

Nanomedicine concepts in the general medical curriculum: initiating a discussion

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Abstract: Various applications of nanoscale science to the field of medicine have resulted in the ongoing development of the subfield of nanomedicine. Within the past several years, there has been a concurrent proliferation of academic journals, textbooks, and other professional literature addressing fundamental basic science research and seminal clinical developments in nanomedicine. Additionally, there is now broad consensus among medical researchers and practitioners that along with personalized medicine and regenerative medicine, nanomedicine is likely to revolutionize our definitions of what constitutes human disease and its treatment. In light of these developments, incorporation of key nanomedicine concepts into the general medical curriculum ought to be considered. Here, I offer for consideration five key nanomedicine concepts, along with suggestions regarding the manner in which they might be incorporated effectively into the general medical curriculum. Related curricular issues and implications for medical education also are presented.

Keywords: medical education, basic science, teaching, learning, assessment, nanoscience curriculum, nanomedicine concepts

The evolving nature of medicine as a profession

The history of the development of medicine as a profession – from antiquity through to the end of the 20th century – provides many vivid examples that illustrate how the practice of medicine (and, correspondingly, of formal medical education for successive generations of medical practitioners) has evolved over time. Pertinent examples may be drawn from a range of historical periods and world cultures, such as the influence of the noted polymath, Imhotep, on the development of ancient Egyptian medicine; the systematic study of “natural” causes of human disease ascribed to Hippocrates, the “Father of Western Medicine”; the *Canon of Medicine* compiled by Avicenna during the Islamic Golden Age; and the remarkable development of anatomy and physiology as rigorously empirical scientific disciplines during the Renaissance period in Europe.¹ Within the Western medical tradition, the years 1850–1913 may be denoted as the period that signified the “rise of science in medicine”.² Conceptually, this may be considered to have led directly to the statement in Abraham Flexner’s seminal 1910 report,³ in which he argued unequivocally that as a “proper basis of medical education”, the fundamental sciences (ie, physics, chemistry, biology) “furnish, indeed, the essential instrumental basis of medical education”.³

As we approach the third decade of the 21st century, it is in the spirit of Flexner’s continuing influence on contemporary medical education to consider how the current general medical curriculum should be adapted to incorporate scientific advances that will influence the nature and conduct of future professional medical practice. Over the past 25 years or so – since approximately 1990 – such advances have been occurring

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explicitly in the field of nanoscale science and technology.⁴ Pertinent to the diagnosis, screening, and therapeutic treatment of human diseases, these specific applications of various nanoscale technologies collectively are referred to as “nanomedicine”,^{5,6} “an emerging field that has the potential to revolutionize individual and population-based health in the 21st century”.⁷

It justifiably may be argued that nanomedicine is not yet a “fully mature” and established discipline.^{8,9} However, the field now is of sufficient maturity (ie, in terms of public and private funding for basic scientific research and development; numerous international professional organizations and conferences; increasing publications in the professional medical and scientific literature; and burgeoning numbers of clinical applications and patient trials^{4,9–12}) to warrant consideration being given to its incorporation into the medical education curriculum and into the repertoire of future medical professional practice.

What is nanomedicine?

Nanoscience, very broadly, may be defined as the study of materials and associated physical, chemical, biophysical, and biochemical phenomena on the scale of ~1–100 nm (ie, 10^{-9} m). While the particular size thresholds stated in this definition still remain the subject of vigorous scientific debate,¹³ the primary appeal of nanoscience (and resulting technological applications) is the potential to control and manipulate matter at the nanoscale. Accordingly, nanotechnology may be conceptualized as the intentional design, production, and applications of materials, structures, devices, and systems by controlling their size and shape in the nanoscale range.¹⁴ Since nanomaterials typically are comparable in scale to the molecular structures comprising biological systems and may be designed to have very specific properties and functions, nanotechnology therefore has the potential to be used in medical applications.^{4,10,11}

In 2004, the European Science Foundation proposed the following definition of nanomedicine:

The field of nanomedicine is the science and technology of diagnosing, treating and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body.¹⁵

While this definition is comprehensive and has become influential in the field, it does not differentiate itself adequately from molecular medicine, which is based on a more conventional biochemical approach.⁶ In order to properly understand ongoing developments in nanomedicine, one

needs to appreciate that the therapeutic properties of nanoscale materials purposely designed for use in medical contexts are, by definition, functions of their specific size and scale. Hence, a critical distinction between nanomedicine and other medical research fields (eg, molecular medicine) “is a focus on significantly changed medically related events that result by concentrating solely on the nanoscale”.¹⁶

Two widely used drugs in clinical cancer therapy (ie, Doxil[®] and Abraxane[®]) are examples of nanomedicines that have been designed for cancer chemotherapy, and which function in this capacity as a direct consequence of their physicochemical behavior at the nanoscale.^{17,18} Both are examples of what are known as “first generation” nanocarrier-based drug delivery systems, where tumors passively are targeted as a consequence of the enhanced permeation and retention effect.^{19–21} In addition to first-generation systems, “second generation” and “third generation” nanocarrier-based drug delivery systems (designed to accomplish more deliberate, active targeting of cancerous cells) continue to be developed for clinical use.^{4,11,12,18,22–27} While the preponderance of current research and clinical applications in nanomedicine is in the area of oncology and enhanced therapies for malignant solid tumors,^{25–30} a range of other efforts also are ongoing. These include, for example, investigational and commercially available nanomedicines for various infectious diseases, cardiac/vascular disorders, endocrine/exocrine disorders, and degenerative disorders;¹² sustained drug release in the treatment of glaucoma;^{9,31} and assessments of “pressing clinical needs amenable to nano-enabled technology” such as intelligent nanobiomaterials for cell therapy to improve heart function, cochlear and retinal implants, skin regeneration, and antimicrobials.⁴

In the USA, public funding for nanomedicine research falls under the aegis of federal funding allocated to the National Nanotechnology Initiative.³² At time of writing, for fiscal year 2016, the funding request for nanotechnology research and development (distributed across 20 participating federal agencies) currently stands at \$1.5 billion. It may be noted that of all participating federal agencies, the National Institutes of Health (NIH)

[...] has the largest request among all agencies in FY 2016 [\$423 million], to address nanotechnology-based biomedical research at the intersection of the life and physical sciences.³²

This indicates a significant investment in nanomedicine research, as broadly defined. However, some perspective may be gained by considering, for example, the NIH estimated fiscal year 2016 budget of just over \$1 billion (\$1,039 million) for diabetes research alone.³³

As indicated above, the majority of currently registered nanomedicine clinical trials focus primarily on therapeutic approaches for malignant solid tumors. Using data obtained from the ClinicalTrials.gov database, Table 1 provides ten examples that have been selected to indicate the range of medical conditions for which various nanotherapeutic and/or nanodiagnostic approaches currently are being employed in clinical trials.

Ultimately, the goal of nanomedicine research and development, followed by appropriately rigorous clinical trial protocols, is to successfully employ nanodiagnostic and nanotherapeutic applications in patient care, ie, completion of the “bench to bedside” cycle. Several clinically approved nanomedicines and nanoformulations have made the

transition from bench to bedside,³⁴ including, for example, Verigene®, a nanodiagnostic platform for the rapid identification of a range of infectious pathogens.^{35–38} In Europe, numerous examples may be noted of commercially available nanotherapeutic products for oral and parenteral administration, respectively.³⁹

Why is there a need for education and training in nanomedicine for future doctors?

In a talk given at Southwestern University’s Brown Symposium in 2014, noted nanomedicine researcher Dr Mauro Ferrari opined that “Between 5%–10% of all cancer drugs [in use today] are nanodrugs. Less than 5%–10% of cancer

Table 1 Selected examples of current registered clinical trials featuring nanotherapeutic/nanodiagnostic applications

Study	Conditions	Nanotherapeutic/nanodiagnostic intervention(s)	ClinicalTrials.gov identifier
Paclitaxel Albumin-Stabilized Nanoparticle Formulation in Treating Older Patients With Locally Advanced or Metastatic Breast Cancer	Male breast cancer; recurrent breast cancer; stage IV breast cancer; etc	Paclitaxel albumin-stabilized nanoparticle formulation	NCT01463072
Magnetic Nanoparticle Thermoablation-Retention and Maintenance in the Prostate: A Phase 0 Study in Men (MAGNABLATE I)	Prostate cancer	Magnetic nanoparticle injection	NCT02033447
A Clinical Study: the Antibacterial Effect of Insoluble Antibacterial Nanoparticles (IABN) Incorporated in Dental Materials for Root Canal Treatment	Endodontic treatment; irreversible pulpitis; infected pulp; etc	Device: IABN	NCT01167985
Curcumin as a Novel Treatment to Improve Cognitive Dysfunction in Schizophrenia	Schizophrenia; cognition; psychosis	Theracurmin formulation of curcumin nanoparticles	NCT02104752
Nanoparticulate Versus Micronized Steroids Delivery for Transdermal Hormone Replacement Therapy (Nanoparticle)	Menopausal syndrome	Drug: micronized estradiol + progesterone Drug: nanoparticulate estradiol + progesterone	NCT02467673
IRon Nanoparticle Enhanced MRI in the Assessment of Myocardial infarction (IRNMAN)	Myocardial infarction; inflammation	Device: ferumoxytol-enhanced MRI	NCT01995799
Investigation of Vascular Inflammation in Migraine Using Molecular Nano-imaging and Black Blood Imaging MRI	Migraine headache; migraine without aura	Drug: Feraheme Drug: cilostazol Other: USPIO MRI Other: BBI MRI	NCT02549898
Evaluation of Nano-crystalline Hydroxyapatite Silica Gel in Management of Periodontal Intra-bony Defects	Chronic periodontitis	Biological: nanocrystalline hydroxyapatite silica gel Biological: bone allograft Procedure: open flap debridement	NCT02507596
Imaging Kidney Transplant Rejection Using Ferumoxytol-Enhanced Magnetic Resonance	Renal transplant rejection	Drug: Feraheme Other: MRI-GE Healthcare 3 Tesla magnet	NCT02006108
A Study of BIND-014 in Patients With Urothelial Carcinoma, Cholangiocarcinoma, Cervical Cancer and Squamous Cell Carcinoma of the Head and Neck (iNSITE2)	Urothelial carcinoma; cholangiocarcinoma; cervical cancer; squamous cell carcinoma of head and neck	Drug: BIND-014 (docetaxel nanoparticles for injectable suspension)	NCT02479178

Notes: Data retrieved and compiled from the ClinicalTrials.gov website in October 2015 using the search term “nanoparticles”, including only studies actively recruiting for clinical study participants and excluding studies with “unknown status”.

Abbreviations: BBI, black blood imaging; MRI, magnetic resonance imaging; USPIO, ultrasmall superparamagnetic iron oxide contrast agent.

doctors know that".⁴⁰ This view is supported by Moore, who (within the context of medical education in the UK where a "foundation programme" broadly is analogous to an "internship" or "residency" program in the USA), warned that:

Currently, nanomedicine rarely features in mainstream medical training or in continuing professional development. [...] Yet, by the time the current intake of medical students graduate as doctors and subsequently complete their two-year foundation programme, many new nanomedical products are likely to be appearing.⁴¹

Both comments underscore the fact that contemporary medicine is becoming increasingly dynamic, with the expectation that rapid advances in nanomedicine research and associated technologies^{42,43} are likely to profoundly impact the conduct of future medical practice. Given the pace with which such developments are occurring, the comparative lack of familiarity held by many current and prospective doctors with regard to nanomedicine suggests an increasingly urgent need for education and training in this field. While the ensuing commentary encompasses the necessity of continuing professional development activities in nanomedicine for current medical professionals, primary focus is given here to the medical education of future doctors.

Tomorrow's Doctors and Scientific Foundations for Future Physicians

In recent years, two influential publications have addressed the need for widespread reform in medical education (including the structure, purposes, and goals of the general medical curriculum) and the professional competencies that will be required for 21st-century doctors. *Tomorrow's Doctors: Outcomes and Standards in Undergraduate Medical Education*⁴⁴ and *Scientific Foundations for Future Physicians*⁴⁵ both provide comprehensive guidelines and recommendations for the medical education of future doctors within the continuously evolving landscape of professional medical practice. In particular, both publications emphasize the necessity of future doctors being able to demonstrate comprehensive knowledge and understanding of the basic sciences that will provide the foundation for their future professional careers. It also is noteworthy that both publications are remarkably consistent in advising that "today's undergraduates – tomorrow's doctors- will see huge changes in medical practice" as a consequence of "continuing developments in biomedical sciences and clinical practice",⁴⁴ and that:

Concerns about the science content in the current pre-medical and medical education curricula [...] are especially important given the increasingly rapid rate at which new knowledge revises our understanding of the sciences fundamental to medicine.⁴⁵

In light of these concerns, the following starkly worded statement becomes all the more troubling:

There is also widespread concern that the basic science content in the medical school curriculum has not kept pace with the expanding scientific knowledge base of medicine and fails to reflect accurately the importance of the sciences in the practice of medicine.⁴⁵

Numerous examples may be found in the medical education literature of commentaries issuing similar warnings.⁴⁶⁻⁵¹ While the commentaries offer a variety of sometimes competing perspectives (eg, in terms of the extent and depth of basic science content in the medical curriculum or the relative importance of the basic sciences compared to the development of clinical diagnostic skills in the professional education of doctors), there is general consensus that unprecedented advances in scientific knowledge and in contemporary medical practice necessitate corresponding adaptations in the general medical curriculum.

Neither *Tomorrow's Doctors* nor *Scientific Foundations* (both published in 2009) included any mention of the terms "nanoscience", "nanotechnology", or "nanomedicine". Given the fact that nanomedicine – in its contemporary sense – very much was a nascent field at the time, this is quite understandable. However, with the extent of nanomedicine research now occurring, and with the range of nanomedical applications being developed and tested in various stages of clinical trials,^{4-6,12,13,20,25-28,40-43} it would be unwise for future editions of these documents (or similar publications by other medical education bodies elsewhere) not to give this due attention. Since nanomedicine distinctly is beginning to influence the way in which we think about future medical therapies and professional practice,⁵ it now becomes incumbent on medical educators to begin giving consideration to the manner in which relevant principles and concepts might be incorporated into the general medical curriculum.

Key nanomedicine concepts: suggestions for their incorporation into the general medical curriculum

Moore⁴¹ has proposed that "a basic training module" in nanomedicine for mainstream medical education and ongoing

professional development ideally ought to feature a number of topics, including terminology; fundamental scientific principles of physicochemical behavior at the nanoscale; applications of nanotechnology in medically relevant fields such as imaging, diagnostics, tissue engineering, and drug design; and applications of nanotechnology to various clinical disciplines (eg, oncology, cardiovascular medicine, neurology, orthopedics). This comprehensive listing of topics is of considerable merit, particularly in terms of articulating broad aspects of nanomedicine in which prospective and current medical doctors ought to be knowledgeable. However, the proposal of a “basic training module” in nanomedicine implies another body of curricular content that might be perceived as distinct and separate to the content already present. Taking into account the ongoing debate regarding the bloated medical curriculum^{47,48,52–57} in addition to recent calls for shorter, “fast tracked”⁵⁸ or accelerated medical programs⁵⁹ a more practicable approach might be to incorporate key nanomedicine concepts appropriately into established “standard” content that already is being taught in the medical curriculum. Five key nanomedicine concepts are presented, with brief suggestions regarding the manner in which they might be incorporated into the existing general medical curriculum.

Size and scale

The particular physicochemical behavior of engineered materials and devices at a specific size and scale (ie, the nanoscale) is the primary concept underlying nanotechnology, including applications related to medical or therapeutic contexts. Surface effects and quantum mechanical effects, respectively, are the main factors that cause nanomaterials to behave very differently when compared to their bulk counterparts.^{60,61} At the nanoscale, the surface area-to-volume ratio of materials and devices increases dramatically, and as a result of this, chemical reactivity, mechanical properties, and catalytic properties typically become significantly enhanced at this scale.

Assuming that students already will have received some exposure to concepts of size and scale in middle/high school science and mathematics classes, introductory content about the behavior of materials and devices at the nanoscale ideally could be introduced in premedical course requirements, specifically in undergraduate-level general physics, chemistry, and biology courses, respectively.^{62–64} Consequently, by the time of admission into a medical program, medical students already would be familiar with the terms “nanoscale”, “nanoscience”, and “nanotechnology”. Further discussion

emphasizing conceptual understanding of size and scale could be continued and reinforced in the first year of a “standard” medical program, most likely within courses such as biochemistry, genetics, and microbiology, respectively. Here, students’ attention could be directed explicitly to the fact that, in general, nanomaterials and associated nanoscale devices typically are comparable in size to viruses, DNA, proteins, subcellular organelles, and gap junctions.^{60,63} While it would not be necessary to discuss the more detailed aspects of, for example, quantum confinement effects, the principle of changed or enhanced physicochemical properties of engineered materials at the nanoscale could be taught as a key concept at this point.

Interaction of nanomaterials with biological systems and design of nanomedicines

As Buzea et al state in their excellent review, “every person has been exposed to nanometer-sized foreign particles; we inhale them with every breath, and consume them with every drink”.⁶⁰ These include viruses, as well as nanoparticles produced by a variety of natural processes and human activities.⁶⁰ In terms of nanomaterials and nanoscale devices designed specifically for use in medical contexts, primary methods of administration include oral, dermal, pulmonary, ocular, and parenteral routes, with the majority of nanomedicines currently in use formulated for parenteral (intravenous) administration.^{65,66} However, upon entering the bloodstream, binding of blood proteins to the surface of injected nanomaterials occurs as part of the body’s immune response. Subsequent opsonization and uptake by the mononuclear phagocyte system promotes removal of the administered nanomedicine from the bloodstream, thus hindering its bioavailability and intended therapeutic purpose.^{65,67–69} In an attempt to “evade” the body’s immune response, several techniques have been developed in order to prevent or reduce this protein binding as much as possible. Typically, these techniques involve modification of the surface properties of nanomedicines with various polymers (eg, polyethylene glycol) that prevent opsonization and phagocyte clearance.^{65,70–73} In addition to issues regarding biocompatibility and biodegradability, ongoing research addressing the interaction of nanomaterials with biological systems and the design of nanomedicines also continues to explore potential toxicological concerns.^{65,73–75}

Within the standard medical curriculum, topics relating to protein binding, cell signaling, immunological responses, and pharmacodynamics/pharmacokinetics are taught in

microbiology, biochemistry, immunology, and pharmacology courses, respectively. It is likely that examples relating to the interaction of nanomaterials with biological systems and the subsequent design of nanomedicines could be incorporated fairly readily into this existing curricular structure.

Mechanisms of drug delivery

As mentioned previously, most nanomedicine research efforts to date have focused on developing therapies for malignant solid tumors.^{21,76–78} Mechanisms for delivery of therapeutic nanomaterials to cancerous tissue occur *via passive or active* nanomedicine drug targeting. Passive targeting occurs as the result of spontaneous drug accumulation in cancerous sites with typically leaky vasculature, leading to the enhanced permeation and retention effect.⁷⁹ Active targeting methods exploit the fact that, at the cellular level, many pathological states may be identified by a display of surface proteins that are absent in healthy cells, or which are overexpressed in comparison to healthy cells. Surface functionalization of nanomedicines with ligands that bind selectively to proteins expressed on the surface of unhealthy tissue allows specific targeting of the nanomedicine to the diseased site.⁸⁰ Ongoing research efforts continue to explore more sophisticated and precise active targeting approaches for cancer therapy.⁶⁵ In addition to cancer therapy, efforts to develop selective nanomedicine targeting also are being extended into antiviral drug delivery⁸¹ and to pathologies affecting the central nervous system (eg, Alzheimer's disease, Parkinson's disease).^{82–85}

Within the standard medical curriculum, principles related to passive and active nanomedicine drug targeting readily could be accommodated within microbiology, biochemistry, pharmacology, and pathology courses, respectively. Given the particular difficulty of targeted drug delivery across the blood–brain barrier, this also may be emphasized in the physiology course component of the existing medical curriculum.

Nanodiagnostics

The use of nanotechnology for clinical diagnostic purposes has developed in response to the demands of clinical diagnostics for increased sensitivity and earlier detection of disease. The central principle describing the mechanism of nanoparticle-based assays is the selective binding of a nanoparticle label or probe to a target biomolecule (eg, DNA, RNA, peptides, antigens, or other small analytes) that typically also will have nanometer-scale dimensions. As a

consequence of binding to the target molecule, a measurable signal – characteristic of the target biomolecule – is produced.^{86–88} Due to the sensitivity with which such target biomolecules (or “biomarkers”) may be measured by nanoparticle-based assays,⁸⁹ “nanodiagnostic devices are expected to eventually supplant diagnostic tools that aren't as sensitive, convenient, efficient, or cost-effective”.²⁰ Sensitivity limitations of current diagnostic tools result in the detection of some diseases only at an advanced stage: for example, current methods of cancer diagnosis rely on “bulk” measurement assays of surface proteins expressed on the surface of malignant cancerous cells or the detection of a solid tumor that already will contain millions of cancerous cells.²⁰ Using a number of *in vitro* and *in vivo* methods,⁸⁹ nanodiagnostic devices are able to detect the presence of relevant biomarkers (eg, surface proteins of cancerous cells or circulating tumor DNA) at much lower levels, and potentially are able to measure the presence of target biomarkers at the level of single cells and molecules.^{68,90} In addition to point-of-care nanodiagnostic methods that have been developed for a range of cancers,^{91,92} point-of-care nanodiagnostics continue to be developed for several other pathologies, including Alzheimer's disease,^{20,93} diabetes,^{94,95} and a number of viral and bacterial infections.^{96–98}

Key principles describing nanoparticle-based assays might be incorporated into a premedical-level introduction to medicine course (including diagnosis and patient care), or perhaps into an introduction to clinical medicine course in the general medical curriculum. Within the basic sciences component of the current general medical curriculum, curricular logistics might make it more challenging to incorporate these principles into a traditional biochemistry or pathology course, since they might be perceived as belonging more in the domain of a clinical sciences or medical laboratory sciences degree program. However, the underlying basic science concepts certainly are applicable and may be taught within the contexts of traditional biochemistry and/or pathology courses (ie, targeted recognition by nanoparticle labels of biomarkers expressed at the cellular/tissue level in various pathologies), and the topic of nanodiagnostics may be reinforced explicitly in the clinical experiences component of the general medical degree program.

Potential ethical issues

The increasing use of nanodiagnostics and nanotherapeutics in identifying and treating a range of human pathologies

raises several ethical conundrums. As one example, if the sensitivity of diagnostic nanotechnologies becomes such that likely malignant cancers may be identified at the level of single cells, then “how many cells from the body must be of a cancerous nature for it to be defined as cancer?”⁹⁹ How might such a scenario lead physicians to reconceptualize how human “disease” is defined, along with appropriate medical interventions?⁹⁹ In addition to general commentaries addressing social and ethical dimensions of nanoscale science and engineering research,^{100,101} a growing body of professional literature continues to address potential ethical issues arising specifically from the use of various nanotechnologies in clinical diagnosis and medical treatment. Key issues include the observation that “nanomedicine is likely to be one of the most – if not *the* most-profitable applications of nanotechnology”,¹⁰² and as other commentators have noted, such “extreme profitability”¹⁰² leads to concerns that global equality in access to health care might be even further compromised.^{103,104} Rather notably, in 2012, the *Journal of Law, Medicine & Ethics* published a special issue that featured a number of perspectives from research scientists, bioethicists, and others^{105–111} addressing potential ethical issues in nanomedicine. While there are concerns that “nanomedical interventions present a higher level of uncertainty than do more conventional biomedical interventions”¹⁰⁷ – particularly with regard to clinical trials of nanomedicines in humans – most commentators agree that, fundamentally, there are no “new” ethical concerns specific to medical nanotechnologies^{102,105,112} that are not subsumed within existing biomedical ethics guidelines.¹¹³ However, there appears to be broad consensus that the potential scope, extent, and technical complexities of medical nanotechnologies justify further, long-term examination of potential ethical implications.^{107,108,114}

Within the existing general medical curriculum, issues pertaining to potential ethical concerns in nanomedicine may be accommodated in a standard professional medical ethics class that utilizes, for example, Beauchamp and Childress’ widely cited four principles of biomedical ethics, ie, respect for autonomy, beneficence, non-maleficence, and justice.¹¹³ Given the critical importance of developing effective skills in doctor–patient communication^{115,116} and the practical inseparability of communication skills and ethical behaviors,¹¹⁷ it also is likely that potential ethical concerns in nanomedicine could be addressed in a number of professional communication and clinical skills courses offered in various general medical curricula.

Anticipated curricular challenges

No attempt is made here to be prescriptive regarding appropriate points at which these five suggested concepts ought to be introduced and taught in the general medical curriculum, nor is it implied that these concepts are exhaustive. Such considerations remain open to debate and rebuttal. Clearly, the concepts listed above are not discrete, and considerable overlap exists between them. They are presented here as a potential guide in terms of how they effectively might be incorporated in a systematic and coherent manner into the existing medical curriculum. At least three significant “curricular challenges” to these suggestions may be anticipated, and these are outlined briefly below.

Excessive basic science content in the general medical curriculum

The ongoing debate concerning “too much” basic science content in the general medical curriculum has been amply documented.^{46–57} This is likely to be one of the primary objections against incorporating key nanomedicine concepts into what long has been argued is an already “overstuffed curriculum”.¹¹⁸ Nevertheless, if there is broad agreement within the medical education community that existing basic science content in the general medical curriculum does not adequately address “the expanding scientific knowledge base of medicine”,⁴⁵ it then becomes necessary to consider the ways in which “medical school curricula must continue to adapt in order to best prepare physicians for practice in the twenty-first century”.⁴⁹ In practical terms, it must be acknowledged that a rapidly increasing basic science knowledge base – together with additional professional medical competencies – physically cannot be accommodated within the existing structure of the general medical curriculum. However, as cogently argued by Brass:

The wrong solution is to reduce traditional *necessary* core material to accommodate new core material. The debate is what is necessary, [...], and what broader restructuring may be required to accommodate the new educational requirements.⁴⁸

Currently, two curricular formats appear to be the primary avenues through which a comparatively small number of prospective medical doctors are exposed to various nanomedicine concepts. First is the MD/PhD program format, in which the express goal of the typically 7- to 8-year program is to produce a new “hybrid” generation of research

physicians who are skilled in the scientific development and clinical use of various medical nanotechnologies.^{119,120} Second is the scholarly concentrations format (occurring during the standard timeline of the regular general medical program), in which students undertake guided independent research projects that address some aspect of the application of nanotechnologies to medical practice.^{121,122} Although these approaches – or variations thereof – have received support in the medical education community,^{7,52,123} it may be argued that neither one satisfactorily resolves the issue of “how broadly [all prospective physicians] in the 21st century should be exposed to the scope of the biological sciences”.¹²⁴ The approaches as described represent excellent career-enhancing opportunities for medical students who wish to undertake laboratory research and become clinician-scientists: however, exposure to key “nanomedicine concepts” cannot remain exclusively in the domain of MD/PhD programs or scholarly concentrations alone if all future physicians are to have some knowledge and competence in nanomedicine.

Basic science vs clinical science components of the general medical curriculum

In addition to differences of professional opinion concerning “too much” basic science in the general medical curriculum, a related curricular debate addresses what typically is perceived to be the poorly articulated nature of the basic science and clinical science components, respectively. Efforts to establish truly integrated medical curricula continue to be undertaken with varying degrees of success.^{49,50,125,126} The issue further is compounded by students who often do not clearly understand the relevance of their basic science classes to clinical care, and by encounters with clinical faculty who do not adequately model the role of basic science knowledge in clinical decision-making.⁴⁸ As proposed above, applicable concepts in nanomedicine should be incorporated comprehensively across the medical curriculum, during both preclinical and clinical stages. Since the physicochemical principles of how nanomaterials interact with biological systems are linked intimately (both conceptually and procedurally) to nanotechnology-enabled diagnostics and therapeutic approaches, it may be argued that nanomedicine is likely to ameliorate rather than exacerbate a perceived discontinuity between basic science and clinical applications. The current growth of “nanotheranostics” (ie, the simultaneous integration of nanotechnology-enabled diagnosis and therapy)^{127,128} also may serve an important

role in making the “disconnect” between basic science and clinical medicine conceptually obsolete.

Testing and assessment

It is well known at all educational levels that assessment drives instruction. Equally significant is the aphorism that “what examinations ask determines what students learn”.¹¹⁸ Within the context of medical schools in the USA (and a number of medical schools in Canada), the Medical College Admissions Test® (MCAT) typically is used as a measure of students’ academic preparedness and ability to successfully undertake a medical program of study.¹²⁹ However, both premedical courses and the MCAT have been criticized on the basis that they do not adequately take into account advances in scientific knowledge at the cellular and molecular levels that will be required for the practice of medicine in the 21st century.^{47,51} Similar critiques may be made of the United States Medical Licensing Examination (USMLE), which also has been claimed to encourage the “binge and purge” mentality of students who do not recognize the importance of the basic sciences in medical practice, and hence tend to memorize basic science information for short-term retention only.^{51,130–133} At time of writing, several significant changes have occurred to the format of both the MCAT and the USMLE. In an effort to “focus on skills and concepts that tomorrow’s doctors will need”, it may be noted that the updated version of the MCAT (April 2015) now tests

[...] cellular and molecular biology topics [...] and biochemistry concepts at the level taught in many colleges and universities in first-semester biochemistry courses [...].¹³⁴

in addition to practical applications of biotechnology “which directly impact humans, such as medical applications, human gene therapy, and pharmaceuticals”.¹³⁴ Such developments are likely to augur well for the eventual introduction of interdisciplinary nanoscience concepts into premedical and basic medical sciences curricula. Concurrent changes in the USMLE include:

Increased numbers of items that assess an expanded range of competency-based content, including foundational science essential for effective healthcare.¹³⁵

Of particular significance is the narrative included in the current *Content Description and General Information* guidelines for both USMLE Step 1 and Step 2 (clinical knowledge), which indicates that:

The content outline is not intended as a curriculum development or study guide. It provides a flexible structure for test construction that can readily accommodate new topics, emerging content domains, and shifts in emphasis. The categorizations and content coverage are subject to change.¹³⁶

While it might not be the intent for these content outlines to serve as curriculum development or study guides, it may be argued that any articulation of content knowledge to be tested or assessed automatically will influence curricular development and instructional priorities. Given the implicit acknowledgment that the USMLE will continue its adaptation to accommodate new topics and emerging content domains,^{136,137} it will be of great interest over the next several years to note the extent to which testing and assessment of applicable nanomedicine concepts are incorporated into this pivotal high-stakes examination.

Concluding comments

Fundamental to the discussion presented here is the unavoidable realization that contemporary medical education must continue to adapt if it is to adequately prepare physicians to practice medicine in the 21st century. As proposed in this article, an important aspect of this adaptation necessarily will include the incorporation of key nanomedicine concepts into the general medical curriculum. It is not my intent here to offer unfounded prognostications on the future of professional medical education and practice: nevertheless, it is difficult not to agree with Kanter, who has argued that the incipient generation of medical doctors and research scientists:

[...] will administer to patients treatments that have not yet been discovered based on heretofore inaccessible understandings and classifications of disease, in a health care environment that surely will undergo significant change.¹³⁸

How we address these significant changes will need to be tempered with careful deliberation and considerable professional judgment. Due to the accuracy, sensitivity, and sophistication of nanotechnology-enabled diagnostic methods, future definitions of what constitute human “health” and human “disease” will need to be reconsidered. How will future doctors diagnose and provide medical treatment to patients who do not necessarily exhibit any overt, observable clinical signs? How will clinical or pathological relevance be determined?⁹⁹ In concert with “organ-on-a-chip”

and “human-on-a-chip” technologies for drug research and discovery,¹³⁹ how might nanodiagnostic methods revolutionize our concepts of “clinical medicine” and the manner in which clinical knowledge, clinical reasoning, and clinical skills are taught and assessed? Will physicians’ development of relevant illness scripts^{140–143} undergo modification, and if so, to what extent?

For the time being, these are presented as rhetorical (and perhaps provocative) questions intended to stimulate discussion and debate. More immediate concerns relate to the impact on the present structure of the general medical curriculum and the restructuring that will need to occur in educational preparation and academic requirements for future students seeking to undertake a medical program of study. As Cavazos has indicated,

Medical schools are particularly good at imparting the skills of the profession to their students, but much else that goes into the making of a physician is acquired long before medical school.¹⁴⁴

If nanomedicine truly is to revolutionize the way in which medicine as a profession will be practiced, perhaps now is an appropriate juncture at which the medical education community reevaluates its philosophy of premedical education^{124,145} and its involvement in the premedical liberal arts and science curriculum to better address current advances in biomedical sciences, medical nanotechnologies, and public health policy. Similar to focused efforts that have occurred to incorporate nanoscale science concepts into undergraduate science and engineering programs (in addition to high school science curricula),^{14,146} corresponding efforts also should be initiated for premedical education and general medical programs of study. More broadly, perhaps now is a particularly opportune time at which to consider the evolution of medical education into a more thoroughly interdisciplinary, integrated teaching and research endeavor.¹⁴⁷

The process of adapting to continued advances in scientific knowledge is an important, and often, a highly challenging task.^{148,149} No less challenging will be the task faced by the medical education community to comprehensively address the issues and implications presented here for discussion.

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