologival processes in relevant models, which includes systems immunology, that modulate human tumor functionality and growth [17, 18, 20]. Accordingly, we are in need of a paradigm shift in combination treatment/targeting strategies that simultaneously augment the antitumor immune responses, and overcome immunosuppressive pathways. This does not necessarily mean that nanoparticles should deliver drugs and modulators to cancer cells [17, 18].

**Example 2:** Another example is the projected figures from the European Technology Platform in Nanomedicine (ETPN) Report [21], which predicts that by 2020 nanoformulations comprising biopharmaceuticals will dominate the market over nanopharmaceuticals of smaller drug molecules. To the best of our knowledge, successful formulation development and clinical outcomes with nanoformulations of therapeutic biomacromolecules are scant to support the predicted figures of ETPN; the most successful nano-package attempts in the development pipeline is still based on small drug molecules, which will most likely dominate the market in years to come. Surprisingly, the ETPN predictions have ignored not only the challenges surrounding the pharmaceutical attributes of the formulation but also the biological barriers en-route to the target. The blood–brain barrier (BBB) serves a good example of the latter. Current attempts in crossing the BBB are based on surface functionalization of nanocarriers with brain cerebral capillary endothelial cell-specific ligands [22]. However, the avidity of the systems described to date is still poor to surmount the BBB. We are still in need of fundamental studies to improve the avidity of the engineered nanosystems with correct pharmaceutical attributes for the desirable targets. If these can be achieved, then biological barriers themselves may serve as targets for selective therapeutic interventions. For instance, neurovascular dysfunction is an integral part of various neurological disorders, and changes in the vascular system of the brain may significantly contribute to the onset and progression of dementia and to the development of a chronic neurodegenerative process [23, 24]. Accordingly, nanomedicine interventions may focus, for instance, at the level of brain capillary endothelial cell to selectively modulate multiple molecular targets that are known to aid pathogenesis of Alzheimer’s and Parkinson’s disease [23, 24].
These approaches will also overcome limitations associated with drug translocation across the BBB.

**Example 3:** The oral route for delivery of pharmaceuticals is the most widely used. However, the ability to deliver orally administered nanopharmaceuticals across the intestinal epithelium is hampered by numerous anatomical barriers that make nanoparticle passage across the gut epithelium to lamina propria and beyond a daunting task [25]. Overcoming these barriers would not only increase the range of oral formulations in terms of improving drug solubility, drug stability and bioavailability but also open doors to treating many chronic conditions that require frequent dosing. A promising approach, but still with its limitations, was exploitation of neonatal Fc receptor (FcRn) for transepithelial transport of immunoglobulin-coated therapeutic liposomes (for insulin delivery) with proven systemic effect demonstrated by Patel and Wild [26]. Twenty-five years later, Pridgen and colleagues [27] exploited the same principle to target FcRn with Fc-tagged polymeric nanoparticles for insulin delivery and yet heralded their study as first to successfully deliver drugs to the systemic circulation with orally administered nanoparticles. The work of Patel and Wild [26] was classified as drug delivery in the past century without the use of “nano” suffix, and sadly ignored. Surely, we are still in need of integrated approaches for nanopharmaceutical design and improvement, but nanomedicine should not reinvent the wheel.

### 44.2 Creative Yet Realistic Path

Nanomedicine research has increased and will increase our fundamental understanding of dynamic and integrated multicellular events pertaining to controlled recognition and processing of nanoparticles and their biological performance [1]. Many nanoparticles are even beginning to act as functional tools for modulating and monitoring intracellular functions, thus enhancing our understanding of interrelated processes that contribute to pathogenesis of many diseases [1, 2]. However, there are recent reports of exaggerated claims of nanomedicine engineering and interpretation of their functionalities [28, 29] which still ignores fundamental biology [30]. The reports and market projections that prematurely focus our time and investment more on latter stages of product development and yet at the same time ignore fundamental research into better understanding of the
interactions of nanoparticles with the immune system as well as detailed mechanistic studies only lead us onto the wrong path. From a therapeutic angle, nanomedicine is still in infancy, yet through careful and systematic approaches, and by addressing outstanding methodological gaps [2, 3], innovative therapeutic platforms with correct pharmaceutical attributes will emerge that will add realistic and fundamental value to medicine and healthcare.

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References


