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Nanotechnological applications in medicine

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Nanotechnology-based tools and techniques are rapidly emerging in the fields of medical imaging and targeted drug delivery. Employing constructs such as dendrimers, liposomes, nanoshells, nanotubes, emulsions and quantum dots, these advances lead toward the concept of personalized medicine and the potential for very early, even pre-symptomatic, diagnoses coupled with highly-effective targeted therapy. Highlighting clinically available and preclinical applications, this review explores the opportunities and issues surrounding nanomedicine.

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Introduction

'Molecular imaging' is a phrase that has come into heavy use within the past decade. It is a broad term, difficult to define. Although the initial use implied imaging novel contrast agents to probe molecular information [1], the current use has evolved to include a wide scope of imaging techniques that use molecular agents or rely on molecular signatures. These include virtually all positron emission tomography imaging (indeed all nuclear medicine techniques requiring radioactive or radiolabeled molecules), magnetic resonance spectroscopy, and other parametric magnetic resonance imaging techniques (like diffusion-weighted imaging). Similarly, the term 'nanomedicine' is difficult to define precisely, as much of what transpires in human biology happens at the nanometer scale. Thus, one might successfully argue that all medicine is 'nanomedicine'. Herein, we discuss nanomedicine as the application of technologies on the scale of approximately 1 to 500 nm toward the goal of diagnosing and treating disease.

Within the past decade, there has been a plethora of new research, development and patent activities around nano-scaled technologies in the health sciences field [2•]. One indicator of this is the flurry of activity around the National Nanotechnology Initiative [3] of the US government and, in particular, those initiatives of the National Institutes of Health (NIH). Within the National Cancer Institute (NCI) alone, the Alliance for Nanotechnology in Cancer program (http://nano.cancer.gov/) has launched eight Centers of Cancer Nanotechnology Excellence (http://nano.cancer.gov/programs/ccne.asp) and twelve Cancer Nanotechnology Platform Partnerships (http://nano.cancer.gov/programs/nanotech_platforms.asp) [4]. The Program for Excellence in Nanotechnology (http://www.nhlbi-pen.info/) of the National Heart, Lung and Blood Institute is another instance of the profuse programs fueling this growing research arena. To help facilitate the transfer of nanotechnological research into clinical practice, the NCI, in conjunction with the National Institute of Standards and Technology and the US Food and Drug Administration (FDA), has also established the National Characterization Laboratory (http://ncl.cancer.gov/).

The overall goal of nanomedicine is the same as it always has been in medicine: to diagnose as accurately and early as possible, to treat as effectively as possible without side effects, and to evaluate the efficacy of treatment non-invasively. The promise that nanotechnology brings is multifaceted, offering not only improvements to current techniques but also providing entirely new tools and capabilities. By manipulating drugs and other materials at the nanometer scale, the fundamental properties and bioactivity of materials can be altered. These tools can permit control over characteristics of drugs or agents such as solubility, blood pool retention times, controlled release over short or long durations, environmentally triggered controlled release or highly specific site-targeted delivery. Furthermore, by using nanometer-sized particles, the increased functional surface area per unit volume can be exploited in various ways.

This review presents some of the more recent successes of applying various new nanotechnological techniques and tools in diagnostic imaging and therapeutics, including both current products and late-stage preclinical research. It will not delve into screening or *in vitro* diagnostics, although nanotechnological applications certainly abound in these areas (e.g. improvements to 'laboratory on a chip' technologies like microarrays and microfluidics [5,6]). Nor will this review focus on the many advances in biomedical laboratory research tools and techniques resulting from nanotechnology.

Diagnostic imaging in nanomedicine

Combining advances in related fields such as genomics, proteomics, drug delivery and molecular imaging, nanomedicine offers the potential to move from a 'one-size-fits-all' approach to one more individually tailored for higher efficacy [1,7]. For diagnosis, this translates to recognition and characterization of very early (even pre-symptomatic) disease providing assessment, preferably non-invasively, akin to that of immunohistochemistry. Of course doing so is complex, requiring simultaneous detection and quantification of multiple markers. Starting with single biomarkers as *sine quo non* for disease, initial successes in nanotechnology-enabled molecular imaging have been made in all imaging modalities including optical [8–10], nuclear [9,11], ultrasound [12,13], computed tomography (CT) [14,15•], and magnetic resonance imaging (MRI) [16–18]. Optical and nuclear techniques are exquisitely sensitive to their respective agents, but are complicated by high background noise. The other major modalities (i.e. MRI, CT and ultrasound) are hampered by relative insensitivity to low concentrations of imaging agent, as would be the case for agents bound to molecular markers. The increased surface area per volume of nanoparticles helps overcome this limitation by coupling each targeted particle with very large payloads of the imaging agent [17].

One of the earliest applications of nanotechnology in MRI was the use of paramagnetic iron oxide particles; when taken up by healthy hepatocytes, these particles could help to distinguish between normal and cancerous liver cells [19]. Other applications of these nanoparticulate iron oxides have been used to highlight lymph node metastases in prostate cancer [20] and atherosclerotic plaques in hyperlipidemic rabbit models [21]. More recently, nanometer-sized constructs such as dendrimers [18,22,23], liposomes [24,25], nanoshells [26], nanotubes [27], nanoemulsions [28], quantum dots [29,30], and even viruses [31] have been developed as imaging agents intended as noninvasive probes or to target biomarkers of disease. Many have moved from *in vitro* to *in vivo* applications, targeting biomarkers such as the overexpressed folate receptor of cancer cells [22], human growth factor receptors (HER2) on tumors [32•], or integrins crucial to angiogenesis around tumors [33,34] and atherosclerotic vessels [35].

Expanding on targeting single biomarkers, recent research has addressed the need for quantification and simultaneous identification of multiple markers. Quantum dots offer a full spectrum of colors to achieve this, but are limited to *in vitro*, small animal or surface applications where optical techniques excel. In a method analogous to multicolored quantum dots, researchers exploiting the unique magnetic resonance spectra of various liquid-core perfluorocarbon nanoparticle emulsions have shown the potential of MRI for quantifying biomarkers (i.e. fibrin deposits, a biomarker for ruptured atherosclerotic plaques) [36] and simultaneously distinguishing and uniquely imaging multiple targeted agents bound in the same location [37•].

Nanotherapeutics

Controlled drug delivery

Unfortunately, early diagnosis is futile if not coupled with effective therapy. Owing in part to the national nanotechnology initiatives, there has been much activity in applying nanotechnology to therapeutics [38–41,42•]. Currently, there are limited numbers of nanomedical products on the market [2•], with the majority being pharmaceuticals that are formulated (or re-formulated) into nanosized structures to manipulate the pharmacodynamics, biodistribution and overall effectiveness. Cosmetological and dermatological applications are well represented, especially with liposomal versions of exisiting drugs [25]. Liposomal packaging of chemotherapeutic agents (e.g. doxorubicin) are also on the market [43]. The surface addition of polyethylene glycol (PEG) of varying dimensions is a common technique used to alter chemical formulations (liposome or otherwise) into 'stealthy' nanoparticles with increased circulating half lives. This technique is employed for many current products with indications including leukemia, neutropenia, hepatitis, and macular degeneration [2•]. Abraxane, a nanoparticle version of paclitaxel bound to albumin, achieves water solubility without harsh excipients, has been shown to be more effective than previous formulations of paclitaxel, and is the first such chemotherapeutic nanoparticle approved by the FDA [44••]. In addition to these drug delivery techniques, advances in nanotechnology and polymer sciences have contributed to techniques such as implantable nanoporous membranes [45,46], controlled-release biochips [47], and transdermal microneedle systems [48].

Site-targeted nanotherapeutics

Beyond clever pharmacokinetic manipulations, a more complex goal of nanotherapeutics is to devise agents that travel within the body undetected to deliver specific therapy — whether chemical, radioactive, genetic or other — to uniquely identified sites having minimal untoward effect elsewhere. Additionally, agents that can, upon their success, 'report back' through non-invasive signaling (i.e. imaging) to provide confirmation and predicted efficacy would greatly alter the current paradigm for treating and following patients. Many novel agents, currently under development and perhaps soon to enter clinical trials, share this ultimate goal [22,32•,38,40,42•,49–54].

An *in vitro* model of atherosclerosis illustrates the potential targeted nanotherapeutic paradigm from diagnosis, through therapy, to serial non-invasive follow-up. In hyperlipidemic rabbits, Winter *et al.* [55••] used integrin-targeted paramagnetic nanoparticles that had previously been shown [35] to detect angiogenesis in very early atherosclerotic disease with MRI. This novel agent provides quantification of the extent of disease and, at the same time, can convey therapeutic doses of an anti-angiogenic drug, fumagillin, which could slow plaque progression. Moreover, following treatment, MRI scans were performed using the diagnostic version of the targeted paramagnetic nanoparticles to monitor the effect longitudinally. The targeted therapeutic nanoparticles not only had a significant anti-angiogenic effect that could be monitored via non-invasive imaging, but the magnitude of response correlated linearly with the degree of image enhancement measured at the time of initial treatment; that is, the images at time of treatment confirmed drug delivery and were predictive of therapeutic efficacy. Furthermore, as the targeted nanoparticle drug delivery concentrated the drug at the desired site, the results were achieved with a total drug dose thousands of times lower than similar studies using conventional drug delivery schemes. Thus, targeted nanoparticles can drastically improve the safety profile of the drug by lowering overall dosage and concentrating levels in disease sites.

Limitations and considerations in nanomedicine

Obviously, not all attempts to apply new nanotechnology approaches in medicine have met with the same success as those cited herein. The new tools are not necessarily intuitive and bring with them new challenges and hurdles. Nanometer-sized structures do not behave in the same predictive ways that single, small-molecule interactions occur. Nanoconstructs, especially multifunctional ones, are complex three-dimensional objects with critical dependence on position, size, shape and charge of interrelated components. Currently, what we know about nanomedicine is dwarfed by what we do not know; most of the challenges have not been defined.

The potential that nanotechnology offers for improved circulating half-life, greater functional surface area, and other benefits is superb, but offset by new, and yet-unknown, constraints. Coupled with changing circulation times, for example, are changes with clearance from the body. If the clearance mechanism for a radiotherapeutic agent is shifted from being cleared in minutes via the kidneys to hours via the liver, this has potential ramifications. Other nanoparticles might be retained not only for days, but potentially for years. In that case, the safety profile for all components becomes of paramount significance. Although the long-term safety of the components of some nanotechnology devices like perfluorocarbons or semiconductors is well described, others, like carbon nanotubes, are not well appreciated. Furthermore, as physical properties of materials are altered at the nanometer level, current safety information cannot be assumed to be accurate for nanoversions. Safety and drug effects are not limited solely to the patient population receiving the final nanomedicine product. The entire manufacture and disposal process also needs to be considered. For example, as nanoparticulates can be very easily aerosolized, standard filtering or protection equipment might not be appropriate. Waste water and other environmental impacts might be different than with customary techniques. The promise of nanotechnology applications in medicine is the breadth of entirely novel techniques; the responsibility is to redefine the safety, function, and environmental effects of the new tools and techniques.

Conclusions

Nanotechnology, in general, is experiencing a rapid growth period with major advances arriving quickly. Accordingly, these advances are applied in the biomedical field in numerous diverse ways. Already, a few medical products are providing a glimmer of the overwhelming benefits nanomedicine will surely provide. Current preclinical research promises new ways to diagnose disease, to deliver specific therapy, and to monitor the effects acutely and non-invasively. This rapid onset and drastic change in methods will create new challenges in the regulatory process, but will also provide a fruitful ground from which many exciting, and yet unimagined, applications of nanotechnology in medicine will arise.

Disclosure statement

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