POTENTIAL CLINICAL RELEVANCE

Nanomedicine: Nanotechnology, Biology, and Medicine
9 (2013) 1–14

Feature Article

nanomedjournal.com

The big picture on nanomedicine: the state of investigational and approved nanomedicine products

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Received 8 February 2012; accepted 23 May 2012

Abstract

Developments in nanomedicine are expected to provide solutions to many of modern medicine's unsolved problems, so it is no surprise that the literature contains many articles discussing the subject. However, existing reviews tend to focus on specific sectors of nanomedicine or to take a very forward-looking stance and fail to provide a complete perspective on the current landscape. This article provides a more comprehensive and contemporary inventory of nanomedicine products. A keyword search of literature, clinical trial registries, and the Web yielded 247 nanomedicine products that are approved or in various stages of clinical study. Specific information on each was gathered, so the overall field could be described based on various dimensions, including FDA classification, approval status, nanoscale size, treated condition, nanostructure, and others. In addition to documenting the many nanomedicine products already in use in humans, this study indentifies several interesting trends forecasting the future of nanomedicine.

From the Clinical Editor: In this one of a kind review, the state of nanomedicine commercialization is discussed, concentrating only on nanomedicine-based developments and products that are either in clinical trials or have already been approved for use.

Key words: Nanomedicine; Biomedical nanotechnology; Nanobiotechnology; Clinical trials; Human subjects research

Nanotechnology will significantly benefit society, producing major advances in energy, including economic solar cells[1] and high-performance batteries[2]; electronics, with ultrahigh density data storage[3] and single-atom transistors[4]; and food and agriculture, offering smart delivery of nutrients and increased screening for contaminants.[5] However, two of the most exciting and promising domains for advancement are health and medicine. Nanotechnology offers potential developments in pharmaceuticals,[6] medical imaging and diagnosis,[7,8] cancer treatment,[9] implantable materials,[10] tissue regeneration,[11] and even multifunctional platforms combining several of these modes of action into packages a fraction the size of a cell.[12,13] Although there have been articles describing the expected benefits of nanotechnology in medicine, there has been less effort placed on providing a comprehensive picture of its current status and how this will guide the future trajectory. Wagner et al summarized the findings of a 2005 study commissioned by the European Science and Technology Observatory (ETSO),[14,15] including a list of approved products and data on developing applications and the companies involved, but with emphasis more on the economic potential than on trends in the technology. A number of articles have analyzed specific sectors of nanomedicine, including liposomes[16,17] nanoparticles (NPs) for drug delivery,[18,19] emulsions,[20] imaging,[21] biomaterials,[22,23] and in vitro diagnostics,[24] but such focused discussions do not provide insight into the overall trajectory of nanomaterials in medicine.

No conflict of interest was reported by the authors of this article.

This work was supported by National Institutes of Health (NIH) / National Human Genome Research Institute (NHGRI) grant #1-RC1-HG005338-01 (S. M. Wolf, PI; J. McCullough, R. Hall, and J. Kahn, Co-Is), through the University of Minnesota's Consortium on Law and Values in Health, Environment & the Life Sciences.

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http://dx.doi.org/10.1016/j.nano.2012.05.013

Please cite this article as: Etheridge M.L., Campbell S.A., Erdman A.G., Haynes C.L., Wolf S.M., McCullough J., The big picture of nanomedicine: the state of investigational and approved nanomedicine products, *Nanomedicine: NBM* 2013;9:1-14, http://dx.doi.org/10.1016/j.nano.2012.05.013

Industry market reports describing companies and their products related to nanomedicine and nanobiotechnology have also begun to emerge in the last several years,[25,26] but this information is difficult to access for the average researcher or engineer, due to the high subscription costs. The objective of this review is then to fill an important gap in literature by analyzing the current nanomedicine landscape (commercialized and investigational nanomedicine products) on a number of important dimensions to identify the emerging trends. This original approach provides a solid groundwork for anticipating the next phases of nanomedicine development, highlighting valuable perspectives relevant to the field.

Scope of analysis

The definitions of "nanotechnology" and "nanomedicine" continue to be an area of controversy, with no universally accepted classification. Because an operational definition is required for the purposes of this study, nanomedicine is taken as the use of nanoscale or nanostructured materials in medicine, engineered to have unique medical effects based on their structures, including structures with at least one characteristic dimension up to 300 nm. Nanomedicine takes advantage of two general phenomena that occur at the nanoscale: transitions in physiochemical properties and transitions in physiological interactions. Many of the early definitions of nanotechnology employ a cut-off around 100 nm (including that of the National Nanotechnology Initiative (NNI),[27] focusing on the former, where quantum effects are often restricted to structures on the order of ones to tens of nanometers.[28,29] However, unique physiochemical behavior sometimes emerges for nanomaterials with defining features greater than 100 nm (e.g., the plasmon-resonance in 150 nm diameter gold nanoshells that are currently under clinical investigation for cancer thermal therapy[30]). In addition, many of the benefits (and risks) of nanomedicine are related to the unique physiological interactions that appear in the transition between the molecular and microscopic scales. At the systemic level, drug bioavailability is increased due to the high relative surface area of NPs,[31] and it has been shown that liposomes around 150 nm to 200 nm in diameter remain in the bloodstream longer than those with diameters less than 70 nm.[32] At the tissue level, many nanomedicine products attempt to passively target sites through the enhanced permeability and retention (EPR) effect, with feature sizes typically in the 100 nm to 200 nm range, but particles up to 400 nm have demonstrated extravasation and accumulation in tumors[33] (although this is an extreme case). At the cellular level, NP uptake and processing pathways depend on many properties,[34] but size is a critical factor. Although optimal cellular uptake for colloidal gold has been shown for sizes of around 50 nm,[35] macrophages can easily phagocytose polystyrene beads up to 200 nm in diameter.[36] So, although much of nanomedicine utilizes feature sizes at or below 100 nm, this cut-off excludes many applications with significant consequence to the field. Thus we chose 300 nm to better encompass the unique physiological behavior that is occurring on these scales. It should also be noted that all this behavior is highly material- and geometry-specific, with much of the previous discussion focusing on spherical NPs, as they are the most prominent in literature. However, many newly developing particles utilize high aspect ratios or nanoscale features on microscale platforms to enhance vascular extravasation[37] and this will still fall under the purview of our definition.

An application will generally move through five developmental phases, from basic science to a commercialized medical product (Figure 1). To depict and analyze the nanomedicine landscape, we focused on identifying applications that are undergoing or on the verge of clinical investigation in human participants, as well as products already approved by the U.S. Food and Drug Administration (FDA) or foreign equivalent. This excludes applications that are earlier in the pipeline, such as those in bench science or early animal testing. Many of the revolutionary nanomedicine technologies anticipated in the literature may be 20 or more years from clinical use. It is difficult to speculate about the forms in which these may finally be implemented and the ultimate impact they may have. For instance, in a 2006 survey, academic, government, and industry experts did not expect to see "nanomachines" capable of theranostics (combined therapy and diagnostics) in human beings until 2025.[38] Our study thus focuses on applications and products that are already being tested or used in humans. These applications and products will have the most significant impact on industry, regulation, and society for the foreseeable future.

Methods

We used a structured sequence of Internet searches to identify nanomedicine applications and products. Targeted searches on PubMed.gov, Google, and Google Scholar, and a number of clinical trial registries produced a range of resources, including journal articles, consumer websites, commercial websites, clinical trial summaries, manufacturer documents, conference proceedings, and patents. All of those were used to identify potential nanomedicine applications and products. Information was gathered on each of the identified applications and products through additional searches, and the results were recorded and sorted in several Microsoft Excel databases. All searches were performed by Michael Etheridge under the supervision of Jeff McCullough (Co-Investigator), with input and feedback from Susan Wolf (Principal Investigator) and the full project working group funded by a grant from the National Institutes of Health (NIH), National Human Genome Research Institute (NHGRI) (#1-RC1-HG005338-01). Although these research methods used a broad range of keywords to conduct the most comprehensive search possible, product literature without mention of nano-related terminology will not be identified through this approach.

To offer a more detailed description of the search methodology and classification process, initial searches were conducted through Web-based search engines including PubMed.gov, Google, and Google Scholar. The initial searches and filtering were conducted in January through March of 2010, then rerun in May of 2011 to capture any new material published in the interim. The search terms used were: "nanomedicine AND product(s)," "nanomedicine AND commercial," "nanobiotechnology AND product(s)," "nanobiotechnology AND commercial," "nanotechnology AND product(s)," "nanotechnology AND commercial," "nano AND product(s)," and "nano AND

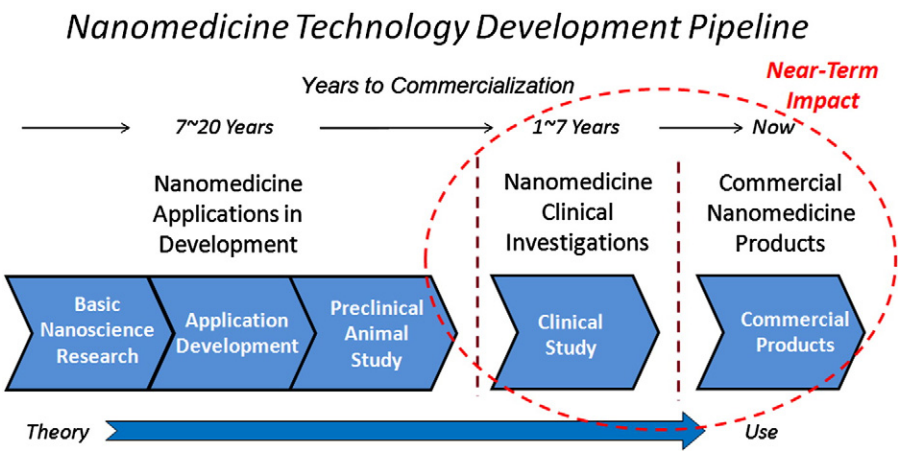

Figure 1. Five general stages of nanomedicine development. This study focuses on the applications and products approved and under clinical investigation because they will have the strongest impact on the direction of nanomedicine over the foreseeable future.

commercial." We filtered the results to capture lists, tables, and databases cataloging nanotechnology applications and products related to medicine (generally identified as "nanomedicine," "nanobiotechnology," or "medical nanotechnology"). These lists, tables, and databases appeared in review articles that detailed applications in a specific sector of nanomedicine and public service websites that cataloged nanotechnology products for consumer awareness (such as The Project for Emerging Nanotechnologies[39]). No significant filtering of the applications and products themselves was performed at this point; all applications and products identified as nanotechnology related to medicine were recorded for further analysis.

We conducted additional searches through Web-based clinical trial registries. ClinicalTrials.gov was the main focus of our research efforts, but the results were supplemented with reviews of: Biomedical Research Alliance of New York (www.brany.com), Current Controlled Trials (www.controlled-trials.com), Forest Laboratories (www.frx.com), International Federation of Pharmaceutical Manufacturers & Associations (www.ifpma.org), Ontario Institute for Cancer Research (www.oicr.on.ca), Stroke Trials (www.strokecenter.org/trials/), and the World Health Organization (www.who.int/trialsearch/). Nine other clinical trial registries were considered but were not used due to redundancy with ClinicalTrials.gov or the impracticality of searching their databases. The initial searches in the clinical trial registries were conducted in March of 2010, then rerun in May of 2011 to capture any new clinical trials posted in the interim. A comprehensive list of 44 nanomedicine-related search terms was developed and used as the basis for keyword searches in the registries (Table 1). The search terms fell into two categories: general nano terminology (nano, nanotechnology, etc.) and specific nanotechnology platforms (NP, liposome, emulsion, etc.). The keyword searches resulted in identification of over 1,000 distinct clinical trials, which were then reviewed for relevance to nanomedicine. Any information provided (such as sponsor, product name, published literature, etc.), was used to conduct follow-up, Web-based searches (through Google and Google Scholar) to identify the nanomedicine application or product involved.

Applications and products identified through the above searches were then subjected to an additional round of Web-based searches to add to the information on each application or product. We reviewed manufacturer websites for product information and additional nanomedicine products in their developmental pipeline. We searched Google Scholar for literature containing technical product details. We consulted FDA.gov for approval status, date, and application number. Additional searches were conducted through Google if more information was still needed. We created a database containing the following information (where available/applicable) for each application or product: product name, sponsoring company/institution, FDA classification, treated condition or device application, delivered therapeutic, nanocomponent, nanoscale dimension, approval status, FDA approval date and application number (for approved products), delivery route, and a short application or product description.

Each application or product was then classified using the following five graduated categories, to describe the likelihood that the application or product involved nanomedicine (per our definition): *Confirmed* – a medical application or product with literature reference citing a functional component with dimension at or less than 300 nm (i.e., "nanoscale"). *Likely* – a medical application or product with literature reference suggesting a functional component on the nanoscale (e.g., literature notes that product takes advantage of EPR effect), but specific size information was not available. *Potential* – medical application or product with a functional component that could be on the nanoscale (e.g., liposomes), but without literature reference providing a strong indication of size. *Unlikely* – medical application or product with literature reference suggesting potential nanocomponent larger than nanoscale (e.g., multilaminar liposomes), but without specific size information. *Questionable* – applications and products identified in literature as "nanomedicine" or "nanotechnology," but without any clear medical relevance or with a size clearly larger than nanoscale.

Results

The targeted search of clinical trial registries yielded 1,265 potentially relevant clinical trial results. Duplicate results and

Table 1
ClinicalTrials.gov search terms with the number of results

Search Terms	Search Results
Aerosol OR Nanoaerosol	159
Colloid OR Colloidal OR Nanocolloid OR Nanocolloidal OR Nanosuspension OR Nanocoll	142
Dendrimer OR Dendrimeric	0
Emulsion OR Nanoemulsion	149
Fleximer	1
Fullerene	0
Hydrogel	113
Hydrosol	0
Liposome OR Liposomal OR Nanosome OR Nanosomal	485
Micelle OR Micellar	10
Nano	21
Nanobiotechnology	0
Nanobottle	0
Nanocapsule OR Nanoencapsulation	0
Nanoceramic	0
Nanocoating OR Nanocoated	0
Nanocomposite	0
Nanocrystal OR Nanocrystallite OR Nanocrystalline	10
Nanodiamond	0
Nanodrug	0
Nano-Enabled	0
Nanofiber OR Nanofilament	0
Nanofilter or Nanomesh	0
Nanogel	0
Nanomaterial	4
Nanomedicine	0
Nanometer	3
Nanoparticle OR Nanosphere	79
Nanopore OR Nanoporous	1
Nanorod	0
Nanoscaffold	0
Nanoscale	3
Nanosensor	0
Nanoshell	0
Nanosilver	1
Nanostructure	4
Nanotechnology	6
Nanotherapeutic	0
Nanotube	0
Nanowire	0
Quantum Dot	0
Solgel	0
Superparamagnetic OR Iron Oxide OR SPIO OR USPIO	66
Virosome	8

trials involving clearly non-nano applications or products were eliminated, leaving 789 clinical trials with potential nanomedicine applications or products. The application/product name and company was identified for each of these trials, yielding a total of 141 unique applications and products (many were associated with multiple trials). Thirty-eight of these were already approved products, being investigated for new conditions or being used as active comparators for new products, and the other 103 were new investigational products. The products identified through the clinical trial search were combined with 222 unique applications and products identified through the literature search, resulting in a total of 363 potential nanomedicine applications and products that were the basis for subsequent analyses. This population was then evaluated on various criteria in an attempt to identify representative trends. A complete listing of these results is included in the Supplementary Material available online at http://www.nanomedjournal.com.

Relevance to nanomedicine and developmental phase

Table 2 provides a breakdown of the numbers of applications and products analyzed by their assigned relevance to nanomedicine and investigational phase. Investigational products that were under study for multiple uses are classified based on their latest phase of development. Applications in Phase 0 and Phase IV trials are classified as preclinical and commercial, respectively. A majority of the applications and products identified did demonstrate a high relevance to the nanomedicine definition used; 247 (or 68%) of the applications and products fell into the confirmed or likely categories. Much of the remaining analysis will focus on this subset, because the other applications and products did not demonstrate clear-cut relevance to nanomedicine. In terms of developmental phase, we found a significant number of commercially available products (100 confirmed and likely) and identified a notable drop-off in the number of products beyond Phase II development.

Year of approval

Our analysis of the year of approval includes only confirmed and likely products that were submitted to the FDA regulatory approval process in the U.S. or a foreign approval process outside the U.S. (i.e., this does not include research-use-only and exempt products) (Figure 2). The analysis uses the FDA approval year if the product is U.S. approved or an equivalent foreign approval year if it is not approved within the U.S. Products with an unknown approval date include foreign products for which a date is not readily available. Most of the products approved before the year 2000 were therapeutics, rather than devices. However, in the last decade, approval for therapeutics appears to have remained fairly steady, whereas there is a marked increase in the number of medical devices.

Size of nanocomponents

Figure 3 shows the mean size of the nanocomponents incorporated in all applications and products for which the information was available. It should be noted that this includes any size information that was available, so the data compare measurements made using a variety of techniques (and in some cases, size data were listed without referencing the measurement technique used). Most applications and products utilize nanocomponents with features at or below 200 nm. The peak at 2000 nm includes a number of products utilizing "nanocrystal" dispersion technology, in which drug particulate is milled down to increase bioavailability, but the resulting size distribution ranges from tens of nanometers up to 2 microns.[40]

FDA intervention type[41]

Of the confirmed and likely nanomedicine products approved for commercial use, seven fall under the FDA classification for biologicals, 38 for devices, and 32 for drugs (Table 3). Of those applications in clinical study, 26 are biologicals, 21 are devices,

Table 2
Number of applications and products found, sorted by developmental phase and by relevance to our definition of nanomedicine

	Investigational							Commercial
	Pre-Clinical	Phase I	Phase I/II	Phase II	Phase II/III	Phase III	Total	
Confirmed	14	29	8	32	3	7	93	54
Likely	18	18	2	10	0	6	54	46
Potential	10	9	1	3	0	3	26	18
Unlikely	1	3	1	2	0	3	10	7
Questionable	3	9	1	2	1	0	16	24
Terminated /Discontinued	1	4	0	5	0	4	14	1
Totals	47	72	13	54	4	23	213	150

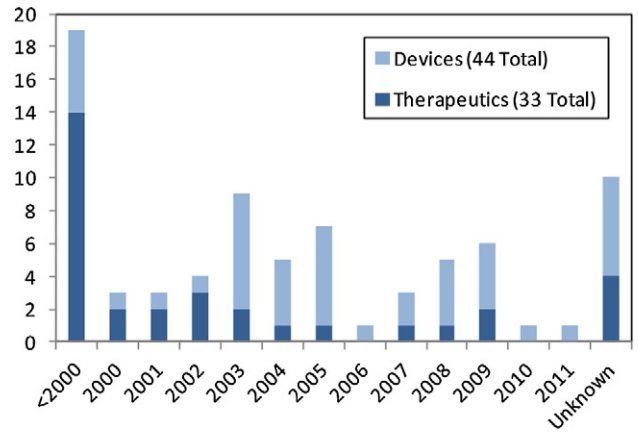

Figure 2. Year of approval for confirmed and likely nanomedicine products identified (search conducted through May 2011).

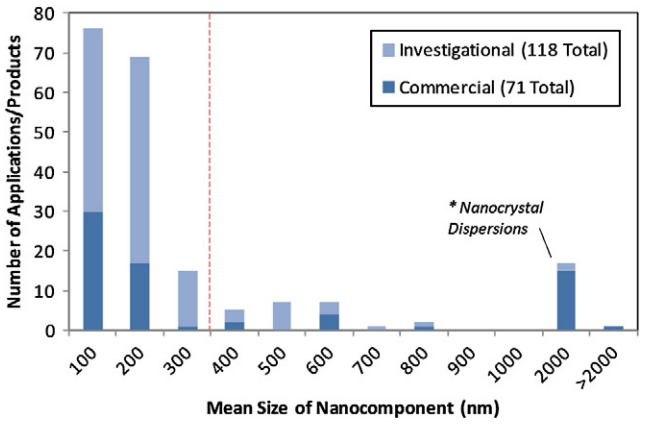

Figure 3. Mean size of nanocomponents for all nanomedicine applications and products for which the data were available. The dotted line indicates the cut-off for this study's definition of nanomedicine, below which a significant number of the products fall. The notable peak around 2000 nm consists of a number of "nanocrystal dispersion" products.

91 are drugs, six are genetic, and two are listed as "other." Thus, the majority of products under clinical study are drugs, but it does appear that nanomedicine biologicals are poised to represent a larger segment of the field then they have in the past. Drugs generally include chemically synthesized, therapeutic small molecules, but most NP imaging contrast applications are also approved under the drug classification. Biologicals are sugars, proteins, nucleic acids, or complex combinations of these substances, or may contain living entities such as cells and tissues. Genetic interventions include gene transfer, stem cells, and recombinant DNA. FDA devices provide medical action by means other than pharmacological, metabolic, or immunological pathways. Products listed as "other" interventions included two NPs that were capable of emitting radiation.

Type of nanostructure

Table 4 provides a breakdown of the type of nanostructures utilized in the confirmed and likely nanomedicine products. The various forms of free NPs were the most prevalent categories, with significant numbers in both commercial products and investigational applications. However, NPs can also be incorporated into nanocomposites and coatings, and these were classified separately. The high level of development in nanoscale liposomes and emulsions should be highlighted; many developing drug-delivery platforms take advantage of liposomal and emulsion formulations.

Applications for therapeutics

"Therapeutics" were generally defined to include drugs, vaccines, and biologicals that are intended to directly remedy a medical condition. The uses for each of the confirmed and likely therapeutic products were grouped into nine categories based on the approved or intended use: cancer treatment, hepatitis, (other) infectious diseases, anesthetics, cardiac/vascular disorders, inflammatory/immune disorders, endocrine/exocrine disorders, degenerative disorders, and others (Figure 4). The number of approved products is similar across all the categories. However, about two-thirds of the investigational applications identified are focused on cancer treatment.

Applications for medical devices

All other applications and products were generally classified as devices and a similar categorization approach was used (Figure 4). The device categories included in vitro testing, in vivo imaging, in vivo device coatings, bone substitutes, dental, medical dressings/textiles, cancer treatment, surgical devices,

Table 3
FDA intervention class for confirmed and likely nanomedicine applications and products

Intervention	Investigational	Commercial
Biological	26	7
Device	21	38
Drug	91	32
Genetic	6	0
Other	2	0
Research Use /Exempt	1	23
Totals	147	100

Table 4
Type of nanostructure for confirmed and likely nanomedicine applications and products, by developmental status

Nanocomponent	Investigational			Commercial		
	Therapeutic	Device	Total	Therapeutic	Device	Total
Hard NP	3	12	15	0	28	28
Nanodispersion	5	0	5	1	1	2
Polymeric NP	23	0	23	9	0	9
Protein NP	4	0	4	2	0	2
Liposome	53	0	53	7	1	8
Emulsion	18	1	19	9	0	9
Micelle	8	0	8	3	1	4
Dendrimer / Fleximer	2	2	4	0	3	3
Virosome	6	0	6	2	0	2
Nanocomposite	0	0	0	0	18	18
NP Coating	0	2	2	0	6	6
Nanoporous Material	0	3	3	0	2	2
Nanopatterned	0	2	2	0	2	2
Quantum Dot	0	1	1	0	4	4
Fullerene	0	1	1	0	0	0
Hydrogel	0	0	0	0	1	1
Carbon Nanotube	0	1	1	0	0	0
Totals	122	25	147	33	67	100

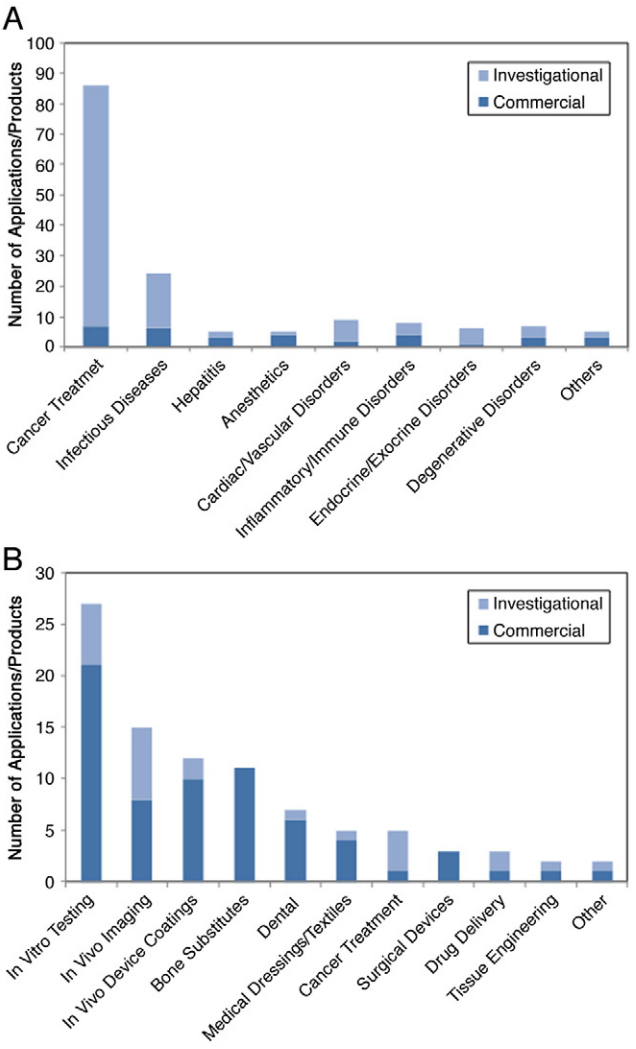

Figure 4. Medical uses for confirmed and likely nanomedicine therapeutics **(A)** and devices **(B)** identified.

drug delivery, tissue engineering, and other. In vitro testing and in vivo imaging were the most prominent categories, followed by in vivo device coatings and bone substitutes. It should also be noted that many fewer investigational devices were found than investigational therapeutics. This may be due to the differences in the nature of the approval processes between drugs and devices; clinical drug data are generated more often than data for devices, which are often approved through alternative approval paths (e.g., the 510(k) pathway).

Administration and targeting

One of the key benefits offered by nanoscale structures in medicine is the ability to achieve unique biodistribution profiles that are not possible with purely molecular or microscale delivery, and well-designed nanosystems offer the possibility to preferentially target specific tissues. One of the important factors in determining the resulting biodistribution profile is the route of administration. The confirmed and likely applications and products identified demonstrated a heavy focus on intravenous (IV) administration (Figure 5). Over 120 (or 73%) of the directly administered applications and products were intended for IV use. Another 15 were intended for topical administration. The remaining products were relatively evenly distributed among intramuscular, subcutaneous, and interstitial injection and oral, aerosol, nasal, and ophthalmic ingestion.

Once a product is administered into the body, the nanoplatform design can take advantage of various mechanisms to affect the subsequent biodistribution and preferentially target a specific tissue. However, the sophistication of targeting varies. As discussed earlier, many delivery platforms are attempting to take advantage of the EPR effect, and this purely size- and geometry-dependent mode of action is generally termed "passive targeting." However, "active targeting" is another term used frequently in literature and, for the purposes of this study, it is defined as utilizing a mechanism beyond size-dependent biodistribution to enhance preferential delivery to a specific tissue.

Further expanding the analysis in Figure 5, 17 of the approved products utilized passive targeting and only one took advantage of active targeting. However, 69 products under clinical study

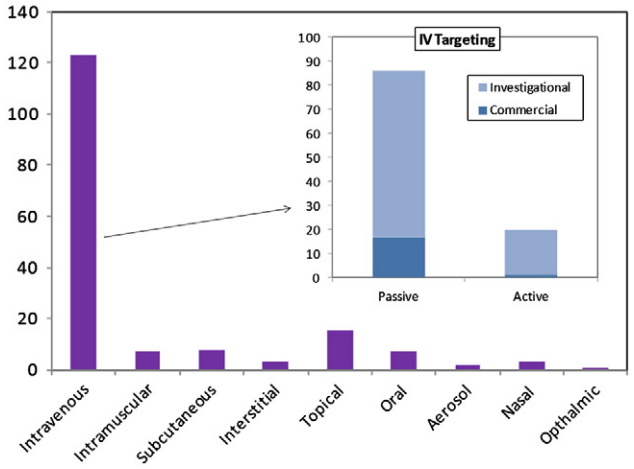

Figure 5. Route of administration for confirmed and likely nanomedicine applications and products identified, with a description of passive versus active targeting for those utilizing IV delivery.

capitalize on passive targeting, and another 19 exploit active targeting. All of the actively targeted products are aimed at diagnosing or treating various forms of cancer (Table 5). The dominant targeting mechanism is functionalizing the NP with ligands (transferrin, antibodies, etc.) for receptors that are overexpressed in the cancer cells or matrix. However, two products take a unique approach, limiting therapeutic activation until the target tissue is reached. Opaxio™ is a polymeric NP that delivers a form of Paclitaxel and is only activated once enzyme activity specific to the tumor site cleaves the therapeutic molecule.[42] ThermoDox® utilizes a thermosensitive lipid, which will only deliver the Doxorubicin payload when an external heat source is applied. This heat source can be limited to the target site, releasing the drug from the liposomes that were passively delivered.[43] A drug emulsion that does not strictly fit the definition of active targeting is also listed but is notable as the only application identified that claims the ability to cross the blood-brain-barrier and thus demonstrates a higher level of targeting than the other passive modes of delivery.[44]

Nanomedicine companies

We found that a total of 241 companies and institutions (universities and medical centers) were associated with the initial 363 products identified. In addition, 169 companies and institutions were associated with the confirmed or likely nanomedicine applications and products, with 54 of these companies and institutions developing more than one application or product (ranging between two and ten). This means that over one-third of the development in the field is occurring at companies and institutions with only one nanotechnology-based application or product. It should also be noted that this only includes companies and institutions directly responsible for developing the nanomedicine applications and products. Other reviews and market reports cite larger numbers of "nanomedicine companies," but these lists often include firms that are investing heavily in nanomedicine development, companies with processes or technology enabling nanomedicine production, and companies developing applications with unrealized or long-term potential in nanomedicine.

Discussion

This study identified a significant number of nanomedicine products approved for or nearing in-human use. It is difficult to extrapolate these numbers directly, because growth in medical industries is so heavily influenced by swings in the economy and regulatory processes. However, we observed some definite trends related to the future of nanomedicine. The most prominent theme throughout is the relative adolescence of the field. Although all the applications identified represent significant technological advancements, they are only scratching the surface of the potential available, and the continued refinement and combination of these technologies will lead to the truly transformative capabilities envisioned for nanomedicine.

One of the major observations in conducting this study is the difficulty in locating basic information on nanomedicine products. This is partly due to the lack of a clear definition and categorization of nanomedicine as a unique product class. However, it is also difficult to identify products that do not use nano-related terminology in their literature, and this can serve as an impetus for companies to avoid nano branding, if they perceive an elevated regulatory effort or negative public perception. This highlights two clear consequences. First, a larger effort, beyond literature-based examination, is required to make an all-inclusive survey of the field. Secondly, such an effort needs to be conducted in a manner that addresses current barriers to nanomedicine development, rather than introducing new ones. However, some progress is being made in this direction, where the National Cancer Institute (NCI) and FDA are leading efforts to standardize characterization of nanomaterials and information collection on nanomedicine products. NCI established the Nanotechnology Characterization Lab (NCL), which developed a "standardized analytical cascade that tests the preclinical toxicology, pharmacology, and efficacy of nanoparticles and devices."[66] These tests provide physiochemical, in vitro, and in vivo characterization of nanoplatforms, supplying results in a standard report format, in an attempt to better prepare products for the clinical approval process. The NCL has characterized over 200 nanomaterials from academia, government, and industry using their standardized protocols.[67] In addition, the FDA Office of Pharmaceuticals Science (OPS) recently released a Manual of Policies and Procedures (MAPP 5015.9) document instructing reviewers on gathering information on nanomaterial size, functionality, and other characteristics for use in a developing database. The document also includes a more inclusive definition of "nanoscale" and "nanomedicine" that encompasses any material with at least one dimension smaller than 1000 nm,[68] which is intended as a broad net to capture all relevant information in these early stages. These steps demonstrate the type of standardization and information sharing that will be necessary to facilitate coordination in this developing field.

The most overwhelming trend observed in the data is the many cancer treatments under development. This circumstance can be tied to the significant investments NCI has made in

Table 5
Confirmed and likely nanomedicine applications and products identified that utilize active targeting

Application(s)/Product(s)	Company	Status	Condition	Nanocomponent	Targeting Mechanism
Ontak [45,46]	Seragen, Inc.	Approved (1999)	T-Cell Lymphoma	Protein NP	IL-2 Protein
MBP-Y003, MBP-Y004, MBP-Y005 [47]	Mebiopharm Co., Ltd	Preclinical	Lymphoma	Liposome	Transferrin
MBP-426 [47–49]	Mebiopharm Co., Ltd	Phase I/II	Solid Tumors	Liposome	Transferrin
CALAA-01 [19,50]	Calando Pharmaceuticals	Phase I	Solid Tumors	NP	Transferrin
SGT-53 [19,51]	SynerGene Therapeutics, Inc.	Phase I	Solid Tumors	Liposome	Transferrin
MCC-465 [48,52]	Mitsubishi Tanabe Pharma Corp	Phase I	Stomach Cancer	Liposome	GAH Antibody
Actinium-225-HuM195 [53]	National Cancer Institute	Phase I	Leukemia	NP	HuM195 Antibody
AS15 [54]	GlaxoSmithKline Biologicals	Phase I/II	Metastatic Breast Cancer	Liposome	dHER2 Antibody
PK2 [48,55]	Pharmacia & Upjohn Inc.	Phase I	Liver Cancer	Polymeric NP	Galactose
Rexin-G, Reximmune-C [56,57]	Epeius Biotechnologies	Phase I/II	Solid Tumors	NP	von Willebrand factor (Collagen-Binding)
Aurimune (CYT-6091) [19,58] Auritol (CYT-21001) [59]	CytImmune Sciences, Inc.	Phase II Preclinical	Solid Tumors	Colloid Gold	TNF-α
SapC-DOPS [60,61]	Bexion Pharmaceuticals, Inc.	Preclinical	Solid Tumors	Liposome	Saposin C
Targeted Emulsions [62,63]	Kereos, Inc.	Preclinical	*In Vivo* Imaging	Emulsion	"Ligands"
Opaxio [42,64]	Cell Therapeutics, Inc.	Phase III	Solid Tumors	Polymeric NP	Enzyme-Activated
ThermoDox [43]	Celsion Corporation	Phase II/III	Solid Tumors	Liposome	Thermosensitive
DM-CHOC-PEN [44,65]	DEKK-TEC, Inc.	Phase I	Brain Neoplasms	Emulsion	PenetrateBlood-Brain-Barrier

nanotechnology over the past decade,[69] the fact that cancer is the worldwide leading cause of death,[70] and the inherent benefits that nanoplatforms offer for therapeutic delivery. However, it might also be due in part to the sense that life-threatening cancers warrant the investigation of treatments using emerging technologies such as nanotechnology. Forty-seven percent of all the confirmed and likely in vivo products were intended for acutely life-threatening conditions (mostly advanced cancers). Some uncertainty about risks, especially longer-term risks, may be more tolerable in such cases.

The majority of the cancer treatment applications identified in this study were aimed at increasing the efficacy of therapeutic delivery, but the envisioned impact of nanotechnology in cancer medicine is much more transformative, including the advent of personalized medicine and point-of-care diagnostics. The keys to this field are adequate identification and understanding of the biomarkers involved in different disease states. Important developments in nanotechnology over the last decade have provided the tools necessary to probe this understanding,[71] while also providing the platforms to implement the improved diagnostics and therapies applying this knowledge. This synergistic role of nanotechnology as both driver and vehicle has allowed the field to reach a tipping point where accelerated growth is likely.

Another theme playing a major role in today's nanomedicine that is likely to undergo significant development in the near future is in vivo targeting. A large number of products utilizing the EPR effect were identified, as well as several taking advantage of more active modes of targeting. The value of targeting in nanomedicine has certainly been acknowledged, but there is still much debate around the role and importance of different factors. Much work is still needed to characterize the full impact of size, shape, surface chemistry, delivery method, the EPR effect, biomolecular targeting, characteristics of polyethylene glycol (PEG)-coatings, formation of the protein corona, and intracellular targeting, before maximally effective delivery can be realized,[59,72,73] but this is and will continue to be a major focus in nanomedicine.

One of the major concerns regarding the use of nanotechnology in the body is the question of persistence. Traditional molecular therapeutics are generally processed by the body and the metabolites are excreted soon after administration, but some NPs have demonstrated persistent in vivo deposits for months or years.[74,75] Examination of the in vivo applications and products identified demonstrates a much higher prevalence of "soft" (157 applications and products) versus "hard" (30 applications and products) nanostructures. The hard NPs identified generally consist of iron oxide, gold, silver, or ceramic, but several applications nearing clinical study plan to use carbon[76] or hafnium oxide[77] NPs. "Soft" is a term generally used in contrast to hard material NPs[78] and here is taken to include liposomes, micelles, emulsions, dendrimers, and other polymeric and protein nanostructures. Iron oxide particles are used in MR contrast[79,80] and cancer thermal therapies.[75,81] Colloidal gold is being used in systemic delivery of therapeutic biologicals[82] and for cancer thermal therapies.[83] Nanosilver is being used in antimicrobial coatings for several implanted devices and catheters.[22,84,85] Ceramic NPs are used as strength and optical enhancers in a number of dental composites.[86] Although all these materials have demonstrated biocompatibility through current standards, there is some question whether persistence in the body may produce longer-term toxicities not seen with current medicines and treatments. A notable number of bone-implant applications also utilized hydroxyapatite[14,62,77,87,88] or calcium phosphate[62,89] nanocrystals (13 applications and products), but these were not included in the hard NP count because these forms naturally occur in the body.[77] It is likely that both hard and soft NPs will find established roles in the future of nanomedicine. Biodegradable platforms will likely be preferred

Table 6
Confirmed and likely nanomedicine products that have been approved by the FDA through the 510(k) process identified

Use	Application(s)/Product(s)	Company	Approval Year	Nanocomponent Description
Bone Substitute	Vitoss [14]	Orthovita	2003	100-nm Calcium-Phosphate Nanocrystals
	Ostim [87]	Osartis	2004	20-nm Hydroxapatite Nanocrystals
	OsSatura [62]	Isotis Orthobiologicals US	2003	Hydroxapatite Nanocrystals
	NanOss [77]	Angstrom Medica, Inc.	2005	Hydroxapatite Nanocrystals
	Alpha-bsm, Beta-bsm, Gamma-bsm, EquivaBone, CarriGen [93]	ETEX Corporation	2009	Hydroxapatite Nanocrystals
Dental Composite	Ceram X Duo [94]	Dentspley	2005	Ceramic NPs
	Filtek [95]	3M Company	2008	Silica and Zirconium NPs
	Premise [14]	Sybron Dental Specialties	2003	"Nanoparticles"
	Nano-Bond [96]	Pentron® Clinical Technologies, LLC	2007	"Nanoparticles"
Device Coating	ON-Q SilverSoaker / SilvaGard™ [97]	I-Flow Corporation / AcryMed, Inc.	2005	Antimicrobial Nanosilver
	EnSeal Laparoscopic Vessel Fusion [39]	Ethicon Endo-Surgery, Inc.	2005	NP-Coated Electrode
	NanoTite Implant [98]	Biomet	2008	Calcium Phosphate Nanocrystal Coating
In Vitro Assay	CellTracks® [14]	Immunicon Corporation	2003	Magnetic NPs
	NicAlert [14]	Nymox	2002	Colloidal Gold
	Stratus CS [62]	Dade Behring	2003	Dendrimers
	CellSearch® Epithelial Cell Kit [99]	Veridex, LLC (Johnson & Johnson)	2004	Iron Oxide NPs
	Verigene [100,101]	Nanosphere, Inc.	2007	Colloidal Gold
	MyCare™ Assays [102]	Saladax Biomedical	2008	"Nanoparticles"
Medical Dressing	Acticoat® [97,103]	Smith & Nephew, Inc.	2005	Antimicrobial Nanosilver
Dialysis Filter	Fresenius Polysulfone® Helixone® [104]	NephroCare	1998	Nanoporous Membrane
Tissue Scaffold	TiMESH [39]	GfE Medizintechnik GmbH	2004	30-nm Titanium Coating

for therapeutic delivery applications, but most of the unique physiochemical behavior arises only in metallic or semiconductor NPs, so these will be required for future imaging and electromagnetic-wave-based therapies.

Nanomaterials for tissue regeneration are an additional highly touted area of development in nanomedicine.[71] However, this study was only able to identify two applications related to tissue regeneration. Both were implantable soft-tissue scaffolds with nanostructured surfaces.[39,90] It is likely that nanomaterials will be critical in developing the surfaces and structures required for ex vivo tissue growth and implantation of engineering tissues, but a better understanding of the adequate conditions and biological signals to trigger growth and proliferation is necessary, before these materials can be properly designed.

As noted in Table 2, fifteen products were identified that were discontinued after approval or during clinical investigation. However, the literature showed no clear reason in common among these cases. One nanocrystal drug formulation was discontinued after being on the market since the 1980s,[91] but there was no indication that this was due to post-market safety concerns; this formulation was most likely displaced by newer products. Reasons for terminating clinical investigation were fairly evenly distributed among lack of efficacy, systemic toxicity, low enrollment, and licensing or funding issues. However, we found no explanation for terminating study in three cases. In addition, a number of other applications and products were associated with clinical trials that had been terminated, but development continued with adjusted drug formulations or for other indications.

The clinical approval process is structured to ensure that sponsors demonstrate adequate safety and efficacy before a product is released to market. However, the 510(k) device approval process has recently come under fire as a potential pathway for allowing unsatisfactory products to market.[92] Our study identified a significant number of nanomedicine products that were approved through the 510(k) process (Table 6), falling into general categories of bone substitutes, dental composites, device coatings, in vitro assays, medical dressings, dialysis filters, and tissue scaffolds. Many of these products have been in use for a number of years without issue. This suggests that safety concerns about the 510(k) process have not been borne out to date by nanomedicine products. That said, information may become available in the future on potential toxicological risks associated with the use of in vivo nanomaterials, and that points to the importance of clearly identifying products that incorporate some form of nanotechnology so they can be adequately tracked.

Much of the forecasted promise of nanotechnology in medicine takes the form of smart technologies, such as theranostic platforms that can target, diagnose, and administer appropriate treatment to different disease states in the body. However, the current study shows that nanomedicine is still in an early state. As with any emerging field of science, progress is made in steps and some developing applications are just beginning to demonstrate higher levels of sophistication. Active forms of targeting have already been discussed, but active nanomedicine can be more generally defined as nanostructures that induce a mechanism of action beyond purely size-dependent biological and chemical interactions. Table 7 lists the additional active applications and products identified (beyond active

Table 7
Confirmed and likely nanomedicine products that exhibit active behavior, beyond active targeting, identified

Use	Application(s)/Product(s)	Company	Status	Nanocomponent	Active Mechanism
Solid Tumor Hyperthermia	NanoTherm [77]	MagForce Nanotechnologies AG	Approved	Iron Oxide NPs	AC Magnetic Heating
	Targeted Nano-Therapeutics [105]	Aspen Medisys, LLC. (Formerly Triton BioSystems, Inc.)	Pre-Clinical	Iron Oxide NPs	AC Magnetic Heating
	AuroShell [83]	Nanospectra Biosciences	Phase I	Gold Nanoshell	IR Laser Heating
Solid Tumor Treatment	NanoXray [77]	Nanobiotix	Phase I	Proprietary NP	X-Ray-Induced Electron Emission
In Vivo Imaging	Feridex IV, GastromarkCombidex (Ferumoxtran-10) [79,106]	Advanced Magnetics	Approved (1996)Phase III	Iron Oxide NPs	Enhanced MRI Contrast
	Endorem, Lumirem, Sinerem [79,106]	Guebert	Approved / Investigational	Iron Oxide NPs	Enhanced MRI Contrast
	FeraSpin [107]	Miltenyi Biotec	Research Use Only	Iron Oxide NPs	Enhanced MRI Contrast
	Clariscan [79]	Nycomed	Phase III	Iron Oxide NPs	Enhanced MRI Contrast
	Resovist [79,106] Supravist [80]	Schering	Approved (2001)Phase III	Iron Oxide NPs	Enhanced MRI Contrast
In Vitro Imaging	Qdot Nanocrystals [108]	Invitrogen Corporation	Research Use Only	Quantum Dot	Fluorescent Emission
	Nanodots [109]	Nanoco Group PLC	Research Use Only	Quantum Dot	Fluorescent Emission
	TriLite™ Nanocrystals [110]	Crystalplex Corporation	Research Use Only	Quantum Dot	Fluorescent Emission
	eFluor Nanocrystals [111]	eBiosciences	Research Use Only	Quantum Dot	Fluorescent Emission
	NanoHC [112]	DiagNano	Investigational (Research Only)	Quantum Dot	Fluorescent Emission
In Vitro Cell Separation	CellSearch® EpithelialCell Kit [99]	Veridex, LLC (Johnson & Johnson)	Approved (2004)	Iron Oxide NPs	Magnetic Separation
	NanoDX [113]	T2 Biosystems	Research Use Only	Iron Oxide NPs	Magnetic Separation

targeting) and several of the areas are discussed in more detail below.

Several forms of electromagnetically activated NPs intended for cancer treatment are currently nearing or progressing through clinical development. NanoTherm® and Targeted Nano-Therapeutics utilize interstitial or intravenous delivery of iron oxide NPs, which are then heated by an externally applied alternating magnetic field, to provide hyperthermia treatment localized to a tumor.[75,81] AuroShell® uses intravenously injected gold nanoshells, which are heated by a fiberoptic, infrared laser probe to provide high temperatures localized to the tumor area.[83] An additional preclinical NP platform, NanoXray™, is excited by x-rays, to induce local electron emission in the tumor, leading to free radicals that cause intracellular damage.[77,114]

NPs are also being used to enhance imaging techniques. Five approved applications utilizing iron oxide NPs for in vivo MRI enhancement were identified, with another four under clinical investigation.[79,80] The iron oxide NPs passively collect in different tissues and provide enhanced contrast due to localized magnetic effects. Six in vitro applications were also identified in which quantum dots with biomolecular tagging are used for fluorescent microscopy. However, uncertainty remains as to whether quantum dots in their current form will ever find in vivo use, due to the potential toxicity associated with the heavy metals used.[115]

Two other products were identified in which iron oxide NPs are used for magnetic detection of cells in vitro (CellSearch® and NanoDX™). The magnetic NPs are tagged with cell-specific markers, and an external field is used to separate or aggregate the bound cells in solution, allowing detection.[113,116] Similar techniques have been used to enhance drug targeting in animal models[117] and have been proposed for detoxifying circulating blood.[118] One Phase I clinical trial attempted to demonstrate the benefits of magnetic drug targeting in humans in the mid-1990s but met with limited efficacy.[119] Some companies are pursuing new methods of magnetically enhanced drug delivery and release but have not yet moved into human trials.[120]

The next phases of development in nanomedicine are likely to take advantage of combined applications in the form of both multimodal treatments (utilizing nanomedicine in combination with current treatments) and theranostic platforms (single nanomedicine applications with multiple modes of action). The MagForce NanoTherm®, magnetically heated iron oxide NPs have already demonstrated synergistic effects in combined treatment with chemotherapy and radiotherapy, allowing lower dosages for each.[121] In addition, Cytimmune's TNF-α labeled gold NPs have been shown to effect tissues perfusion and increase sensitivity to thermal therapies,[122] offering potential preconditioning for a number of applications. Gold NPs have also demonstrated the capability to thermally treat tumors under laser excitation[83] and are under preclinical study for disease diagnosis through surface-enhanced Raman spectroscopy.[123] These current technologies could be combined in an endoscopic application for real-time diagnosis and treatment for many gastrointestinal cancers. As the basic capabilities of NPs are established through single modes of action, it is likely that combined nanomedicine treatments will become more prevalent.

Nanomedicine is a very diverse field and that characteristic creates some difficulty in creating clear definitions, as well as effective oversight and regulation. A detailed search of the literature, clinical trial data, and the Web identified 247 applications and products that were confirmed or likely nanomedicine interventions (under our definition) and that were

approved for use, under clinical study, or on the verge of clinical study. The intended uses ranged from the treatment of clinically unresectable cancers to antibacterial hand gels; the technologies ranged from liposomes, which have been in pharmaceutical use for decades, to hard NPs, for which limited long-term clinical data are available and questions of persistence in the body have arisen. This study reveals two clear needs that should be addressed for any regulatory approach for nanomedicine to succeed: 1) developing an effective and clear definition outlining the field and 2) creating a standardized approach for gathering, sharing, and tracking relevant information on nanomedicine applications and products (without creating additional barriers for medical innovation). Both the NCL and FDA are taking steps in the right direction, but broader-reaching efforts are necessary to clarify the definition of "nanomedicine," track key data, and facilitate coordination among agencies in this complex arena.

A categorical analysis of the identified applications and products also provides insight into the future directions of the field. We found a pronounced focus on development of cancer applications. This is likely a result of several factors, including heavy investments made by NCI, the prevalence and impact of cancer in society, and the reality that the risks of many nanomedicine trials may be offset by the benefit sought in treating life-threatening cancers.

Finally, although nanomedicine has already established a substantial presence in today's markets, this analysis also highlights the infancy of the field. This is not to downplay the advances made to date; engineered nanoscale materials have already provided medical enhancements that are not possible on the molecular or micro scale. However, a large portion of the nanomedicine applications identified are still in the research and development stage. Continued development and combination of these applications should lead to the truly revolutionary advances foreseen in medicine. Now is the time to put in place effective data-gathering strategies and analytical approaches that will advance understanding of this field's evolution and help to optimize development of nanomedicine and assure sound approaches to oversight.

Acknowledgments

The contents of this article are solely the responsibility of the authors and do not necessarily represent the views of NIH or NHGRI. Thanks to the "Nanodiagnostics and Nanotherapeutics: Building Research Ethics and Oversight" Working Group for valuable input on methodology and analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nano.2012.05.013.

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