Nanotechnology in Hospital & Pharmaceutical

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Abstract

Nanotechnology has changed our lives dramatically and influenced every sector of the research, engineering and also business community. Nanotechnology is a rapidly growing science of producing and utilizing nano-sized particles, that measure in nanometer. In other words, nanotechnology is the art of characterizing, manipulating and organizing matter systemically, at the nanometer scale, which has created a revolution in science, engineering, technology, drug delivery and therapeutics. The size of typical accessible structures is in the sub-micrometer range, being within the limits of optical resolution and barely visible with a light microscope. This scale is about 1/1000 smaller than structures that could be resolved by the naked eye, but still 1000 times larger than an atom. Recent developments are addressing the size range below these dimensions and because a typical structure size is in the nanometer range, the methods and techniques are defined as nanotechnology.

There is an argue that nanotechnology in pharmaceutics is simply a new version of colloid science, but nanotechnology is clearly not a miniaturized version of the well colloidal drug delivery systems, such as microemulsions, emulsions and liposomes. Rather, nano-sized systems could be designed into a more sophisticated system associated with its physical dimension of less than 100 nm. Nanotechnology, as a novel technology, offers opportunities for the production of new generation of sophisticated drug delivery systems. There are now a wide range of nano-systems, not only nanoparticles and nanocapsules but lipid complexes, polymeric micelles, etc. In this regard, professor Florence believes that nanotechnology of course is much more than the nanoparticles themselves and it is indeed the growth of technologies based on such small-scale systems.

He also mentions that what makes nanotechnology a new and exciting subject is the ability not only to manipulate nanoparticles and nanosystems, but also the new techniques available to measure and indeed visualize materials in the nanometer size range. Particles produced through nanotechnology are small and since the particle size is crucial, the maintenance of particle size is therefore of great importance. For instance, nano-sized particles possess very high surface to volume ratios and therefore, this property causes an interaction between the surface and mucus layer to occur. On the other hand, due to the huge surface area, surface properties of particles play an important role in protecting the active agents from degradation.

In recent years, we have been faced with an explosion in the design, development and characterization of novel nanofabricated devices for drug delivery. Professor Rytting, in his recent editorial in the *International Journal of Pharmaceutics,* has specified the various areas in which nanotechnology is being used, as follows:

- drug discovery (including combinatorial chemistry and synthesis on the molecular and macromolecular scale),
- nanoanalysis including bioanalysis using miniaturized probes, microarrays and lab-on-a-chip approaches,
- utilizing approaches used by the body in fluid flow and targeting,
- drug delivery systems having sizes in the nanometer range (e.g. liposomes, nanoparticles, micro-emulsions, dendrimers, etc.),
- implantable devices that can sense blood levels and automatically administer drugs,
- nanoscale biomaterials including biomimetics,
- biological macromolecules (e.g. proteins, enzymes, DNA and RNA based nanostructures, molecular assemblies, biomolecules, cells, biochips, etc.),
- molecular sensors and biosensors, as well as clinical diagnostic techniques,
- gene delivery and expression.

Aspects of nanotechnology have been utilized by pharmaceutical scientists for many years in drug product formulation and delivery, leading to the development of nanoparticulate systems and it is conceivable that the tomorrow's nanotechnology products will have the same impact on our daily lives, as the invention of other technologies

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Introduction

Drug particles in the nanometer size range have unique characteristics that can lead to enhanced performance in a variety of dosage forms. Formulated correctly, particles in this size range are resistant to settling and can have higher saturation solubility, rapid dissolution, and enhanced adhesion to biological surfaces, thereby providing a rapid onset of therapeutic action and improved bioavailability. Scientists use nanotechnology to approach classical and novel drug delivery applications. We provide services for producing, formulating, and characterizing Nanoparticles for a wide array of applications including, but not limited to, oral, pulmonary and parenteral delivery. Controlled and targeted delivery is one of the most enviable requirements from a carrier, which involves multi-disciplinary site specific or targeted approach. Nanoparticulate drug delivery system may offer plenty of advantages over conventional dosage forms, which includes improved efficacy, reduced toxicity, enhanced biodistribution and improved patient compliance. Pharmaceutical nanoparticles are subnanosize structure, which contain drug or bioactive substances with in them and are constituted of several tens or hundreds of atoms or molecules with a variety of sizes (size from 5 nm to 300 nm) and morphologies (amorphous, crystalline, spherical, needles, etc). It is necessary to use additives (surfactants, dispersants, and metals) to obtain uniform and stable particles. With further processing steps, nanostructured powders and dispersions can be used to fabricate coatings, and components or devices. These different types of nanoparticles are prepared according to prerequisite and straightforwardly reaches to the desired site to deliver bioactive therapeutic and diagnostic agents. Although opportunities to develop nanotechnologybased efficient drug delivery systems extend into all therapeutic classes

of pharmaceuticals, many therapeutic agents have not been successful because of their limited ability to reach to the target tissue. In addition, the faster growth opportunities are expected in developing delivery systems for anti-cancer agents, hormones and vaccines because of safety and efficacy shortcomings in their conventional administration modalities. For example, in cancer chemotherapy, cytostatic drugs damage both malignant and normal cells alike. Thus, a drug delivery strategy that selectively targets the malignant tumor is very much needed. Additional problems include drug instability in the biological milieu and premature drug loss through rapid clearance and metabolism. Similarly, high protein binding of certain drugs such as protease inhibitors limits their diffusion to the brain and other organs. However, nanotechnology for drug delivery applications may not be suitable for all drugs, especially those drugs that are less potent because the higher dose of the drug would make the drug delivery system much larger, which would be difficult to administer.

Literature Review

The emergence of nanotechnology is likely to have a significant impact on drug delivery sector, affecting just about every route of administration from oral to injectable, according to specialist market research firm NanoMarkets.

And the payoff for doctors and patients should be lower drug toxicity, reduced cost of treatments, improved bioavailability and an extension of the economic life of proprietary drugs.

"This is an impressive list [but] also impressive is the fact that many of the categories of nano-enabled drug delivery systems are already close to or at the point of marketing," unlike many of the 'futuristic' applications claimed for nanomedicine, he said.

NanoMarkets expects the dosing benefits of nano-enabled drug delivery systems to be extended to compounds used in treating both infectious disease and cancer, and has identified six types of drug delivery systems in which nanotechnology is likely to have a significant impact.

- For **injectable drugs**, nanotechnology is already generating new dosage forms that are easier to administer, more pleasant for the patient receive and confer a competitive advantage in the marketplace.

  For example, at the start of this year Johnson & Johnson revealed that Elan's NanoCrystal technology would be used in a Phase III clinical trial for an injectable formulation of paliperidone palmitate, a drug for schizophrenia, notes Moradi. This is a new 'nano formulation' of an older drug which overcomes the original's insolubility, by reducing the particle size to under 200 nm.

- Nanotechnology is also opening up new opportunities in **implantable delivery systems**, which are often preferable to the use of injectable drugs, because the latter frequently display first-order kinetics (the blood concentration goes up rapidly, but drops exponentially over time). This rapid rise may cause difficulties with toxicity, and drug efficacy can diminish as the drug concentration falls below the targeted range.

- In contrast, implantable time release systems may help minimize peak plasma levels and reduce the risk of adverse reactions, allow for more predictable and extended duration of action, reduce the frequency of re-dosing and improve patient acceptance and compliance.

- Nanotechnology adds to these the benefits, says Moradi. Citing pSivida's BioSilicon product, he notes that this nanostructured material effectively stores an active compound in nanosised pockets that release minute amounts of drug as the silicon dissolves. pSivida is currently exploring biodegradable implantable methods for tissue engineering and ophthalmic delivery.

- Nano-implants will also be used in the not-too-distant future for treating cancer. Among the first nanoscale devices to show promise in anti-cancer therapeutics and drug delivery are structures called nanoshells, which NanoMarkets believes may afford a degree of control never before seen in implantable drug delivery products.

Methods

Nanoshells typically have a silicon core that is sealed in an outer metallic core. By manipulating the ratio of wall to core, the shells can be precisely tuned to scatter or absorb very specific wavelengths of light. For example, gold encased nanoshells have been used to convert light into heat, enabling the destruction of tumours by selective binding to malignant cells. A physician can use infrared rays to pass harmlessly through soft tissue, while initiating a lethal application of heat when the nanoshells are excited.

Some researchers are also experimenting with temperature-sensitive drug delivery control methods, using nanoshells that release their payload only when illuminated with the proper infrared wavelength.

Despite these advances, the vast majority of consumers prefer an **oral drug delivery system** to implantables or injectables. With this in mind, various development groups are working to enhance traditional oral delivery systems with nanoengineered improvements.

"There are some areas where nano-enhanced drugs could make a big difference in increasing oral bioavailability and reducing undesirable side effects. By increasing bioavailability, nanoparticles can increase the yield in drug development and more importantly may help treat previously untreatable conditions," notes Moradi.

Because of the blood brain barrier (BBB) many new chemical entities aimed at treating brain disorders have proved not to be clinically useful. Nanoparticles have been demonstrated to cross the BBB with little difficulty and companies such as Germany's NanoPharm have developed systems capable of reaching the brain for anaesthesia (Dalargin; an analgesic), cancer drugs, and various other therapeutics.

The company claims several advantages over existing systems, including no requirement to open the BBB, the ability to deliver potentially any drug, whether hydrophilic or hydrophobic, and no need to modify the drug itself, which may affect its activity.

Meanwhile, researchers at the University of Texas at Austin have described a means of using nanospheres for oral drug delivery. These nanosphere carriers are derived from

hydrogels, which are highly stable organic compounds that swell when their environment becomes more acidic. They have been successfully formulated into controlled-release tablets and capsules, which release active compounds when the hydrogel body swells.

NanoMarkets also suggests that nanomaterials provide a unique opportunity for rapid **topical delivery** of active compounds. Given their very small size, nanoparticles are able to enter human tissues and cells quickly, and companies such as Novavax have already developed regulated topical systems that take advantage of the unique properties of micellar nanoparticles.

Novavax has is developing two hormone replacement therapies, called Estrasorb (which received FDA approval in October 2003) and Androsorb which successfully completed Phase I human trials in 2003.

Meanwhile, the number of FDA-approved polymers available for use on skinis increasing rapidly, according to Moradi, so the industry has been presented with opportunities to create new **transdermal platform** designs with improved 'on-skin' properties and diffusion of active molecules compared to current patches.

This interesting trend is expected to result in smaller and less invasive patches that increase the universe of available drug candidates," according to Moradi. In some cases, he adds, electronics are even being integrated into patch-like platforms involving wound care, monitoring, and diagnostic methods.

Finally, nanotechnology is finding new applications in the area of **toxin removal**. Colloidal dispersions have been demonstrated to remove potentially lethal compounds from the bloodstream, including high concentrations of lipophilic therapeutics, illegal drugs, and chemical and biological agents.

A team of scientists at the University of Florida and Clarkson University in Potsdam, New York, has demonstrated favourable results to this end, using biocompatible microemulsions. These oil-in-water systems have a rapid and efficient absorption capacity for many target molecules that are frequently overdosed, whether this be

intentional or accidental. The microemulsions use a polymeric surfactant, in combination with an ionic co-surfactant.

NanoMarkets believes that not only will the nano-enabled drug delivery market be one of the first true nanomedicine markets to evolve, but as it does so, the revenues from nanoenabled drug delivery systems will be quite large.

Discussion

As of August 21, 2008, the Project on Emerging Nanotechnologies estimates that over 800 manufacturer-identified nanotech products are publicly available, with new ones hitting the market at a pace of 3–4 per week. The project lists all of the products in a publicly accessible online inventory. Most applications are limited to the use of "first generation" passive nanomaterials which includes titanium dioxide in sunscreen, cosmetics and some food products; Carbon allotropes used to produce gecko tape; silver in food packaging, clothing, disinfectants and household appliances; zinc oxide in sunscreens and cosmetics, surface coatings, paints and outdoor furniture varnishes; and cerium oxide as a fuel catalyst.

The National Science Foundation (a major distributor for nanotechnology research in the United States) funded researcher David Berube to study the field of nanotechnology. His findings are published in the monograph Nano-Hype: The Truth Behind the Nanotechnology Buzz. This study concludes that much of what is sold as “nanotechnology” is in fact a recasting of straightforward materials science, which is leading to a “nanotech industry built solely on selling nanotubes, nanowires, and the like” which will “end up with a few suppliers selling low margin products in huge volumes." Further applications which require actual manipulation or arrangement of nanoscale components await further research. Though technologies branded with the term 'nano' are sometimes little related to and fall far short of the most ambitious and transformative technological goals of the sort in molecular manufacturing proposals, the term still connotes such ideas. According to Berube, there may be a danger that a "nano bubble" will form, or is forming already, from the use of the term by scientists and entrepreneurs

to garner funding, regardless of interest in the transformative possibilities of more ambitious and far-sighted work.

Nano-membranes have been produced that are portable and easily-cleaned systems that purify, detoxify and desalinate water meaning that third-world countries could get clean water, solving many water related health issues.

Because of the far-ranging claims that have been made about potential applications of nanotechnology, a number of serious concerns have been raised about what effects these will have on our society if realized, and what action if any is appropriate to mitigate these risks.

There are possible dangers that arise with the development of nanotechnology. The Center for Responsible Nanotechnology suggests that new developments could result, among other things, in untraceable weapons of mass destruction, networked cameras for use by the government, and weapons developments fast enough to destabilize arms races ("Nanotechnology Basics").

One area of concern is the effect that industrial-scale manufacturing and use of nanomaterials would have on human health and the environment, as suggested by nanotoxicology research. Groups such as the Center for Responsible Nanotechnology have advocated that nanotechnology should be specially regulated by governments for these reasons. Others counter that overregulation would stifle scientific research and the development of innovations which could greatly benefit mankind.

Other experts, including director of the Woodrow Wilson Center's Project on Emerging Nanotechnologies David Rejeski, have testified that successful commercialization depends on adequate oversight, risk research strategy, and public engagement. Berkeley, California is currently the only city in the United States to regulate nanotechnology; Cambridge, Massachusetts in 2008 considered enacting a similar law, but ultimately rejected this.

Calls for tighter regulation of nanotechnology have occurred alongside a growing debate related to the human health and safety risks associated with nanotechnology. Furthermore, there is significant debate about who is responsible for the regulation of nanotechnology. While some non-nanotechnology specific regulatory agencies currently cover some products and processes (to varying degrees) – by "bolting on" nanotechnology to existing regulations – there are clear gaps in these regimes. In "Nanotechnology Oversight: An Agenda for the Next Administration," former EPA deputy administrator J. Clarence (Terry) Davies lays out a clear regulatory roadmap for the next presidential administration and describes the immediate and longer term steps necessary to deal with the current shortcomings of nanotechnology oversight.

Stakeholders concerned by the lack of a regulatory framework to assess and control risks associated with the release of nanoparticles and nanotubes have drawn parallels with bovine spongiform encephalopathy ('mad cow's disease), thalidomide, genetically modified food, nuclear energy, reproductive technologies, biotechnology, and asbestosis. Dr. Andrew Maynard, chief science advisor to the Woodrow Wilson Center's Project on Emerging Nanotechnologies, concludes (among others) that there is insufficient funding for human health and safety research, and as a result there is currently limited understanding of the human health and safety risks associated with nanotechnology. As a result, some academics have called for stricter application of the precautionary principle, with delayed marketing approval, enhanced labelling and additional safety data development requirements in relation to certain forms of nanotechnology.

The Royal Society report identified a risk of nanoparticles or nanotubes being released during disposal, destruction and recycling, and recommended that "manufacturers of products that fall under extended producer responsibility regimes such as end-of-life regulations publish procedures outlining how these materials will be managed to minimize possible human and environmental exposure" (p.xiii). Reflecting the challenges for ensuring responsible life cycle regulation, the Institute for Food and Agricultural Standards has proposed standards for nanotechnology research and development should be integrated across consumer, worker and environmental standards. They also propose

that NGOs and other citizen groups play a meaningful role in the development of these standards.

In October 2008, the Department of Toxic Substances Control (DTSC), within the California Environmental Protection Agency, announced its intent to request information regarding analytical test methods, fate and transport in the environment, and other relevant information from manufacturers of carbon nanotubes. The purpose of this information request will be to identify information gaps and to develop information about carbon nanotubes, an important emerging nanomaterial.

The biological and medical research communities have exploited the unique properties of nanomaterials for various applications (e.g., contrast agents for cell imaging and therapeutics for treating cancer). Terms such as *biomedical nanotechnology*, *bionanotechnology*, and *nanomedicine* are used to describe this hybrid field. Functionalities can be added to nanomaterials by interfacing them with biological molecules or structures. The size of nanomaterials is similar to that of most biological molecules and structures; therefore, nanomaterials can be useful for both in vivo and in vitro biomedical research and applications. Thus far, the integration of nanomaterials with biology has led to the development of diagnostic devices, contrast agents, analytical tools, physical therapy applications, and drug delivery vehicles.

Nanotechnology-on-a-chip is one more dimension of lab-on-a-chip technology.Magnetic nanoparticles, bound to a suitable antibody, are used to label specific molecules, structures or microorganisms. Gold nanoparticles tagged with short segments of DNA can be used for detection of genetic sequence in a sample. Multicolor optical coding for biological assays has been achieved by embedding different-sized quantum dots into polymeric microbeads. Nanopore technology for analysis of nucleic acids converts strings of nucleotides directly into electronic signatures.

Result

The overall drug consumption and side-effects can be lowered significantly by depositing the active agent in the morbid region only and in no higher dose than needed. This highly selective approach reduces costs and human suffering. An example can be found in dendrimers and nanoporous materials. They could hold small drug molecules transporting them to the desired location. Another vision is based on small electromechanical systems; NEMS are being investigated for the active release of drugs. Some potentially important applications include cancer treatment with iron nanoparticles or gold shells. A targeted or personalized medicine reduces the drug consumption and treatment expenses resulting in an overall societal benefit by reducing the costs to the public health system. Nanotechnology is also opening up new opportunities in implantable delivery systems, which are often preferable to the use of injectable drugs, because the latter frequently display first-order kinetics (the blood concentration goes up rapidly, but drops exponentially over time). This rapid rise may cause difficulties with toxicity, and drug efficacy can diminish as the drug concentration falls below the targeted range.

1. How is the term “Doctor’s patient” defined? If a doctor has seen a patient once, and the patient comes again after few weeks for a different complaint, can a doctor refuse his services to him?
2. If the request for home visit is for a different complaint, unrelated to the complaint of original visit, can the home visit be refused?
3. How can anybody qualify “an emergency”based on vague facts given by the patients attendents over the phone? Most of the times, the parents perceive any minor problems as an emergency and pester the doctor to hurry up. In such cases, how is the emergency be defined? Is it right to define the emergency on retrospect, when vague history is given to the doctor over the phone?
4. Is it legally correct to print “house calls regretted” on the prescription, even though that is the policy of the doctor?

Doctors are often approached by patients, their relatives or legal advisers for an expert opinion on complaints of medical negligence or medical malpractice.

This situation has become more frequent of late since the consumer courts usually insist that the complainant brings a medical expert's opinion to support the case or else face dismissal of the complaint (1). This is ostensibly done to reduce the number of frivolous complaints (2) which would otherwise drown an already overburdened and under-equipped consumer court machinery. However, this puts the complainant in a difficult situation. Doctors are generally reluctant to give adverse comments against other doctors. The main reason for this reluctance is that the medical community is quite closeknit and inter- connected. Thus, especially amongst private practitioners, very few are willing to stick their necks out at the cost of antagonising any of their fellow professionals.

Doctors in public sector institutions, one would expect, would be more forthcoming in giving their opinions in such cases. But even amongst public sector doctors, there are very few who are willing to come into the open. While most are not averse to going through the available facts of the case and expressing their opinions orally, very few are willing to identify themselves and certify on paper . This is due to several factors. The rules governing public service doctors state that they have to take the permission of their employers before making any affidavit. The employers may be willing to grant permission if such an opinion is requested by the court. The court, however, insists on a medical expert's opinion before even admitting the case in court! Thus the complainant is caught in a Catch- 22 situation. No private practitioner is willing to give an opinion in writing, and the public sector doctor wants the court's request before he gives an opinion! (3)

We have discussed this problem with several legal minds and learn that a public sector doctor does not need to take permission from his employer for giving an opinion or even making an affidavit as long as the case does not pertain to public sector hospitals and as long as he provides his services free of charge.

There are other factors too which restrain public sector doctors from giving written opinions. They, themselves, may be contemplating starting private practice and would not like to lose any goodwill within the profession. Their spouses or close relatives may be in

private practice. They may be directly or indirectly acquainted with the doctor against whom the complaint is made. Moreover, now that public hospitals are also covered under the Consumer Protection Act, they are exposed to medico- legal trouble themselves, especially when you take the inadequate infrastructure available to them for catering to their huge patient load.

In this mess, what is the aggrieved patient or his relatives to do? As such cases - where the complainant comes up against a blank wall in seeking medical opinions - keep increasing, so will the frustration and disgust of the public. They may lose faith in the ability of the legal system to provide justice in medico- legal cases.

One alternative is for the consumer court to appoint a panel of doctors from the various specialities. The case records could be sent to the relevant panelist for an unbiased opinion. Another alternative is for voluntary organisations to set up such panels. The case reports can be sent to the relevant panelist but the medical opinion is given under the imprimateur of the organisation. The advantage of this system is the elimination of the sense of isolation for the doctor who is giving the opinion. Yet another option for the court to conceal the identity of the medical expert who gives the written opinion. This will surely make it easier for doctors willing to give their opinions without being pressurised.

Conclusion

Nanotechnology, shortened to "**nanotech**", is the study of the controlling of matter on an atomic and molecular scale. Generally nanotechnology deals with structures of the size 100 nanometers or smaller in at least one dimension, and involves developing materials or devices within that size. Nanotechnology is very diverse, ranging from extensions of conventional device physics to completely new approaches based upon molecular self-assembly, from developing new materials with dimensions on the nanoscale to investigating whether we can directly control matter on the atomic scale.

There has been much debate on the future implications of nanotechnology. Nanotechnology has the potential to create many new materials and devices with a vast range of applications, such as in medicine, electronics and energy production. On the other hand, nanotechnology raises many of the same issues as with any introduction of new technology, including concerns about the toxicity and environmental impact of nanomaterials, and their potential effects on global economics, as well as speculation about various doomsday scenarios. These concerns have led to a debate among advocacy groups and governments on whether special regulation of nanotechnology is wanted.

References

Cristina Buzea, Ivan Pacheco, and Kevin Robbie (2007). "Nanomaterials and Nanoparticles: Sources and Toxicity". Biointerphases 2: MR17. http://scitation.aip.org/getabs/servlet/GetabsServlet?prog=normal&id=BJIOBN000002000000400MR17000001&idtype=cvips&gifs=Yes.

N. Taniguchi (1974). On the Basic Concept of 'Nano-Technology. Proc. Intl. Conf. Prod. London, Part II British Society of Precision Engineering.

^ Eric Drexler (1991). Nanosystems: Molecular Machinery, Manufacturing, and Computation. MIT PhD thesis. New York: Wiley. ISBN 0471575186. http://www.e-drexler.com/d/06/00/Nanosystems/toc.html.

^ a b Kahn, Jennifer (2006). "Nanotechnology". National Geographic 2006 (June): 98–119.

^ Rodgers, P. (2006). "Nanoelectronics: Single file". Nature Nanotechnology. doi:10.1038/nnano.2006.5.

^ Nanotechnology: Developing Molecular Manufacturing

^ "Some papers by K. Eric Drexler". http://www.imm.org/PNAS.html.

^ California NanoSystems Institute

^ C&En: Cover Story - Nanotechnology

^ Regan, BC; Aloni, S; Jensen, K; Ritchie, RO; Zettl, A (2005). "Nanocrystal-powered nanomotor.". Nano letters 5 (9): 1730–3. doi:10.1021/nl0510659. PMID 16159214. http://www.physics.berkeley.edu/research/zettl/pdf/312.NanoLett5regan.pdf.

^ Regan, B. C.; Aloni, S.; Jensen, K.; Zettl, A. (2005). "Surface-tension-driven nanoelectromechanical relaxation oscillator". Applied Physics Letters 86: 123119.

doi:10.1063/1.1887827.

http://www.lbl.gov/Science-Articles/Archive/sabl/2005/May/Tiniest-Motor.pdf.

^ Wireless nanocrystals efficiently radiate visible light

^ Clarkson, AJ; Buckingham, DA; Rogers, AJ; Blackman, AG; Clark, CR (2004). "Nanostructured Ceramics in Medical Devices: Applications and Prospects". JOM 56 (10): 38–43. doi:10.1007/s11837-004-0289-x. PMID 11196953.

^ Levins, Christopher G.; Schafmeister, Christian E. (2006). "The Synthesis of Curved and Linear Structures from a Minimal Set of Monomers.". ChemInform 37. doi:10.1002/chin.200605222.

^ "Applications/Products". National Nanotechnology Initiative. http://www.nano.gov/html/facts/appsprod.html. Retrieved 2007-10-19.

^ "The Nobel Prize in Physics 2007". Nobelprize.org. http://nobelprize.org/nobel_prizes/physics/laureates/2007/index.html. Retrieved 2007-10-19.

^ Das S, Gates AJ, Abdu HA, Rose GS, Picconatto CA, Ellenbogen JC. (2007). "Designs for Ultra-Tiny, Special-Purpose Nanoelectronic Circuits". IEEE Transactions on Circuits and Systems I 54 (11): 2528–2540. doi:10.1109/TCSI.2007.907864.

^ Berg, J.M. et al. (2002). Biochemistry (5 ed.). W.H. Freeman & Co.. ISBN 0716747383.

^ Omori, M. and Watabe, N., Eds., Mechanisms of biomineralization in animals and plants, Tokai University Press, Tokyo (1980)

^ Perry, C. C. (2003). "Silicification: The Processes by Which Organisms Capture and Mineralize Silica". Reviews in Mineralogy and Geochemistry 54: 291. doi:10.2113/0540291.

^ Weiner, S., and Lowenstam, H.A. (1989). On Biomineralization. Oxford University Press. ISBN 0-19-504977-2.

^ Mann, S. (2005). Biomineralization. Oxford University Press. ISBN 0895736721.

^ Edited by Astrid Sigel, Helmut Sigel, Roland K. O. Sigel (2008). Astrid Sigel, Helmut Sigel and Roland K.O. Sigel. ed. Biomineralization: From Nature to Application. Metal Ions in Life Sciences. 4. Wiley. ISBN 978-0-470-03525-2.

^ Sarikaya M (1999). "Biomimetics: materials fabrication through biology". Proc. Natl. Acad. Sci. U.S.A. 96 (25): 14183–5. doi:10.1073/pnas.96.25.14183. PMID 10588672.

^ Currey, J. D. (1977). "Mechanical Properties of Mother of Pearl in Tension". Proceedings of the Royal Society of London. Series B, Biological Sciences (1934-1990) 196: 443. doi:10.1098/rspb.1977.0050.

^ Currey, JD (1999). "The design of mineralised hard tissues for their mechanical functions.". The Journal of experimental biology 202 (Pt 23): 3285–94. PMID 10562511.

^ Heuer, A.; Fink, D.; Laraia, V.; Arias, J.; Calvert, P.; Kendall, K; Messing, G.; Blackwell, J et al. (1992). "Innovative materials processing strategies: a biomimetic approach". Science 255: 1098. doi:10.1126/science.1546311.

^ Whitesides, G.; Mathias, J.; Seto, C. (1991). "Molecular self-assembly and nanochemistry: a chemical strategy for the synthesis of nanostructures". Science 254: 1312. doi:10.1126/science.1962191.

^ Aksay, I.A., et al. (2000). "Self-Assembled Ceramics". Ann. Rev. Phys. Chem. 51: 601.

^ Sarikaya, M., et al., Mechanical property–microstructural relationships in abalone shell, Vol. 174, Materials Research Society (Pittsburgh, PA 1990) p. 109

^ Lin, A., Meyers, M.A., et al., Growth and structure in abalone shell, Mater. Sci. Eng. A, Vol. 390, p. 27 (2005); Growth of Nacre in Abalone Shell, Acta Biomater., Vol. 4, p. 131 (2008); Biological Materials: Structure & Mechanical Properties, Prog. Mat. Sci., Vol. 53 (2008)

^ Menig, R., Meyers, M.H., Meyers, M.A. and Vecchio, K.S., Quasi-static and dynamic mechanical response of Haliotis rufescens (abalone) shells, Acta Mater., Vol. 48, p. 2383 (2000)

^ Schäffer, T.E., et al., Does abalone nacre form by heteroepitaxial nucleation or by growth through mineral bridges?, Chem. Mater., Vol. 9. p. 1731 (1997)

^ Fritz, M. and Morse, D.E., Formation of highly organized biogenic polymer/ceramic composite materials: the high-performance microaluminate of molluscan nacre, Coll. Int. Sci., Vol. 3, p. 55 (1998)

^ Evans, A.G., Aksay, I.A., et al., Model for the robust mechanical behavior of nacre, J. Mater. Res. Soc., Vol. 16, p. 2475, p. 2485 (2001)

^ Song, F., Zhang, X.H. and Bai, Y.L. Microstructure and characteristics in the organic matrix layers of nacre, J. Mater. Res., Vol. 17, p. 1567 (2002); Structural and mechanical properties of the organic matrix layers of nacre, Biomaterials, Vol. 24, p. 3263 (2003)

^ Meyers, M.A., Lin, A., et al., Mechanical strength of abalone nacre: role of the soft organic layer, J. Mech. Behav. Biol. Mater. (in press)

^ Ghalanbor Z, Marashi SA, Ranjbar B (2005). "Nanotechnology helps medicine: nanoscale swimmers and their future applications". Med Hypotheses 65 (1): 198–199. doi:10.1016/j.mehy.2005.01.023. PMID 15893147.

^ Kubik T, Bogunia-Kubik K, Sugisaka M. (2005). "Nanotechnology on duty in medical applications". Curr Pharm Biotechnol. 6 (1): 17–33. PMID 15727553.

^ Leary, SP; Liu, CY; Apuzzo, ML (2006). "Toward the Emergence of Nanoneurosurgery: Part III-Nanomedicine: Targeted Nanotherapy, Nanosurgery, and Progress Toward the Realization of Nanoneurosurgery". Neurosurgery 58 (6): 1009–1026. doi:10.1227/01.NEU.0000217016.79256.16. PMID 16723880.

^ Shetty RC (2005). "Potential pitfalls of nanotechnology in its applications to medicine: immune incompatibility of nanodevices". Med Hypotheses 65 (5): 998–9. doi:10.1016/j.mehy.2005.05.022. PMID 16023299.

^ Cavalcanti A, Shirinzadeh B, Freitas RA Jr., Kretly LC. (2007). "Medical Nanorobot Architecture Based on Nanobioelectronics". Recent Patents on Nanotechnology. 1 (1): 1–10. doi:10.2174/187221007779814745.

^ Boukallel M, Gauthier M, Dauge M, Piat E, Abadie J. (2007). "Smart microrobots for mechanical cell characterization and cell convoying". IEEE Trans. Biomed. Eng. 54 (8): 1536–40. doi:10.1109/TBME.2007.891171. PMID 17694877.

^ Project on Emerging Nanotechnologies. (2008). Analysis: This is the first publicly available on-line inventory of nanotechnology-based consumer products.

^ Applications for Nanotechnology

^ Berube, David. Nano=Hype: The Truth Behind the Nanotechnology Buzz, Amherst, NY: Prometheus Books, 2006

^ Savage, N., Diallo, M., Duncan, J., eds., Nanotechnology Applications for Clean Water, Norwich, NY: William Andrew Publishing, 2008

^ Testimony of David Rejeski for U.S. Senate Committee on Commerce, Science and Transportation Project on Emerging Nanotechnologies. Retrieved on 2008-3-7.

^ Berkeley considering need for nano safety (Rick DelVecchio, Chronicle Staff Writer) Friday, November 24, 2006

^ Cambridge considers nanotech curbs - City may mimic Berkeley bylaws (By Hiawatha Bray, Boston Globe Staff)January 26, 2007

^ Recommendations for a Municipal Health & Safety Policy for Nanomaterials: A Report to the Cambridge City Manager. July 2008.

^ Lubick, N. (2008). Silver socks have cloudy lining.

^ Murray R.G.E., Advances in Bacterial Paracrystalline Surface Layers (Eds.: T. J. Beveridge, S. F. Koval). Plenum pp. 3 ± 9. [9]

^ Elder, A. (2006). Tiny Inhaled Particles Take Easy Route from Nose to Brain.

^ Weiss, R. (2008). Effects of Nanotubes May Lead to Cancer, Study Says.

^ Paull, J. & Lyons, K. (2008). "Nanotechnology: The Next Challenge for Organics" ([dead link]). Journal of Organic Systems 3: 3. http://www.organic-systems.org/journal/Vol%203(1)/pdf/03-22%20NanoPaullJOS3.pdf.

^ "Nanoparticles used in paint could kill, research suggests". Telegraph. 2009. http://www.telegraph.co.uk/health/healthnews/6016639/Nanoparticles-used-in-paint-could-kill-research-suggests.html.

^ Bowman D, and Hodge G (2006). "Nanotechnology: Mapping the Wild Regulatory Frontier". Futures 38: 1060–1073. doi:10.1016/j.futures.2006.02.017.

^ Davies, JC. (2008). Nanotechnology Oversight: An Agenda for the Next Administration.

^ Rowe G, Horlick-Jones T, Walls J, Pidgeon N, (2005). "Difficulties in evaluating public engagement initiatives: reflections on an evaluation of the UK GM Nation?". Public Understanding of Science. 14: 333.

^ Maynard, A.Testimony by Dr. Andrew Maynard for the U.S. House Committee on Science and Technology. (2008-4-16). Retrieved on 2008-11-24.

^ Faunce TA et al. Sunscreen Safety: The Precautionary Principle, The Australian Therapeutic Goods Administration and Nanoparticles in Sunscreens Nanoethics (2008) 2:231–240 DOI 10.1007/s11569-008-0041-z. http://law.anu.edu.au/StaffUploads/236-Nanoethics%20Sunscreens%202008.pdf . Retrieved 18 June 2009.

^ Royal Society and Royal Academy of Engineering (2004). Nanoscience and nanotechnologies: opportunities and uncertainties. http://www.nanotec.org.uk/finalReport.htm. Retrieved 2008-05-18.

^ Nanotechnology web page. Department of Toxic Substances Control. 2008. http://www.dtsc.ca.gov/TechnologyDevelopment/Nanotechnology/index.cfm.

^ "About Nanotechnology - An Introduction to Nanotech from The Project on Emerging Nanotechnologies". Nanotechproject.org. http://www.nanotechproject.org/topics/nano101/. Retrieved 2009-11-24.

^ "Nanotechnology Introduction Pages". Nanotech-now.com. http://www.nanotech-now.com/nano_intro.htm. Retrieved 2009-11-24.

^ "The Twinkie Guide to Nanotechnology • News Archive • Nanotechnology Project". Nanotechproject.org. 2007-10-22. http://www.nanotechproject.org/news/archive/the_twinkie_guide_to_nanotechnology/. Retrieved 2009-11-24.

^ "Nanotechnology & Society". Springer.com. http://www.springer.com/philosophy/ethics/book/978-1-4020-6208-7. Retrieved 2009-11-24.

^ "Nanoethics: The Ethical and Social Implications of Nanotechnology". Wiley. http://www.wiley.com/WileyCDA/WileyTitle/productCd-0470084170.html. Retrieved 2009-11-24.

^ "The Ethics and Societal Impact of Nanotechnology". Nanoethics.org. http://www.nanoethics.org/wiley.html. Retrieved 2009-11-24.