Exploring whether 'nano-' is always necessary

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Introduction

When approached to write an opinion article relating to nanotechnology, our initial thoughts were to examine the impact a range of current and future 'nanotechnologies' are having (and may have) on the healthcare industry, an area of mutual interest and professional involvement for both authors. However, when deciding on which technologies we should include, and which we should not, we found ourselves compelled to explore the true meaning and definition of 'nanotechnology'. Following an examination of numerous articles on the subject, and drawing on our personal experience, including numerous interactions with colleagues in both academia and the private sector, we were surprised at the large variation in definitions of nanotechnology and the practices to which the term is applied. What is more we saw no definition that adequately captured all the aspects that we feel underpin its true essence, and which reflected the true potential of this broad technological area.

Accordingly, we decided to focus this article on exploring whether a 'true' definition of nanotechnology does, or even can, exist. This exploration in turn addresses some additional questions on nanotechnology which are all too often brushed under the proverbial carpet. Namely: what advantages, if any, are obtained by crowding a disparate set of technologies under one definition? And, assuming there are advantages, is a loose or broad definition better than a tight, narrow one?

One final clarification before continuing; it may appear to some that we are merely dealing in arguments of semantics and philosophy, ultimately running around in circles to try and answer the questions: what is in a word, and why does it matter? This is certainly an aspect of our quest, and it is an aspect which caused the authors some concern. However, unlike most words, the meaning attributed to nanotechnology can profoundly affect decisions made by those developing, investing in, using, or in some way involved with this space. Indeed, it is a widely acknowledged fact that the mere process of defining a set of disparate technologies as 'nanotechnology' has helped create the significant buzz that pervades all things 'nano'. Both fuelling, and fuelled by, this buzz are significant levels of both private and public investment

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into so called 'nanotechnologies'. Whilst it is undeniably the case that the 'nano' umbrella is getting bigger, it is not entirely clear whether it is new technology or simply the 'nano' prefix that is proliferating at the higher rate.

Because of this confusion and the vulnerability of the stakeholders involved in this area,[1] a clear understanding of what is being referred to when the word nanotechnology is used will be to the advantage of all concerned. Furthermore, virtually every technology labelled with the 'nano' prefix is currently placed in the same conceptual box for both investment and development opportunities. We feel that this 'broad brush' approach will ultimately (and is already beginning to) distort perceptions of nanotechnology's possibilities, and accordingly, we seek to define nanotechnology in a more controlled and meaningful way. Of course, some argue that a loose definition of nanotechnology is preferable and indeed necessary. However, when the host of a party mixes a fruit punch they are mixing and manipulating molecules, but surely they are not performing/using nanotechnology according to any meaningful definition. This may be an extreme example; however, it sets the scene for the kind of conceptual issues we will be tackling throughout the next few pages.

We therefore aim to generate a rigorous definition for nanotechnology and to test it against three examples of healthcare-related technologies that at one time or another have had the 'nano' label attached to them. We then proceed to examine whether a clear benefit is forthcoming when these technologies are viewed with our definition in mind; furthermore, if there is a benefit, to whom it is relevant? Ultimately, we seek to qualitatively show how an accurate and specific definition of nanotechnology can help separate those technologies that have the potential to be truly disruptive and distinct from those which are merely another stage of miniaturization.

Defining nanotechnology

We first seek to illustrate why there exists a range of opinion related to what is and what is not nanotechnology. The following four versions of a definition broadly sum up the most common definition types we encountered:

1. The use of objects less than a few hundred nanometres and less in size.
2. The use, by deliberate manipulation and placement, of objects under a few hundred nanometres in size.
3. The use, by deliberate manipulation and placement, of objects less than a few hundred nanometres in size to achieve a desired outcome in a specific application.
4. The use, by deliberate manipulation and placement, of objects less than a few hundred nanometres in size, to achieve a desired outcome in a specific application, by harnessing material properties that are only available where nanoscale features exist.

We therefore have four very similar-sounding definitions that get progressively loaded with caveats and we will now examine what each definition represents and what is implicit from the underlying differences. A strict definition of technology involves the application of science to solving a real-world problem. If we take this line and follow it to exclusion, then definitions 1

[1] Stakeholders include investors (private and public) researchers, grant agencies and ultimately (in terms of the end benefits of these technologies) society at large.

and 2 above are rendered null as they are referring to a form of nanoscience. In other words we could say according to the definition of technology, unless one is actually using nanoscience to solve a real problem then one cannot be 'doing' nanotechnology. Modification of version 1 to include a problem-solving element is entirely possible (for example including nanoscale particles in paint to improve its scratch resistance), however it would still lack the precision and control elements. Taken to the extreme one could begin to wonder whether nanotechnology is even a newly emerging area of science, given that it arguably underpins the first patent ever awarded in England (and there is evidence of similar processes being employed in Ancient Greece). In 1449 the glassmaker John of Utynam was awarded a patent for his method of making stained glass, in which he used the properties of nanosized metallic particles to create different hues. Of course this was a somewhat unwitting process at the time (the atomic force microscope being invented some five centuries later—he could never have known the size of his particles) but it is a classic example of how a strict definition of nanotechnology can break down. Most people would agree that the inventor of stained glass was probably not a nanotechnologist as he had no rigorous understanding of how the colour changes he observed were taking place, but does the fact that we now understand what was producing the changes in colour mean that the modern day process of stained glass manufacture can actually fall within a strict definition of nanotechnology? We would argue that it does not, on the grounds that the activity is not new and the incorporation of particles lack precision in terms of their physical placement. So with reference to version 4 above and with the intention of testing whether a single definition can be realistically adhered to (without potentially alienating a large portion of the world's scientific community) we will hinge our discussion on the following working definition of nanotechnology:

'***The deliberate and controlled manipulation, precision placement, measurement, modelling and creation of sub-100 nanometre scale matter, in order to create materials, devices, and systems with fundamentally new properties and functions.***'

This definition not only specifies a definite scale (now broadly accepted as the 'nanoscale' threshold below which emergent material properties occur), but includes a couple of words that provide an element of refinement that many definitions lack. The words are 'deliberate' and 'controlled'. These words mean that many technologies, otherwise caught under the nanotech umbrella, can no longer be included. For example John of Utynam under this definition cannot be considered an exponent of true nanotechnology, and neither can his modern day counterparts. Other examples can be seen in many materials now entering commercial markets which often ascribe their properties (such as strength, stiffness, wear resistance) to nanoscale features, but it is frequently true that the use of these nanoscale components is a byproduct of a wider process, within which nano-particles are created and used. Their inclusion in a process or material happens in such a way that the accuracy of terms such as 'deliberate' and 'control' may be up for debate. For example, the act of incorporating a nanoscale particle into car bodywork paint may be deliberate, however the control element is realistically limited to the volume fraction of particles and their placement is a largely random process.

The latter half of our working definition focuses on the uses of nanotechnology ('…in order to create materials, devices, and systems with fundamentally new properties and functions'). It highlights clearly that we are not simply talking about the next stage of miniaturization.

Unlike the move from the macro to the micro when all tools and devices got smaller, the move from the micro to the nano will facilitate a new breed of tools and devices the likes of which have previously not been possible. The reason for this is dependent on two major factors:

1. Dramatic changes in material properties below the 100 nm scale.
2. The relationship between the nanoscale and the fundamental building blocks of life.

We have attempted to summarize the two points above in the context of each other, as shown in Figure 1 (see also Figure 2). The diagram illustrates the principal changes that occur when one begins to approach the nanoscale, which in many cases relate to the breakdown of classical physics as one approaches the quantum level. For example, below 100 nm the electronic and magnetic properties of materials begin to change, principally due to the fact that the mean free path of electrons within most materials coincides with lengths at the nanoscale. The other key factor of interest is that interactions between the fundamental building blocks of life, and indeed the building blocks themselves, occur in the 1 to 100 nanometre regime. This suggests that nanotechnologies may offer some unique insights into the way in which biological systems operate, and in turn create unique opportunities to revolutionize our understanding of the way in which the human body works and therefore the way in which it may be repaired in the event of malfunction. (It should also be noted that biological systems can provide unique insights into the way in which nanosystems operate, and in turn create opportunities to revolutionize our understanding of this new scientific frontier).

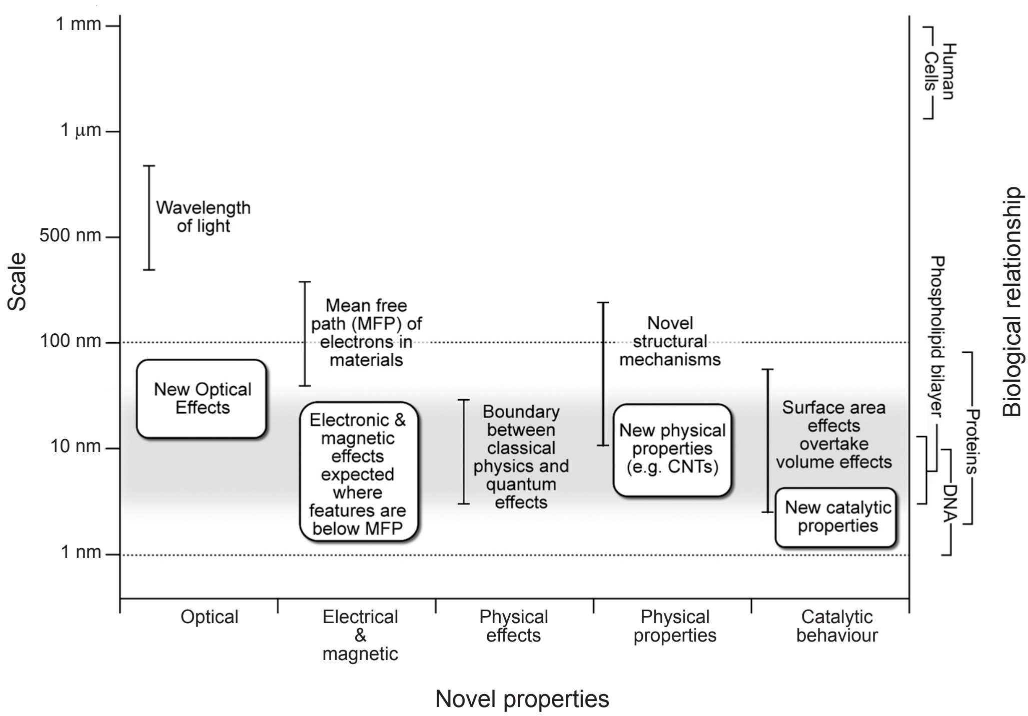

Figure 1. Properties that nanotechnologists hope to exploit with reference to scale and the size of biological structures. Of importance is the fact that the most basic building blocks of life exist at the nanoscale, which opens up the possibility of interfacing with biology at a fundamental level.

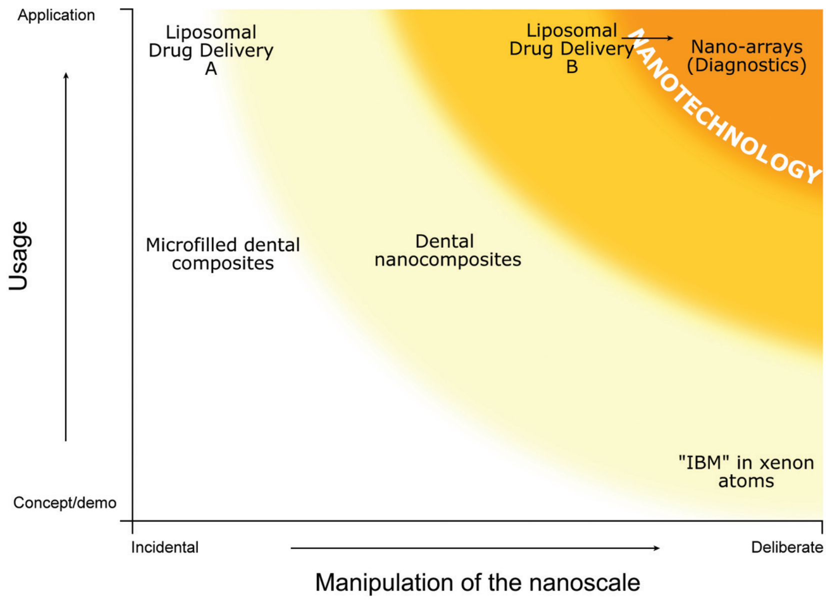

Figure 2. Diagram illustrating the relationship between a variety of examples of systems incorporating nanosized features, demonstrating one way in which nanotechnology could be viewed. Both axes are continua in an effort to represent the notion that no single example should be fixed in place, but may shift position on the diagram depending on the outcome of future developments. 'IBM' in xenon atoms is an example of deliberate atomic placement and so one could argue that it is truly nanotechnology, but without any obvious application beyond generating awareness of possibilities we have concluded that it should not occupy the same space as the diagnostic tools built using very similar methods. Microfilled dental composites were an unwitting use of nanotechnology almost 30 years ago which found an application, although not markedly different to others, hence the position halfway along the Usage scale. In contrast the products marketed today as dental nanocomposites have advanced slightly along the Manipulation axis as they are deliberately employed, but not all the way as the nanoscale is manipulated in a relatively clumsy manner. Meanwhile liposomal drug delivery could occupy a number of positions depending upon one's point of view. Drug delivery is clearly an application, however the manipulation of the nanoscale could be viewed as an incidental result of employing biochemical reactions in the production of liposomes (A). Alternatively one could take the view that since the conditions to result in liposome formation through a biochemical reaction (which takes place at the nanoscale) were deliberately created, so this example should move closer to being a true example of nanotechnology (B).

We suggest that our working definition facilitates a greater level of clarity than those previously given and provides for the separation of potentially revolutionary technologies (nanotechnologies) from the incremental improvements to modern day living that happen to contain a nanosized feature ('nano-activities', e.g. scratch-proof car paint). On this foundation we will examine more closely some areas of healthcare technology which encompass aspects of nano-activity that could impact upon their respective industry and research sectors. Included in our examination are: the addition of nanosized particles to mediate mechanical characteristics of a material; the use of chemical phenomena to achieve defined drug delivery goals; and the creation of high-throughput diagnostic tools through the creation of arrays of protein binding sites. We will frame these technologies within the context of our definition and in doing so illustrate the difficulties and ultimately the advantages of adopting or at least considering a strict definition, which we believe centre upon enabling those seeking to fund the research and development of nanotechnologies to better identify genuine examples of nanotechnology, from among what is chiefly hype.

Aesthetic restorative dentistry

The nano- prefix is presently fuelling interest in certain types of filled resin materials used in dentistry. White fillings offered by practitioners in place of the grey amalgam restorations are predominately dispersed particle composites that derive their mechanical characteristics from the presence of a hard, inorganic reinforcement held within a comparatively soft organic resin matrix. The strength of the interface between the two components ultimately influences the mechanical properties of the system and is promoted through the application of a silane bonding agent to the surface of particles. Contemporary examples of such materials are supplied in paste form in a variety of shades to match natural teeth and are incrementally packed into a prepared cavity, each increment being cured by irradiation with light of the intensity and wavelength required to stimulate photo-initiators resulting in hardening of the composite through polymerisation of the resin. Filler particle technology has been much investigated as the size, shape and volume fraction of the particles influence a number of characteristics of such composites including mechanical properties, the degree of polymerization shrinkage on curing, coefficient of thermal expansion, radio-opacity and ultimately the aesthetics of any dental restoration, in terms of the similarity of the dentist's work to adjacent natural teeth. Figure 3 provides an indication of the developments that have taken place within the last 35 years. Early composite materials contained glass filler particles up to 100 μm in size and were susceptible to roughening as preferential wear of the soft resin component resulted in its gradual abrasion around particles near the surface of the restoration. In turn, the exposed particles at the surface of a restoration could be plucked out, leaving a layer of unreinforced, comparatively soft resin and the wear cycle would begin once more. 'Micro-filled' composites were next explored with ~0.05 μm colloidal silica particles being incorporated into the resin matrix. The principal difficulty encountered with such materials was that incorporation of a sufficiently high filler loading to result in the desired mechanical characteristics made mixing very difficult because the surface area to volume ratio of the particles became too high once a certain proportion was added. This difficulty was partially solved by incorporating pre-polymerized particles comprising a mixture of resin and filler into a resin that already contained an achievable filler loading. Useful volume fractions of filler could then be added to the base resin and as a consequence dentists took advantage of the improved polishing characteristics offered by the micro-filled materials; large particles in conventional composites were ripped away from the surface during polishing, leaving a pit and therefore ruining the surface lustre. Hybrid materials next appeared, utilising a combination of conventional (5–20 μm) and micro-filled (0.05 μm) approaches to improve mechanical strength and toughness whilst reducing the risk of matrix abrasion through surface roughening. These were swiftly followed by 'micro-hybrid' composites in which micro-filled materials containing 0.05 μm silica particles were further reinforced with glass particles < 1 μm in size to address similar mechanical issues but also to improve the degree of polish that could be achieved. It may therefore be viewed as something of an inevitability that those interested in dental materials would hit upon nanotechnology as the next port of call, although it could be argued that they had already done this given the somewhat obvious similarity between particle sizes in the microfill and hybrid systems, as illustrated in Figure 3.

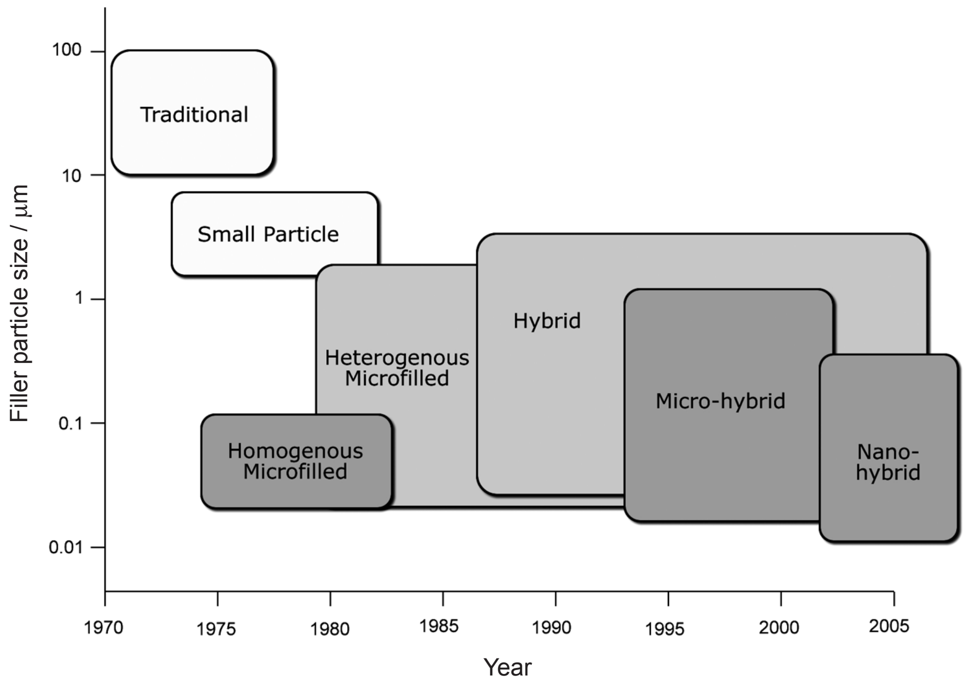

Figure 3. The evolution of filler particle size in filled resin dental restorative materials (reproduced with kind permission from Dr Will Palin, Lecturer in Dental Materials, University of Birmingham, School of Dentistry, UK). Readers may like to consider the existence of homogenous microfilled composites in the late 70s (sub-100 nm particle sizes) and the fact that nanocomposites are now being marketed with such enthusiasm. Clearly something has changed. The difficulty for researchers of dental composite materials is to identify precisely what has changed. Bulk mechanical properties today are not dramatically different from those that were achieved 30 years previously. The capacity to polish materials to a good aesthetic finish was possible with homogenous microfilled materials and yet is a promoted as a key feature of the more modern nanocomposite materials. One could point to the combination of polishability and mechanical properties offered by the more modern materials, but again, the improvement over older versions is so incremental that to hail them as a new generation of materials (particularly when nanotechnology is responsible for such dramatic changes elsewhere) is stretching the bounds of common sense.

Recent innovation has seen the introduction of composite materials containing filler particles that by dint of their size mean that the term 'nano-filled composite' has begun to pervade the dental lexicon. One manufacturer has made available a material containing two distinct particle species; primary particles or 'nanomers' with sizes in the range 5–75 nm and 'nanoclusters', which are 1 µm aggregates of primary particles (20–75 nm).[2] Whilst the

[2] Mitra, S.B., Wu, D. & Holmes, B.N. An application of nanotechnology in advanced dental materials. *J. Am. Dent. Assoc.* **134** (2003) 1382–1390.

nanomers can unarguably occupy nano-territory (they are < 100 nm in size and so fit the most basic definition), the nanoclusters have evoked a range of responses ranging from curiosity from materials scientists to outright indignation from competitor dental composite manufacturers. Competitors have pointed to the product and asked whether it is simply a micro-filled composite that has been given a new name, and although possibly misplaced in this instance it is a fair question. The plethora of dental composites on the market cannot realistically be attributed to the relentless march of dental science and must be ascribed at least in part to the work of the marketing executives whose job it is to ensure that their company is seen as progressive and at the cutting edge of its business. Indeed some would argue that there has been hardly any development of a ground-breaking nature in dental composites since the 1950s when Bowen first patented his novel dental filling material.[3] Numerous studies have demonstrated that in terms of mechanical properties, aesthetics and handling characteristics there is very little to choose between a large number of materials available on the market today and their older counterparts. So whilst the question regarding renaming of an old technology was fair, it was peculiar to hear it from a competitor company who, it could be assumed, were engaged in similar activity to some extent. In any case, there are extensive semantic arguments to be had which would ultimately lead nowhere, for example:

"These nanoclusters are inappropriately named simply because each cluster is ~1 μm in size."

"OK, so how big is a ***micro***scope...?"

However from the scientific perspective the fact that the clusters comprise aggregates of primary particles is of interest from a number of standpoints. The question of whether it is really nanotechnology or not becomes less significant, at least until sufficient is understood about the behaviour of such systems to say whether or not properties are derived from the fact that nanosized features are present, or whether an arrangement of larger-scale particles would do a similar job. For example the interaction of a propagating crack with a cluster is likely to be very different from the interaction that would take place with a solid particle. Such materials could therefore offer improved toughness, assuming the resin phase and silane bond agent has successfully penetrated the interstices in the cluster to form a fully interpenetrating structure, as cracks could be furcated and arrested within the resulting network rather than deflecting off a solid particle and continuing their propagation. Improvements in polishing characteristics have been reported with claims being made that the clusters can be ground down, due to their relatively friable nature, in comparison to a conventional dense particle. Rather than being pulled out from the surface they are abraded and left flush with the surrounding matrix creating a smooth, lustrous finish.

So, is the dental materials company that produces a material containing features that are truly nanoscale employing nanotechnology according to our working definition? In this case we would have to say no, as while the materials produced are novel in terms of their constituent parts, their mechanical, handling and aesthetic characteristics are not dramatically different to anything that has been achieved already by other means. Not only is the 'controllability' line very murky, these materials do not satisfactorily demonstrate radical new properties. So now

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3 Bowen, R.L. Dental filling materials comprising of vinyl-silane treated fused silica and binder consisting of the reaction product of bisphenol and glycidyl methacrylate. US Patent 3,066,112 (1962).

that we have abruptly discarded the notion of such materials as true exemplars of nanotechnology, are we in any way advantaged? From the patient perspective it makes little if any difference. Equally from the laboratory science perspective it does not make much difference, the material is still there to be researched, understood and developed further where appropriate. However from the point of view of the dentist having to purchase materials for use within his or her practice, or from the investor seeking to put money into nanotechnology, things are a little different. We argue that there is an advantage to the purchaser of such a material who, armed with an awareness of what the material can actually do in comparison to other types, may see past the marketing hype and potentially save themselves some money whilst achieving an identical clinical outcome (although we have not researched costs in this case). From the point of view of an investor in research, be they a business angel seeking to back a start up company or a UK Research Council evaluating an academic research proposal it also pays to adopt a very critical frame of mind. Are those proposing the investment doing so in a completely open manner, or are they in the business of hyping their proposed activity with something that sounds revolutionary, but in reality is not? Investors usually seek a return, whether that is financial (e.g. venture capital, business angel) or in terms of knowledge and useful technology (e.g. the UK Research Councils) so it is therefore paramount that those wanting to invest in a true nanotechnology understand that they would be doing a disservice to themselves and other more genuinely disruptive technologies by investing in a technology that, whilst being perfectly good and potentially profitable, will never truly revolutionize the business space in which it exists.

Drug delivery

Drugs that target only the moieties of disease whilst leaving the rest of the human physiology unaffected have been of interest to clinical and laboratory scientists alike since the early 1900s when Paul Ehrlich first explored the concept of a magic bullet therapy whilst seeking a cure for syphilis. Nowadays this notion has been adopted by many and as a general public we are now regularly exposed to advertisements for pain relief products that amongst other things claim to "target the source of pain". Once again it appears that the marketing executives have us at something of a disadvantage. The notion of targeting implies precision and if we pursue a combative line one could be forgiven for thinking that the drug (bullet) only affects the area where pain is felt (target). Of course one can obliterate a target with something rather more destructive than a bullet but we tend to view this as problematic only in terms of collateral damage during armed conflict; it doesn't generally occur to people that the pain relief products they ingest wind up in every part of the body defined by the metabolic pathway of the drug, in addition to the target. However the benign nature of painkilling drugs designed to treat headaches is in stark contrast to the highly toxic drugs required in chemotherapy for treatment of cancer, for which the side-effects can include fatigue, sickness, loss of appetite, diarrhoea, constipation, mouth ulcers, hair loss and reductions in blood cell count. This is not an exhaustive list and although chemotherapy drugs affect patients in different ways there is a real need in this situation for something that can be delivered specifically to the site of disease, possibly at a specific rate, which avoids the side effects arising from wide dispersal of pharmacological agents through the body.

One area of drug delivery technology that has been employed with chemotherapy drugs[4] and is of particular interest in the context of this essay is the use of vesicles comprising a phospholipid bilayer inside which is trapped an agent to be delivered to a specific site, the vesicles being more commonly known as liposomes. Liposomes were first described in a 1965 paper by Bangham et al.[5] and there has since been an explosion of interest in liposomes which range in composition, size, shape and numbers of vesicle lamellae (layers). In terms of their application liposomes are almost exclusively employed in the delivery of agents in solution to a specific site. The most frequently occurring examples are in drug delivery, including via intraoral, intravenous and topical routes, however it is not only potentially life-saving drugs that may be delivered. Related examples of liposomes in action include their use in 'cosmeceuticals'; products designed to deliver (for example) so-called anti-ageing products to the skin, whilst food technologists have also employed liposomes as a means to deliver certain flavours to the tongue when a product is eaten. More recently examples of modified liposomes have been described that are capable of a burst release of entrapped solute through stimulation of a trigger mechanism (either chemical, thermal or in response to irradiation with certain wavelengths of light), rather than the gradual release associated with conventional liposomes.

So are liposomes an example of nanotechnology? If we temporarily suspend our working definition of nanotechnology and concentrate upon others that centre around the concepts of molecular manipulation and self-assembly then there is a robust argument for their inclusion at point B in Figure 2. Phospholipid molecules are deliberately exposed to aqueous conditions that cause them to spontaneously assemble into vesicles, which may themselves be nanoscale depending upon the conditions employed. However if we return to our working definition things appear less clear. The first and most obvious discrepancy lies in the precision placement aspect as it cannot realistically be argued that discrete molecules are placed in position, instead their position in the bilayer (which is not fixed in any case) is the incidental result of chemical interactions, and the formation of the bilayer itself is reliant upon normal biochemical processes, so we might alter our view and argue that in Figure 2 liposomes should occupy position A. That said, a bilayer would not form unless a deliberate effort to create the correct conditions was made, so it appears that even the working definition that we had hoped would eliminate all confusion is still open to interpretation. This brings us to an interesting parallel debate; when does chemistry become nanotechnology and *vice versa*? The borderline is a grey area, and as we have just conceded, our working definition has left some room for interpretation, so we will not attempt to split the two disciplines. Apart from anything else we would be guilty of forgetting that nanotechnology is an umbrella term that covers a wide range of disciplines. In this case a deliberate effort to harness the chemistry of nanosized molecules can result in the formation of a nanosized vesicle for use in overcoming a clinical problem. The precision placement aspect of our definition remains ambiguous, however the use and creation of nanosized objects is undisputable, as are the real world benefits arising from having drug delivery routes that are truly targeted. Under our working definition there is room for argument

[4] Allen, T.M., Mehra, T., Hansen, C. & Chin, Y.C. Stealth liposomes: an improved sustained release system for 1-beta-D-arabinofuranosylcytosine. *Cancer Res.* **52** (1992) 2431–2439.

[5] Bangham, A.D., Standish, M.M. & Watkins, J.C. Diffusion of univalent ions across the lamellae of swollen phospholipids. *J. Mol. Biol.* **13** (1965) 238–252.

either way, but viewed from another perspective it is quite possible that our working definition is too rigid, or that we are attempting to apply it too rigidly. We realistically do not want to go down the line of dismissing something as "not nanotechnology" if it does not involve the precision placement of single atoms, one at a time by a robotic assembler, a point that was recently argued by Drexler[6] with reference to the interpretation of Richard Feynman's original vision of self-replicating atomic assemblers. Of course, we must keep in mind the argument from our introduction; mixing liquids to create a party beverage, whilst being an example of molecular manipulation, cannot sensibly be called nanotechnology if some adherence to our working definition is desired, as clearly, there is no conscious effort to manipulate molecules at the nanoscale in this sort of mixing. Similarly where liposomes are concerned it is accepted that spontaneous assembly will happen due to chemistry that is already well understood.

We can gain a rudimentary insight into the liposome scientists' perspective of their own work by undertaking a quick review of the number of published research articles containing certain search terms. We investigated three different journal article search engines, namely PubMed[7] ScienceDirect[8] and Web of Knowledge[9] and searched for the terms "liposome", "liposome AND nanoparticle" and "liposome AND nanotechnology", originally for articles published between 1965 and 2005. Our results are summarized in Figure 4.

What is immediately clear from Fig. 4 is that for each search engine employed there are a very large number of articles that contain the word liposome, but only a comparatively small number that contain "liposome" in addition to a nanorelated term (note the use of the log scale).

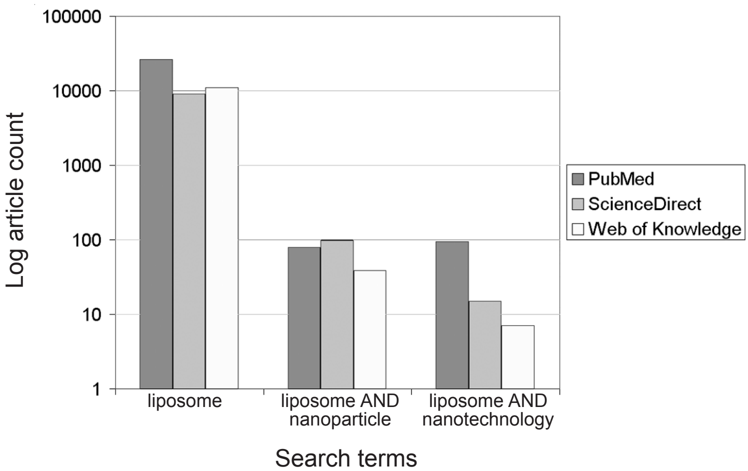

Figure 4. Histogram summarizing the frequency of occurrence of search terms using a variety of journal article databases. The number of articles containing the word liposome is dramatically in excess of those that containing a nano-related word suggesting that although the technology could be described as nanotechnology, it is not a word that those working the liposomes feel the need to apply.

[6] Drexler, K.E. Nanotechnology: from Feynman to funding. *Bulletin of Science, Technology and Society* **4** (2004) 21–27.
[7] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?DB=pubmed.
[8] http://www.sciencedirect.com.
[9] http://wok.mimas.ac.uk/.

In fact, with only one exception (ScienceDirect, using the term "liposome AND nanoparticle") it is the case that less than 0.5% of published articles on liposomes since 1965 actually contain a nano-reference. With this in mind we then decided to limit the searches to a more recent period (1997–2005), to investigate whether the frequency of occurrence of a nano-related term was markedly different in the period following the popularization of "nano" as a buzz word. The results of this inquiry are presented in Figure 5 and what is immediately clear is that the co-occurrence of "liposome" with a nano- term has increased in the 1997–2005 timespan compared with the 1965–2005 time span. In most cases the value has almost doubled, however the interesting finding remains that at the most only 2.25% of authors writing about liposomes have included the word nanoparticle in their article. In addition, instances of the word nanotechnology in addition to liposome are < 1% for every search engine, suggesting that a very clear minority of those reporting on liposomes may be accused of hopping onto the nanobandwagon. Admittedly these data are a rudimentary indication at best and must be treated with some caution. We certainly do not claim to have read the (for example) 26 200 articles returned by PubMed containing the word 'liposome', nor even confirmed by reading abstracts that the context is appropriate, so there may well be cases where an author has referred to liposomes without their work actually involving liposomes, or where a nano prefix has appeared without any claim by the author that their work is an example of nanotechnology.

As a means to furthering the examination of our working definition we shall ignore the rudimentary nature of the search and assume that the results from the survey are indicative of real trends. In this case the interesting question is why the number of liposome researchers using

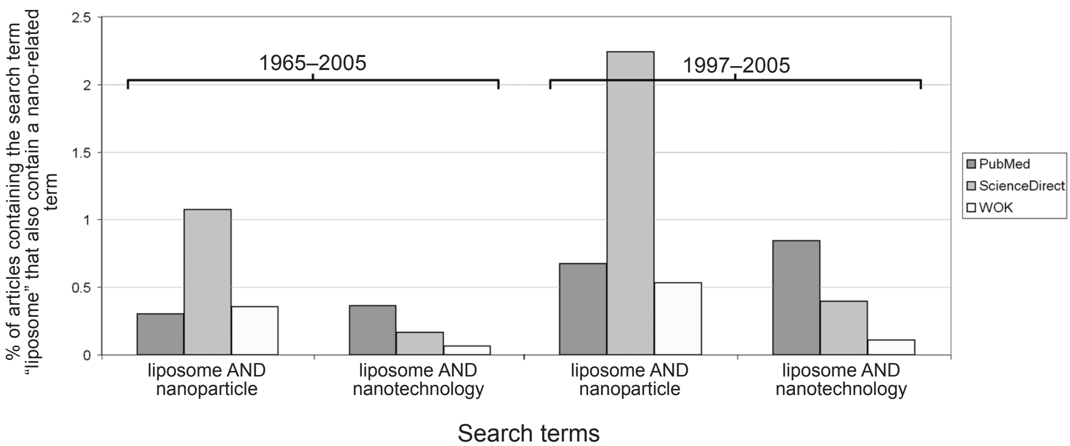

Figure 5. Histogram showing the percentage of the total number of articles containing the word 'liposome' that also contain a nano-related term for the date ranges specified. Data is presented to allow comparison between two date ranges 1965–2005 and 1997–2005. For example the ScienceDirect database indicates that just over 2% of the total number of articles containing the word 'liposome' published in the 1997–2005 date range also contained the word 'nanoparticle', whilst less than 0.5% include the words 'liposome' and 'nanotechnology'. Overall these data seem to suggest that regardless of the relationship of the date of publication to the popularization of the 'nano' prefix, it is a minority of liposome scientists who actually employ the prefix.

the nano prefix is so low when there is a strong argument for the inclusion of liposomes under the nanotechnology banner? One possible answer may lie in the perception of liposomes as a technology in their own right. Applications of liposome science are considered 'sexy', that it to say they are viewed as exciting, of real-world benefit and as being potentially profitable. It could simply be the case that liposome scientists do not feel the need to employ buzz-words to raise the profile of their work. Alternatively, perhaps the majority of liposome scientists view their work as biochemistry, and not at all like the early vision of nanotechnology involving tiny robots assembling items atom by atom. Whatever the case it is clear that, even under a rigorous definition, this example could be a nano-activity (the manipulation of the nanoscale occurs by default) or a nanotechnology (the manipulation of the nanoscale is controlled and deliberate), depending upon one's perception (as is illustrated in Figure 2).

Diagnostic technology

The perfect diagnostic tool would be a low cost system that could analyse tiny sample volumes within seconds to provide completely accurate results indicating what is, and what was about to be, wrong with a patient. This sort of thing has previous been confined to the medical bays featured in episodes of Star Trek, however nanoscience is presently being employed in the creation of biochemical assays that have the potential to get close to the goal of rapid, one step diagnosis of ailments.

Historically, to assay a sample, one would need to test a different piece of the sample in numerous different Petri dishes or test tubes to find out what was inside. More recently, bolstered by a greater understanding of cellular structure, genes, DNA and proteins; new methods have been created which allow significantly higher throughputs for assays. Liquid chromatography, mass spectrometry, and gel electrophoresis, to name but a few, have all found their place in the assaying world. However, it has been the capability to miniaturize the Petri dishes of old, and cram thousands of test sites onto a single 2×2 cm chip that has led to the greatest breakthrough in recent assaying technology. We are of course referring to the 'micro-array'.

Over the last 10 years, much effort and investment has been applied to developing and commercializing oligonucleotide (oligo) micro-arrays / biochips, to the point that full-genome scale biochips are now available from several manufacturers. However, it is more complex molecules such as proteins (of which a human carries an estimated 1 000 000 compared to 25 000–35 000 genes), that represent the great bulk of nature's bio-chemical repertoire and currently represent the greatest challenge to life-science.

Whereas genes encode the structure of an organism, proteins are the effector molecules; they are the primary markers of disease, the targets of most drugs and the ultimate components for diagnostic and biosensing tools. While significant research based upon the old oligo[10] micro-array technology is currently underway into the preparation of protein arrays, the inherent differences between these types of biomolecules means approaches to protein assaying based on existing genomic technology will only ever be of limited effectiveness. A key to future discoveries in life science and pharmacology, and to diagnostic/prognostic/therapeutic applications in the clinic, will be the ability to assay the key biochemical components of life in

[10] i.e. oligomers of DNA.

massively-parallel formats (while this primarily refers to proteins it also includes cDNA, RNA, peptides, antibodies, lipids, small molecules, lysates etc., all the way through to cells and tissue). Clearly, an alternative fabrication technology is needed for preparing arrays of larger or more complex molecules.

Enter nanotechnology. Already companies are developing biochips which use as their substrates nanoscale clusters which are capable of binding individual protein capture agents (biomolecules that will attach onto only one protein type), orienting them correctly for diagnostic uses and enabling instantaneous read out of binding events. These nanoscale clusters are very deliberately selected and deposited onto surfaces which are protein resistant, and their emergent properties (defined extremely accurately due to the atomic specificity of the individual clusters) are used both to bind the capture agents, and for analysing any binding with target molecules in the sample, hence the unambiguous categorization of such technology in Figure 2. A nano-array of this description will facilitate order of magnitude improvements in the sensitivity, consistency and speed of biochips, and eventually facilitate coverage of the entire proteome, enabling diagnostic tests for precursors to every known disease or condition. The revolution in healthcare such a tool will bring is significant.

If we take the example of a dentist as a provider of primary care we could now imagine that when a patient goes in for a dental check up, a sample of the patient's saliva is taken and placed onto a nanotechnology-based biochip. By the end of the dental examination, the dentist could have a full read out of the patient's health condition and would be able to indicate if there were any precursors to serious conditions present in the body and refer the patient to the necessary specialists for further checks. With only minimal impact upon clinical routine such a tool would truly revolutionize the way in which dentists work and were perceived by their patients, as well as affecting the way the healthcare system operates in a wider context. Such a tool need not only be confined to dentists, but could be employed by almost any provider of primary care, even marketed as a self-testing system for individual users (the "worried well") to purchase at a pharmacy, assuming the system could be packaged as a black-box solution. Such an approach to the monitoring of health would sit well with the notion that prevention is better than cure and could ultimately save significant amounts of the time and money that are currently deployed in the treatment of those for whom preventive measures are too late. Compare this ground-breaking scenario to the impact composite fillers are having on the dental and wider health industry (bearing in mind that the differences between a wide range of composite products are minimal and that the National Health Service in the UK still prescribes the use of amalgam as a filling material) and you'll see a clear example of the different impact a true nanotechnology can have compared to a nano-activity. This is precisely why we feel the need to differentiate.

Summary and conclusions

Through examination of technologies in the context of our working definition of nanotechnology we are able to distinguish the power of "true" nanotech from incidental use of small objects that facilitate the application of the nano- prefix. However this distinction has not been without its difficulties, and as was reasonably clear from the drug delivery example it seems to be the case that even the most well-intentioned definition may not be rigidly applicable to every situation and is open to some interpretation. It is important to recognize that we do not wish to discount the value of many incremental improvements to an area of technology or expertise but feel there is a strong argument, in the case of nanotechnology as a descriptor, for some consideration of whether it is sensible to direct the finite resource available to support the research and development of true nanotechnology into innovations that do not have the same disruptive potential but are similarly badged.

It is a fact that any invention must be commercialized before it becomes available to an end user, and that finance is involved at every stage from product conception, through development and ultimately to purchase. This means that analysis of risk versus return also occurs at every stage. It is therefore inevitable that those seeking to persuade others to part with money will employ any means that can be reasonably justified to promote their innovation above others. As an umbrella term, 'nanotechnology' is so broad that it is a relatively simple matter to demonstrate involvement in the field even when one is operating a great distance from the cutting edge. As a consequence the term has proliferated and will probably continue to do so.

We are concerned that ultimately more harm than good could come from the overproliferation of the term nanotechnology through the obfuscation of potentially ground-breaking developments by the more basic, close-to-market, money-spinning ideas. It is our hope that we have been able to arm the readers of this article with a definition that can be used to distinguish less worthy technologies from the genuine article, or at the very least engender a questioning attitude that will result in scrutiny of innovations labelled as nanotechnology. Hopefully it is clear that at the very least one must decide on what one's perception of nanotechnology actually is in relation to a particular field before deciding whether a given technology genuinely offers a step change or only incremental improvement in its area of application. Of course, all of this assumes that it is the consumers (be they customers searching for a product in store or financiers looking to back a new innovation) who are responsible for deciphering what they are being sold/told, and if we take it as inevitable that the term will be exploited (albeit reasonably depending upon one's definition) then this should certainly hold. However we remain hopeful that those behind new developments will be able to bear in mind arguments such as ours when deciding how best to promote their work. Asking whether 'nano-' is necessary might not be a bad idea now and again.