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Leading Opinion

On the nature of biomaterials☆

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ABSTRACT

The situations in which biomaterials are currently used are vastly different to those of just a decade ago. Although implantable medical devices are still immensely important, medical technologies now encompass a range of drug and gene delivery systems, tissue engineering and cell therapies, organ printing and cell patterning, nanotechnology based imaging and diagnostic systems and microelectronic devices. These technologies still encompass metals, ceramics and synthetic polymers, but also biopolymers, self assembled systems, nanoparticles, carbon nanotubes and quantum dots. These changes imply that our original concepts of biomaterials and our expectations of their performance also have to change. This Leading Opinion Paper addresses these issues. It concludes that many substances which hitherto we may not have thought of as biomaterials should now be considered as such so that, alongside the traditional structural biomaterials, we have substances that have been engineered to perform functions within health care where their performance is directly controlled by interactions with tissues and tissue components. These include engineered tissues, cells, organs and even viruses. This essay develops the arguments for a radically different definition of a biomaterial.

1. Introduction

We all recognise that the meaning of words, and the ways in which words are used, change with time. To some, this is a beneficial process as this evolution brings richness and diversity to language. To others, it is detrimental, leading to confusion and disarray. In the context of scientific terminology, it is extremely important that there is consistency over the words we use. However, as the progress of science and technology is now very fast, we often find that multiple words are simultaneously introduced, by different people or different communities, for the same phenomena, or alternatively that one term is simultaneously introduced by different people for different phenomena. The confusion that has arisen in patent litigation over the multiple uses of the term 'stent', as in an intravascular stent, a stented heart valve, a stent-graft and a stent-valve, provides just one example of how this can impact medical technology. Over time, the confusion that can reign in either scenario has to be resolved through an evolutionary process, hopefully based on sound etymological arguments coupled with common sense. It often happens that the really difficult situations arise with the simplest of words, whose roots can have multiple meanings, particularly where there are common but widely abused pre- or suffixes. It is easy to anticipate the confusion that will arise with the plethora of technical words that have emerged with the prefix nano- for example. At the present time, it is the use of words with the prefix bio- that is causing some difficulties, since this prefix alludes to 'life or living things', and there are many ways in which we can interpret 'life or living'. Within the field of biomaterials science we can readily appreciate, from scientific, legal, regulatory and clinical perspectives, the difficulties that the terms 'biopolymer' and 'bioceramic' pose, since they could either imply something derived from life or something used to the benefit of life, which are usually very different. However, we cannot solve these issues without addressing the even more important, and more generic, issue, about what is the meaning of 'biomaterial' itself.

☆ *Editors Note*: This Leading Opinion Paper is based upon a series of presentations given by the author during 2008 and 2009, including the Termis-Asia Pacific Meeting in Taipei, the Indian Society for Biomaterials and Artificial Organs in Katmandu and the Biomaterials Asia Conference in Hong Kong. It forms the second of a series of essays that will be published, in different journals, on the subjects of the principles of biomaterials selection. Since the author is Editor-in-Chief of the journal, the paper has been refereed by six senior referees and revised on the basis of their reports. The opinions expressed in the review are, however, the sole responsibility of the author. It should also be noted that the reference list cannot represent the totality of literature on the nature of biomaterials, but points to some of the more significant literature that reflect the changing emphasis on the character of biomaterials.

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After more than fifty years of use, and perhaps abuse, but certainly with a great deal of uncertainty about the correct meaning and the acceptable boundaries to the scope of the word, it is time to reassess where we stand with this meaning. This Leading Opinion Paper addresses this important issue of what is the essential nature of a biomaterial.

Before starting on the analysis of the interpretation of this word, it is necessary to propose a few ground rules. First, we have to accept that there is no final arbiter to the meaning of any word; no one can prevent anyone using words to mean what they wish. However, it is by strong arguments, in this case scientific arguments, that the best usage of words can be proposed such that it is in (almost) everyone's own interest to follow the recommended definition or usage. Secondly, some words which have no rational basis whatsoever become part of everyday language so rapidly, even if so illogically, that it is impossible to reverse the process and their common use has to be accepted, or perhaps, accommodated. Nanomaterial is one such word, where I have argued that it should not exist, but accept that it does through common usage and have to recognise its existence [1]. The discussion about nanomaterial provides a hint of the analysis of a biomaterial that follows, since a prefix which is an indicator of scale cannot specify the integer that follows (in this case a material) unless that integer can be qualified by that scale. In other words, it is very clear what a nanometre is because nano-means 10^{-9} and a metre is a measure of length. In the case of nanomaterial, what is it about the material that is 10^{-9}. Is it the dimension of a crystal within the material, or of a grain boundary, a domain, or a molecule, or is it a parameter of a surface feature of the sample, or perhaps of the resistivity or thermal conductivity of the material. Clearly this is nonsense, but one has to accept that nanomaterials are here to stay, with even some journal titles containing the word.

Thirdly, we also have to accept that different disciplines can use the same word with entirely different meanings, and with no confusion. An orthopaedic surgeon can examine a dislocation in a very different context to that witnessed by an electron microscopist studying a deformed metal crystal. This also occurs in everyday language and we are used to it. However, because so many of our difficulties arise with these hybrid creations that contain a common word and a potentially confusing prefix, the usage can get too close for comfort. A large automotive manufacturer now has a Biomaterials Department that is responsible for new naturally derived materials and fuels [2], for example, and paper has been described as a 'forest biomaterial' [3].

2. Early consensuses

There are two issues at stake with the meaning of a biomaterial. The first, as alluded to above, concerns the direction in which the prefix 'bio-' is pointing; are we taking out of life or putting into life. The second, which has become an even bigger point, concerns the concept of what is a material.

Although there had been several attempts to define biomaterials and the scope of biomaterials science before, it was not until a Consensus Conference on Definitions in Biomaterials Science, in 1987, of the European Society for Biomaterials [4], derived a considered and debated definition, that some consistency was achieved. This determined that a biomaterial was '*a non viable material used in a medical device, intended to interact with biological systems*.' This matter was debated at a further conference a few years later, in which reference to non viability was deleted [5], and the situation was later discussed by the current author in a contextual dictionary of biomaterials science published in1999 [6]. The preferred definition at that time was '*a material intended to interface with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body*'. It was noted that some other dictionaries took the opposite view on the significance of 'bio'; for example, Larousse Science defines a biomaterial as '*a solid material which occurs in and is made by living organisms, such as chitin, fibrin or bone*' [7].

We must recognise here that the preferred 1999 definition given above implies that the scope of biomaterials is still solely within the domain of health care (rather than energy, foodstuffs, general chemicals, etc.). This would, perhaps, have been slightly easier to sustain if the word was 'biomedical material'. However, just as the more logical but longer term 'nanostructured material' has had to give way to 'nanomaterial', common usage based upon either laziness or conciseness has determined that 'biomaterial' is preferred to 'biomedical material'. We also note that the definition emphasizes that the material has to interface with tissues when performing its function – the power supply and microelectronic components within a hermetically sealed pacemaker do not qualify as biomaterials. The remainder of this Opinion is predicated on the correctness of this position that biomaterials are solely associated with the health care domain and has to have an interface with tissues or tissue components.

3. The evolution of materials science and health technology

It is sensible to consider today's optimal meaning of 'biomaterial' from two different perspectives, the first being concerned with the evolution of materials science and the wide range of materials options that have opened up during the last decade or so, and the second being the evolution of heath care technologies.

Dealing first with materials science, the classical view of a material has been '*a substance of which things are made*'. Materials scientists were taught that there were three primary types of material, *metallic*, being based on the metallic bond, *ceramic*, based on ionic bonds and *polymeric*, based on covalent bonds. In addition there were hybrids, which could either be entirely synthetic, usually referred to as composites which typically would be combinations of ceramics and polymers, or the natural equivalents of these composites, including bone, wood, and ivory. Obviously each of these categories contained many subdivisions. The metallic materials included pure metals and alloys, ceramics included glasses, glass–ceramics and carbons, the polymers included thermosets, thermoplastics, elastomers and textiles. As biomaterials science emerged, the conventional view of materials, as being tangible pieces of substances from which useful objects were made, prevailed. The stems of hip replacements were made of metals, artificial arteries were made of textiles, dentures and intraocular lenses were made of acrylic polymers; classical materials, classical technologies, classical concepts. These concepts are depicted in Fig. 1 for some common devices in the cardiovascular area.

However, these boundaries between material classes have now been eroded; those substances derived from clear, chemically defined primary interatomic and intermolecular bonds are being replaced by those of greater structural complexity that arise from quite different concepts, including those of nanotechnology and self assembly processes inspired by nature. Indeed it is one of the fundamental tenants that is driving nanoscience and nanotechnology that is at the heart of the revolution in materials science (or materials chemistry as it is so often called now), and that is the replacement of top down manufacturing by bottom up synthesis. With hindsight it is obvious that we thought of materials as being substances of which things were made as long as and simply because, we visibly saw the objects being made by classical manufacturing or engineering processes.

Let us consider a few of the constraints that would exist if we retained the concept that a material is a substance of which things

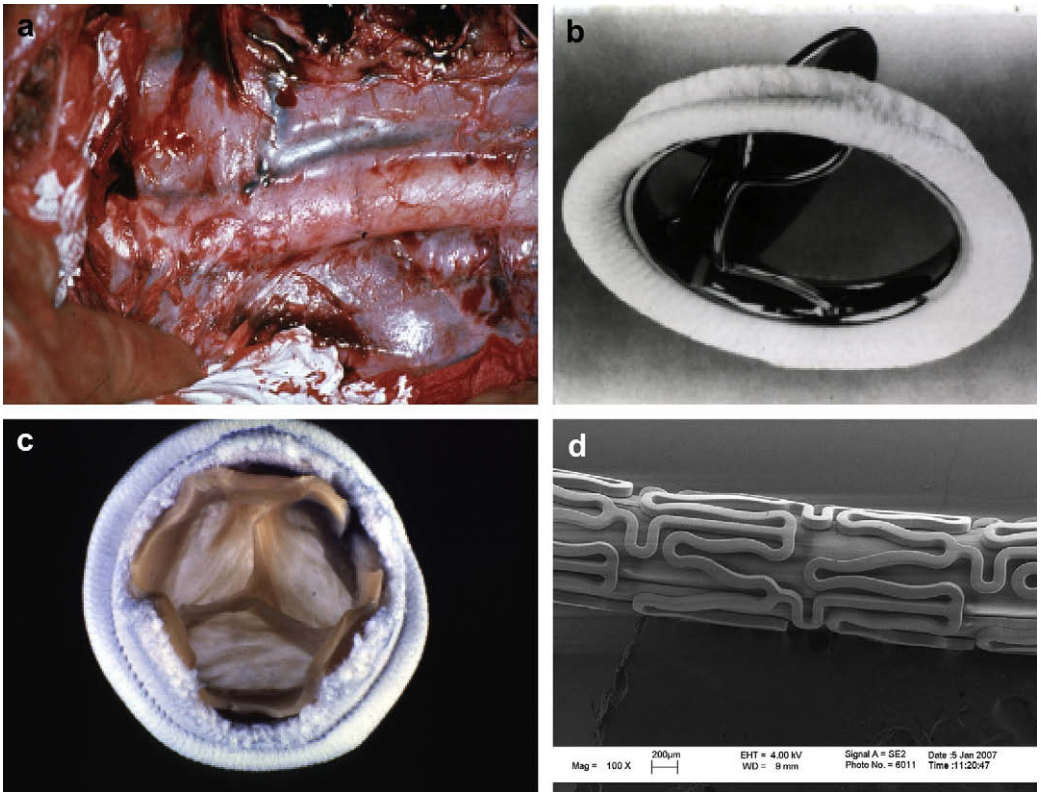

Fig. 1. Classical materials, classical technologies. (a) Vascular graft; made from conventional textiles (polyethylene terephthalate) or microporous polymers (polytetrafluoroethylene), produced by standard textile or polymer processing techniques. (b) Mechanical heart valve; made from an alloy such as one based on titanium or cobalt-chromium, a carbon such as pyrolytic carbon, and a sewing ring made of a textile such as polyethylene terephthalate, produced by standard metal forming processes such as machining and electrochemical milling, chemical vapour deposition of carbon, and textile fabrication processes. (c) Bioprosthetic heart valve; made from natural porcine aortic valve or pericardium, with polymer (e.g. acetyl copolymer) or metal (e.g. Elgiloy) frame and sewing ring (as in (b) above), produced by standard materials processing techniques for the frame, and sequences of cutting, sewing and chemical treatment of the animal tissue. (d) Intravascular stent; made from either a self expanding, shape memory alloy such as nickel–titanium or a plastically deformable alloy such as stainless steel, sometimes coated with a drug-loaded polymer such as a paclitaxel or sirolimus loaded styrene–isobutylene–styrene triblock copolymer or polyethylene-co-vinyl acetate/poly *n*-butyl methacrylate copolymer, typically manufactured by laser cutting and polymer coating techniques.

are made. The first is that a material has to be a solid; in classical usage we do not make things of liquids and gases. The second is that, if something is made from this substance, we should be able to see it, or hold it. Thirdly, there is an implicit assumption here that the things which are made will be inanimate, the equivalent of being non viable in the first of the biomaterial definitions above. All of these positions now have to be challenged.

Now consider the constraints of being used in health care with a specific interface with living systems. The physical manifestations of implantable devices obviously fit into this concept but there are many situations where this is not so easy to see and where, at the very least, some lateral thinking is required in order to make the connection. Does a substance used totally *ex vivo* within regenerative medicine qualify as a biomaterial, including a non-viral vector used to effect gene transfer to cells within a bioreactor? Does a material used *ex vivo* in a diagnostic role qualify? And what about an antibacterial substance that is used to minimize methicillin resistant *Staphylococcus aureus* (MRSA) infections on ancillary clinical equipment? One thing is for sure; the concept of a biomaterial as a substance that is useful for making objects for health care applications where that use is predicted on directly interfacing with the tissues of a patient, is outdated and in need of reform.

4. Boundaries for the contemporary usage of biomaterials

Before we go down a route which determines that a biomaterial is anything one wishes it to be, it would be useful to set out some clear boundaries determined by contemporary usage around the year 2010. We can first discuss the inanimate/non viable issue and then move onto biological activity.

4.1. Viable and non viable concepts

I think it reasonable to state, unequivocally, that normal human tissues or organs do not constitute biomaterials. A normal bone in a living person is not a biomaterial, nor is an artery, an eye or a tooth. The same would apply to any tissues of living animals. Nor do I think it appropriate to get around this clear demarcation by using multiple nouns, as in the forest biomaterials example quoted before.

We now come to a crucial issue. What happens if we transplant tissue from one part of a patient to another part, as in a skin or bone graft, or if we transplant tissue to a patient from a donor, be that a living or dead donor, either human or animal. It would make sense to consider any tissue or organ that is not manipulated in any way during the transplantation procedure other than to ensure the graft survival (for example by adjusting temperature) as being a living tissue or organ and not a biomaterial. If, however, that tissue or organ is manipulated in order to change its character or to modify the anticipated response from the recipient, it is equally reasonable to consider that as a biomaterial. If the tissue was bovine pericardium or an anatomical porcine aortic valve, and it was treated with some chemical(s) to render it sterile, non-immunogenic and acellular, this would qualify as a biomaterial under the most general of the above concepts, being a non viable material

that interfaces with the tissues of the patient in order to restore control over blood flow. What happens, however, if that acellular valve is now treated with a process that allows it to be re-inhabited by the recipient's own cells, such that it is a 'living' valve? This tissue should also qualify as a biomaterial since it has been engineered in order to fulfill its intended function. Naturally there may be some dispute about the degree of manipulation that separates the living transplant or graft from the latter example, which I believe it would be correct to call an engineered organ or graft, but this demarcation line will have to evolve. There has already been discussion around this point within the regulatory procedures that separate tissue engineering products from implantable devices [8].

4.2. Tissue engineering scaffolds

This discussion may be now extended to tissue engineering itself. For the avoidance of doubt, I now define tissue engineering as '*the creation (or formation) of new tissue for the therapeutic reconstruction of the human body, by the deliberate and controlled stimulation of selected target cells through a systematic combination of molecular and mechanical signals*'. There is no mention of a biomaterial in this definition, and indeed it is widely recognised that tissue engineering does not have to involve a conventional biomaterial at all. If we consider the classical tissue engineering paradigm [9], however, we should note that a material, in the form of a scaffold or matrix, is

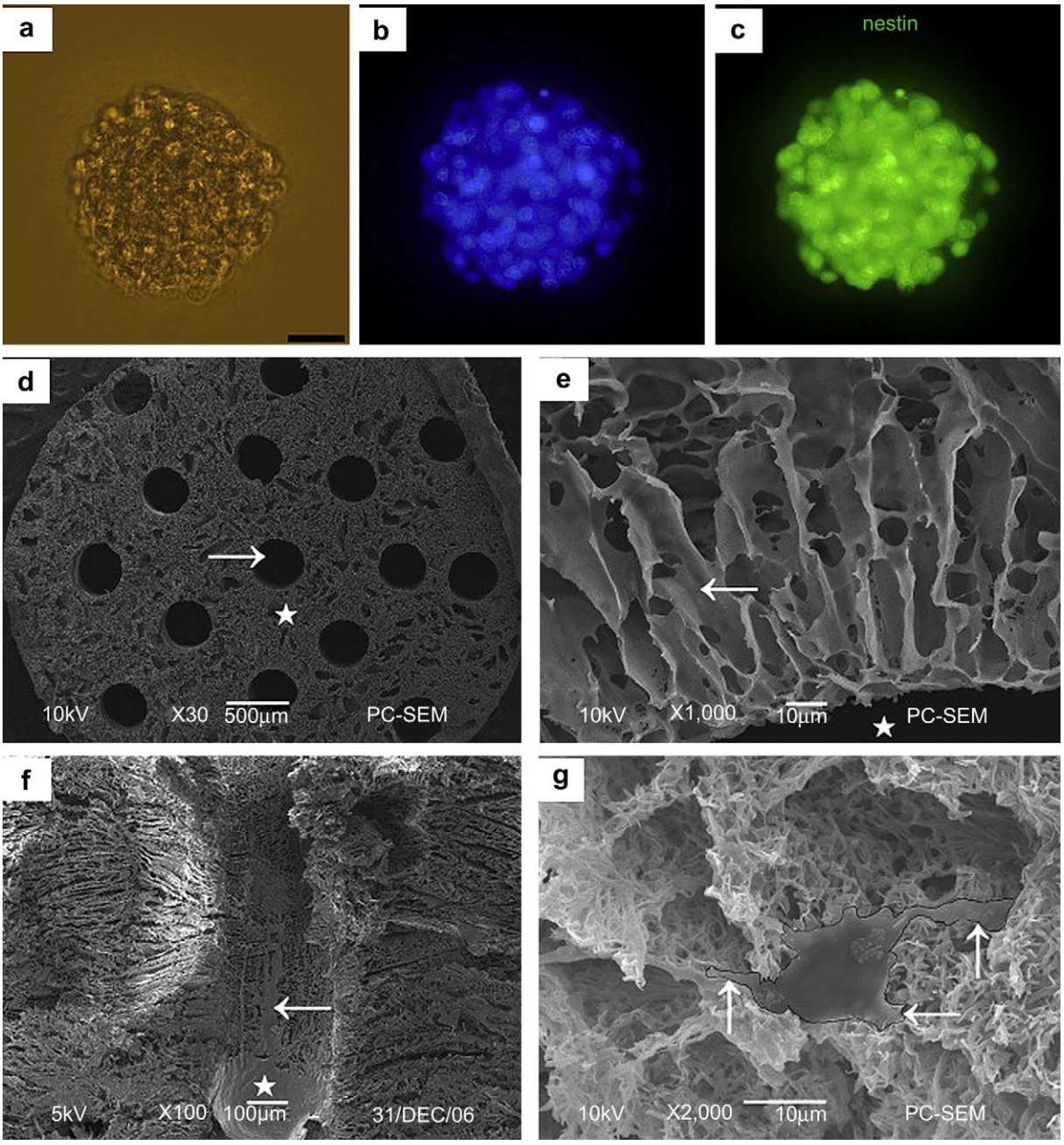

Fig. 2. An example of cellular infiltration, in the form of neurospheres, into a porous PLGA scaffold, taken from Xi Xiong et al. [10], courtesy of Elsevier. (a) A neurosphere was visualized under light microscope. (b) Nuclei in the neurosphere were labeled by Hoechst-33324. (c) Cell bodies were stained with antibodies against nestin, (d) SEM of a transverse section of PLGA scaffold shows 16 tubes (arrow). There are numerous pores with variable diameters (asterisk) between tubes. (e) Longitudinal section of PLGA was imaged under a high magnification of SEM. Arrow points to the radial channel that extends from the scaffold tube (asterisk). (f) A neurosphere (asterisk) is attached to the wall of PLGA tube. Some cells migrate out of the neurosphere (arrow). (g) In the PLGA scaffold, a cell extends processes (arrow) from the cell body. Scale bar in (a) = 20 μm in (a–c).

usually used to provide form or shape to the tissue engineered construct that develops during this process, and to facilitate the delivery of those molecular and mechanical signals. Nobody should have any difficulty with the notion that a porous polymeric scaffold or a hydrogel matrix is encompassed by the concept of a biomaterial. But what should we call the composite of scaffold and cells seeded within it. Furthermore, if, during the *ex vivo* process, within a bioreactor, that scaffold degrades and is replaced by the regenerated tissue, is the result a biomaterial? For example, Fig. 2 shows the development of a composite structure involving neurospheres and a degradable polyglycolic-lactic acid scaffold [10]. On one side of this discussion is the potentially uncomfortable concept of a process that starts with a biomaterial and a suspension of cells and which ends up, after stimulation by added molecules and applied stresses, as a new viable biomaterial. On the other hand, what is different about this regenerated tissue and the repopulated xenogeneic or allogeneic graft. There is none; they are both engineered tissues, which must be synonymous with a biomaterial. Obviously there may be some difficulties with the separation of cell therapies from tissue engineering strategies but these will be resolved. In the majority of cases where autologous cells are used, for example in autologous chondrocytes implantation, not only is there significant manipulation (i.e. engineering) of the cells but also their insertion into the patient is often assisted by some construct.

We may take this argument one step further. In recent years, within regenerative medicine, we have seen the emergence of the technology of cell sheet engineering [11]. This involves culturing cells, for example cardiomyocytes, within a system that utilises a thermoresponsive polymer as the substrate, as depicted in Fig. 3. The cells can be allowed to grow to confluence and form a two dimensional sheet on the substrate. By changing the temperature, the surface energy of the polymer substrate markedly changes and the sheet of cells lifts off and can be harvested and used therapeutically, for example in the treatment of the myocardium following an infarct [12], on the periodontium [13] or on the surface of the eye [14]. The question naturally arises as to whether the thermoresponsive polymer, the characteristics of which control the formation of the cell sheet, is to be considered as a biomaterial, even though it is discarded once the cell sheet has lifted off. We come to that discussion a little later, but here we have to consider whether the cell sheet is a biomaterial. The prevailing argument has to be that this sheet is an engineered tissue and as such is a biomaterial.

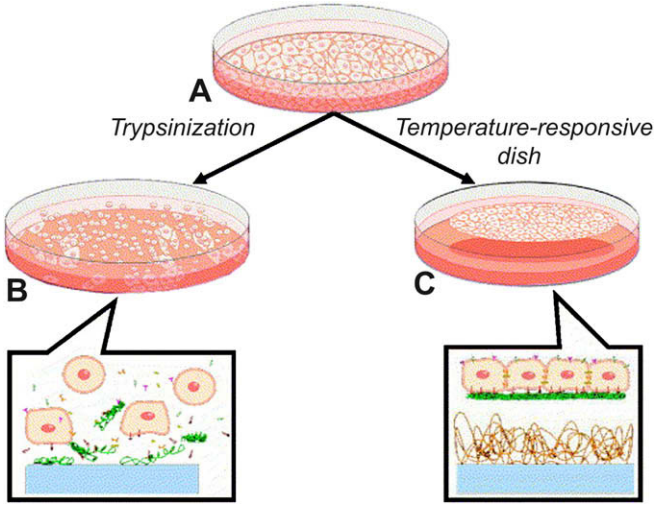

Fig. 3. Temperature-responsive culture dishes. (A) During cell culture, cells deposit extracellular matrix (ECM) molecules and form cell-to-cell junctions. (B) With typical proteolytic harvest by trypsinization, both ECM and cell-to-cell junction proteins are degraded for cell recovery. (C) In contrast, cells harvested from temperature-responsive dishes are recovered as intact sheets along with their deposited ECM, by simple temperature reduction. Reproduced, with permission of Elsevier from Yang et al. [11].

This is consistent with the position of Kasza et al. [15] that a cell may be considered a material. Cells have many properties that are analogous to classical materials, for example viscoelasticity, and it may be considered that they are highly advanced stimuli-responsive polymeric systems. Discussions of such analogies have focused on the character and role of the cytoskeleton, Smith et al. [16] describing this as an active polymer-based scaffold. Trepat et al. [17] state that 'the cytoskeleton of the adherent living cell is the most complex form of soft matter that exists in nature', while Stamenovic describes the rheological behaviour of mammalian cells in terms of a soft glass model [18], as do Kollmannsberger and Fabry [19]. Both Ingber [20] and Bao and Suresh [21] make similar types of arguments. It is clearly a very big step to say that any cell is a biomaterial, but these types of discussion, emerging during the last few years, support the view that a collection of engineered cells constitutes a biomaterial.

4.3. Pharmacological activity

Now let us come to the question of whether a biomaterial can have any form of biological activity, and if so, where are the boundaries with pharmacological activity. We have to recognise here that there are enormous implications, from regulatory, economic and political perspectives, of the demarcation between medicinal products and medical devices and I do not wish to enter that territory now. This discussion is concerned with the demarcation between a biomaterial, of which a medical device may be made, for example, and the biologically active constituent of a pharmaceutical product. It may well be, as argued recently by myself [22], that the best performance of the vast majority of implantable devices is achieved when the biomaterials used in their construction are chemically and biologically inert; no biological, let alone pharmacological, activity should be sought in these devices. However, at least in theory, there are some exceptions, either with the intention of promoting some biological activity such as bone regeneration, or minimising undesirable activity such as infection or blood clotting. We also recognise that some materials are used with the express intention of delivering some biologically or pharmacologically active agent to the patient; the concept of drug delivery devices is of course well known [23]. We may use essentially the same arguments here as with tissues or organs, this argument being centred on the qualification of engineering a drug or a tissue.

There can be no dispute that a medical device that delivers a drug to a patient via a mechanism in which the drug, for example morphine or insulin, in unmodified form, is placed within a reservoir and is then infused into the patient by physico-chemical means (as in an osmotic pump), involves classical biomaterials in the construction of the device and a separate pharmaceutical agent, and there is no confusion between them [24]. Similarly, there is no confusion between the biomaterial and the drug when we are using a drug depot where the delivery is controlled by a combination of diffusion, erosion and degradation [25].

The situation is not quite so straightforward when we consider a material – drug combination that is intended to enhance the performance or quality of a medical device. Two such applications may be considered here, both of which expose the benefits and dangers of such combinations.

The first is the bone morphogenetic protein (BMP)-supplemented collagen used to enhance bone regeneration in spinal fusion. It is well known that spinal fusion, especially when involving two vertebrae in the lumbar spine, can be very effective in resolving chronic pain

associated with a degenerated intervertebral disc. Conventional devices that effect such fusion involve, for example, a titanium or PEEK cage incorporating autogenous bone. The now well-known ability of some of the BMP family, especially BMP-2 and BMP-7, to accelerate bone regeneration, has led to the use of such active components, either in difficult cases or indeed as a first approach, in spinal surgery, typically with a collagen sponge soaked in a recombinant BMP-2 solution placed inside one of the cages [26]. For the purposes of this Leading Opinion Paper, the main issue is whether a biomaterial is involved here (apart from the obvious cage material), but the answer is not a simple one, and we must look more carefully at what is going on. The first regulatory approval in the USA for these products made a clear demarcation between the lumbar spine and elsewhere in the spinal column [27]. Nevertheless, it transpired that the product was being used, off-label, in the cervical spine, and problems soon emerged. In the cervical spine, the BMP-2 was released, but the proximity of the airways lead to a difficulty in breathing as the drug had a pronounced inflammatory potential outside of bone [28]. The real issue was that soaking the collagen sponge in BMP-2 solution pre-operatively led to a situation where there was no control over, and probably no knowledge of, the concentration of this very active protein, either in the product or in the surrounding tissues. All of this suggests that it is not tenable to consider such products as simple combinations of materials and drugs. The pharmacokinetics and pharmacodynamics of the active component in such products cannot be assumed to be analogous with those of the active component itself. This, in my opinion, is equivalent to saying that, by incorporation within the collagen, the BMP-2 has been re-engineered. It follows that the combination of collagen and BMP-2 has to be considered as a biomaterial in its own right.

The second example is that of the drug eluting intravascular stent. The issues here are fairly well known, and indeed provide a good commentary on the biocompatibility of implantable medical devices [22]. Balloon angioplasty is a good technique, saving lives but leading to early re-stenosis [29]. Intravascular stents provide an effective short term solution [30], but do not fully prevent re-stenosis [31]. The best remedy is to use a drug eluting stent, wherein a highly active anti-proliferative drug such as paclitaxel is incorporated into a polymer coating on the stent, which is intended to minimise the hyperplasia observed within the smooth muscle cells and endothelium [32]. The problem, again, is the determination of the optimal level of the drug, and the optimal release rate. It is perhaps of no surprise that these stents have reduced the level of re-stenosis clinically [33], but have also resulted in higher levels of the far more damaging thrombo-embolic events [34]. The result is that some studies are now showing that the overall level of success and satisfaction with angioplasty coupled to drug eluting stents is less than that associated with the coronary artery by-pass surgical techniques that it was intended to replace. One of the unknown factors here has been the uncertainty over the activity of these powerful drugs when used in combination with polymeric coatings, or indeed, when coupled in any way to classical biomaterials surfaces. Again it would appear that treating materials and drugs as quite separate entities does not serve the patient well, and I suggest that this should be remedied by considering the totality of the classical material with an engineered drug as a new biomaterial.

Taking this subject in a somewhat different direction, new entities may also arise from the coupling of drugs to specific carriers. Already the coupling of some anticancer drugs to antibodies, serum proteins or synthetic polymers through a cleavable linker has been achieved, appearing to provide a method for improving the therapeutic index of cytotoxic agents. Drug–antibody conjugates using highly potent drugs such as calicheamicin or maytansins have entered clinical trials. Drug conjugates have been prepared with *N*-(2-hydroxypropyl) methacrylamide (HPMA) copolymer or polyethylene glycol conjugated with doxorubicin or paclitaxel, as has an albumin-binding doxorubicin conjugate [35]. As a further example, we see in Fig. 4 a schematic representation of the preparation of a degradable prodrug-based hydrogel, with encapsulation of a hydrophobic drug in the gel, and subsequent enzyme-triggered single (path-1) and multiple (path-2) drug-delivery [36]. Here enzyme catalysis is used to disassemble supramolecular hydrogels to control the release of encapsulated drugs and provides an opportunity to design a wide range of enzyme-specific low-molecular-weight hydrogel. The prodrugs self assemble to form hydrogels that subsequently encapsulate a second drug. Upon enzyme-triggered degradation, the hydrogel releases single or multiple drugs.

These prodrugs hold great promise, where a highly active but also highly toxic drug can be conjugated to an entity which protects against severe cytotoxicity and also facilitates direct targeting, the drug being released when, and only when, it is cleaved from its carrier at the target site. These conjugates are regarded as nanoscale entities, which lead to the general discussion, to be considered below, of how nanostructured objects fit into the grey areas between substances and materials, but it makes sense here to

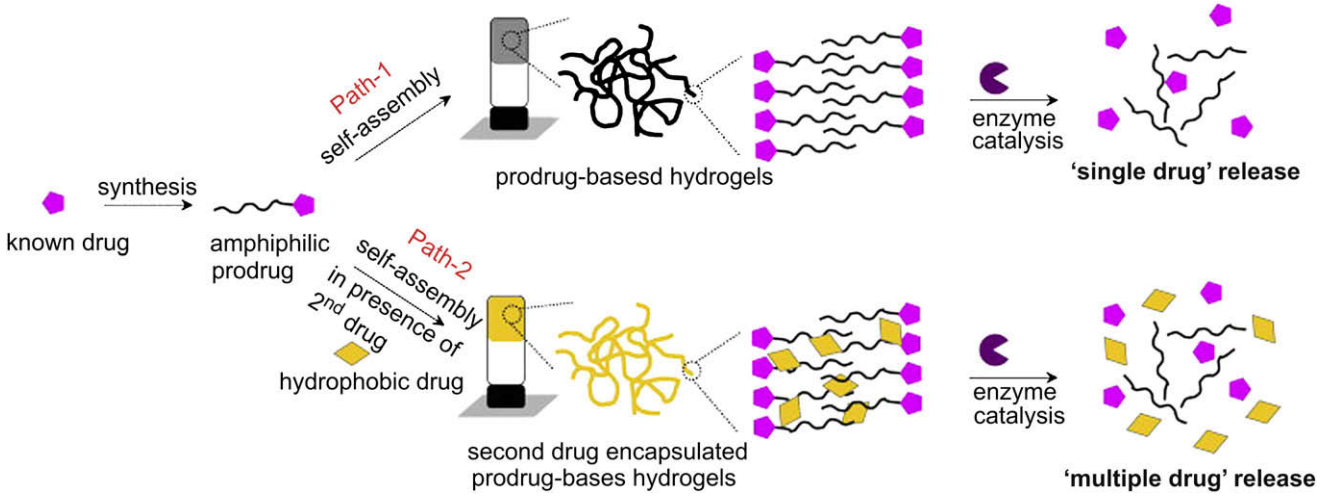

Fig. 4. Schematic representation of the preparation of degradable prodrug-based hydrogels, encapsulation of hydrophobic drug in the gel, and subsequent enzyme-triggered single (path-1) and multiple (path-2) drug-delivery. Reproduced from Vemula et al. [36] with permission of Elsevier.

consider these prodrugs as biomaterials. As with the discussion of engineered cells as biomaterials, there may be some uncertainty over the boundary between conventional pharmaceuticals and engineered drugs, such as prodrugs, and it may take time for clear distinctions to emerge.

4.4. Gene therapy

If we accept the argument that the engineering of a pharmaceutical molecule such that it is coupled to a different non-pharmaceutical molecule, which facilitates its accurate, controlled, functional delivery to a target site results in the formation of a new class of biomaterial, then we should consider whether the same argument applies to the products of gene therapy. Gene therapy has the potential to treat a disease by replacing, altering, or supplementing a gene that is either absent or abnormal, a condition that is responsible for that disease. The question arises as to how the desired gene(s) is targeted to the desired cell(s) in a safe and efficient manner, and the similarity with the precise delivery of a potent drug is clear. Developments of this technology over the last couple of decades have led to the dual approach of viral and synthetic vectors for the gene delivery [37].

It is logical to deal with the latter of these vectors first in this essay. An overview of the design of non-viral vectors was published by De Laporte et al. in 2006, a schematic of the modular system being shown in Fig. 5 [38]. Two major classes of non-degradable, non-viral systems emerged first, based on cationic lipids and cationic polymers, including poly(ethylenimine), poly(2-dimethylaminoethyl methacrylate) and poly-L-lysine [39,40]. These are analogous to the molecules used in prodrugs since they may form complexes with DNA, typically called polyplexes, as a 'polymer–DNA ion complex' and are able to introduce the DNA into target cells [41]. Developments are being presented on a rapid basis, including degradable systems such as water-soluble cationic polymers and degradable polymeric micro- and nanoparticles [42], in which DNA is embedded in a degradable polymer matrix, and also with chitosan [43] and calcium phosphates (shown in Fig. 6) [44]. There is also much interest in the delivery of siRNA as well as DNA in these systems [45]. I believe there is little argument that these systems, in which DNA or siRNA is complexed with molecules or nanoparticles of non-pharmaceutical character, qualify for the descriptor 'biomaterial'.

It is well-known, of course, that these so-called non-viral vectors have been introduced because of concerns over the viral vectors, for which safety issues still exist, even though they are far more efficient than the non-viral vectors at this stage [46]. The relevant question is whether these viral vectors are also biomaterials. In line with arguments in 4.1 there is no doubt that a virus is not a biomaterial. But I have argued above that an engineered tissue and that an engineered drug should be considered as biomaterials. It is logical that if a non-viral vector is a biomaterial then a viral vector should also be considered as such if the viral component can be considered as an engineered virus. This is indeed the case. Consider the statements made by Schaffer et al. [47] in an excellent review of the status of viral vectors. Viruses have evolved in nature to efficiently deliver their own genetic payload to specific cells. However, standard molecular biology methods can be employed to swap therapeutic transgenes in place of some or all of the viral genes. Several gene delivery barriers restrict the efficiency of this approach, including immunity and cell-surface binding. Although

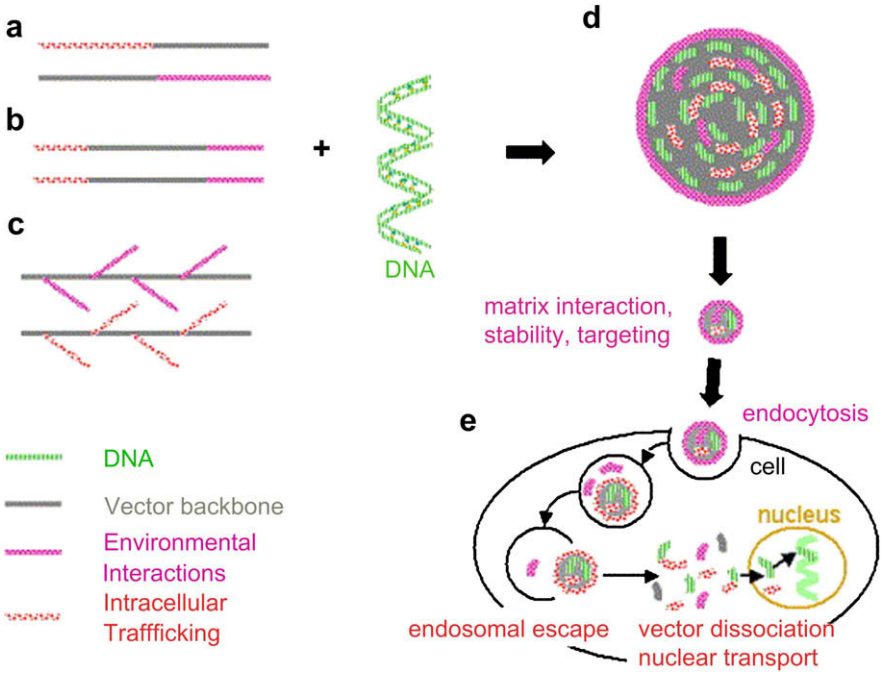

Fig. 5. The modular design of non-viral vectors, a schematic reproduced from De Laporte et al. [38], with permission of Elsevier. Modules associated with vector design are: vector backbone (grey), functional groups for regulating environmental interactions (purple), and intracellular trafficking (red). The vector backbone, typically containing polymers, lipids, or polysaccharides, is designed for DNA binding and complexation. The function of the vector backbone is augmented by the attachment of groups that address the extracellular and intracellular barriers. The environmental functional groups can serve to limit interactions with serum components, promote specific cell binding or tissue targeting, or facilitate interactions with the extracellular matrix or biomaterials. The intracellular functional groups aim to enhance nuclear accumulation of the DNA either by facilitating endosomal escape, movement along the cytoskeleton, or nuclear pore trafficking. The individual modules can be assembled in different ways (a–c) for complexation with DNA (green), which may affect the structure and function of the resulting non-viral vector. (d) Schematic illustrating the distribution of the modules and DNA throughout the vector cross section, with the desired organization of functional groups regulating the environmental interactions presented primarily on the exterior and the groups for intracellular trafficking protected within the vector interior for activity following internalization. (e) Vectors are internalized by endocytosis and must subsequently escape the endosome for transport to the nucleus. Additionally, the modular components must dissociate from the DNA to allow for transcription.

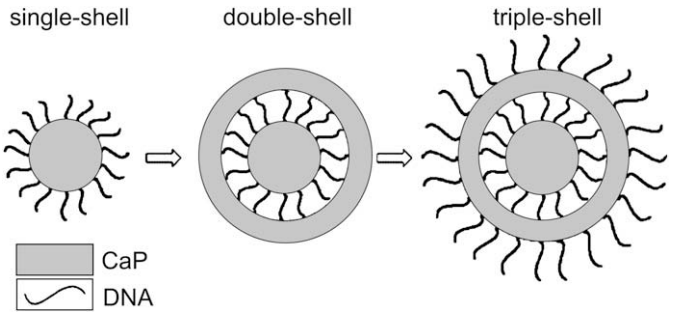

Fig. 6. Schematic representation of three types of calcium phosphate/DNA nanoparticles, reproduced from Sokolova et al. [44], with permission of Elsevier.

methods emerge for viruses to overcome such barriers over evolutionary timescales, these are not necessarily relevant to therapeutic gene delivery, and new specificities and efficiencies have to be derived by protein engineering methods. These could include, for example, engineering the viral attachment proteins with respect to the vector scaffold. Crucially, it is becoming possible to engineer single viral proteins with defined functions to create complex vector systems that offer user-defined gene delivery properties. I believe, therefore, that the case is established to consider all engineered vectors for gene delivery as biomaterials. This argument is strengthened by the fact that optimisation of gene delivery may well be achieved by non-viral modifications to viral vectors, for example by surface coating [48,49].

4.5. Diagnostic and imaging systems

Diagnostic and imaging procedures are immensely important in all areas of clinical medicine, but they take in special significance in oncology, where early stage diagnosis is crucial in determining outcomes of therapy. The molecular targeting of cancer cells and the ability to capture signals from the targeted cells with appropriate sensitivity and accuracy are clearly important issues. Conventional techniques using fluorescent organic dyes have significant limitations and new, superior techniques are emerging. At the same time, the emphasis has been moving away from simple soluble dyes, which could never be regarded as 'materials', towards more complex functional agents, and these may well be considered as biomaterials.

There are several important examples here, the first involves quantum dots [50]. These are fluorescent particles of semiconducting materials, typically of size range 2–6 nm. They have several advantages over more conventional fluorophores, with broad adsorption spectra and narrow emission spectra. They can be engineered to emit light at precise wavelengths and are, therefore suitable for multiple labelling of biological molecules within cells, where several conjugation routes are available. For example, significant steps have been taken to develop quantum dot based probes for the detection of HER2 (human epidermal growth factor receptor) status in breast cancer, which should assist in the delivery of molecular-targeted therapy [51]. There has also been progress in demonstrating the potential for in vivo imaging for cancer detection, for example using quantum dots conjugated to alpha-

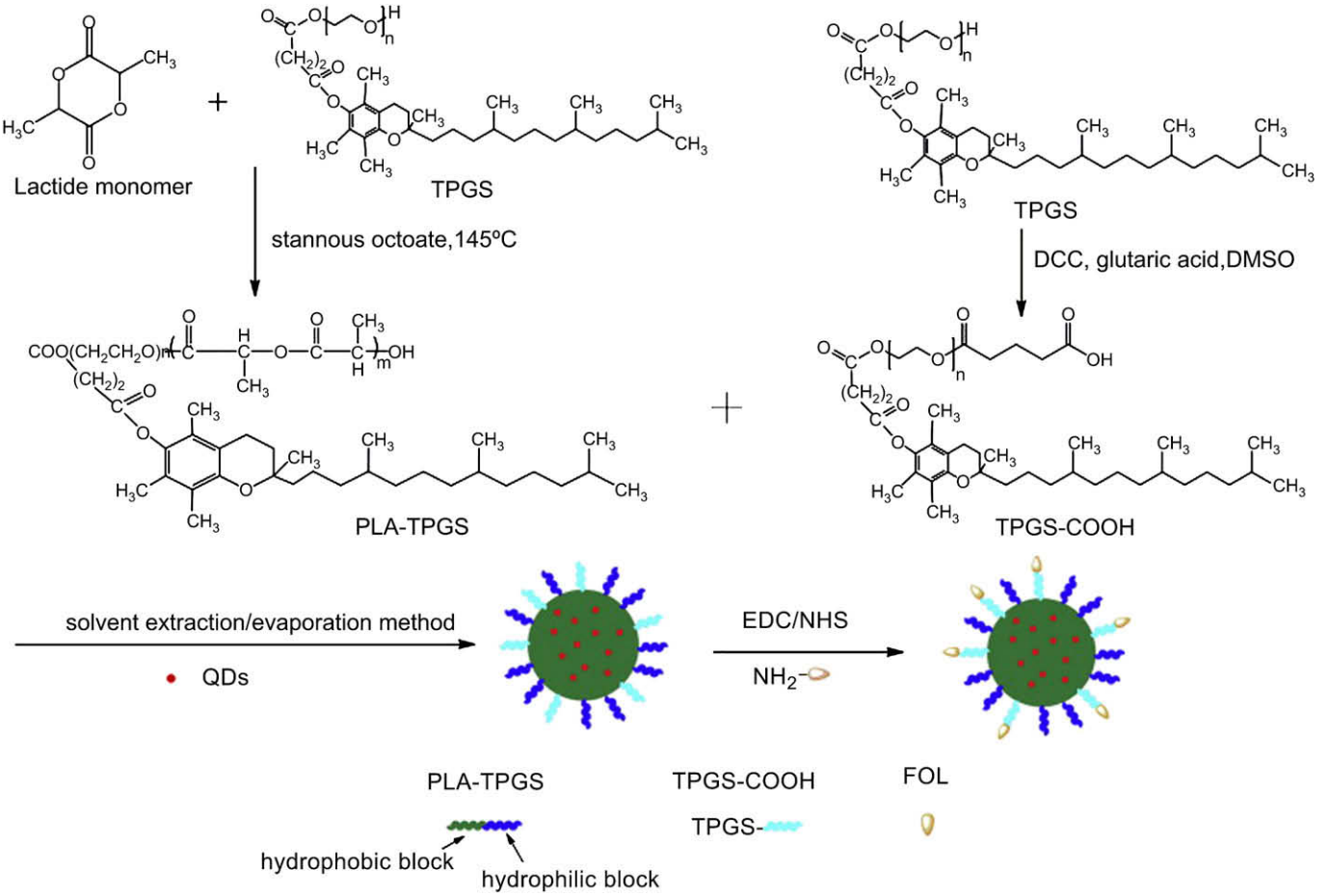

Fig. 7. Scheme for preparation of quantum dot loaded polylactide–Vitamin E TPGS copolymer and Vitamin E TPGS-COOH blend nanoparticles with folate decoration, reproduced from Pan and Feng [53] by permission of Elsevier.

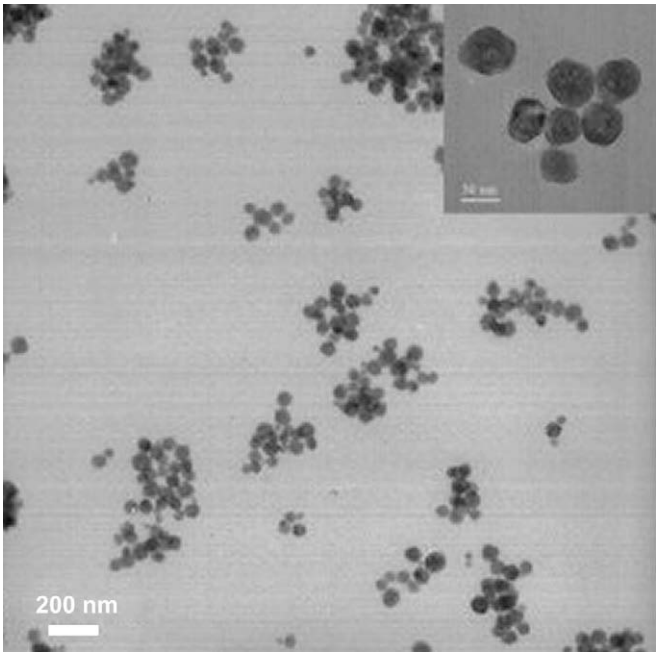

Fig. 8. Transmission electron micrograph of $NaYF_4$:Yb,Er nanoparticles coated with 25 kD polyethyleneimine used for fluorescent imaging of cells, reproduced from Chatterjee et al. [54] by permission of Elsevier.

fetoprotein monoclonal antibody for the detection of hepatocellular carcinoma [52]. Pan and Feng [53] have also shown how to prepare folate decorated, quantum dot loaded biodegradable nanoparticles for cancer diagnosis, as seen in the schematic in Fig. 7.

The second example is the upconversion phosphor nanoparticles [54]. These usually have a crystalline matrix that is doped with lanthanide ions, and it has been suggested that the rare earth based nanoparticles have lower toxicity than is associated with semiconductor based quantum dots. The co-called upconversion process is associated with the fact that such materials absorb two or more photons and discharge the added energy as emissions with higher wavelengths than the absorbed radiation. A transmission electron micrograph of these nanoparticles is shown in Fig. 8. They have already been used for in vivo imaging in small animals.

It is perhaps arguable whether a nanoparticle based fluorophore used purely in laboratory procedures for diagnosis should be considered as a biomaterial, but as these eventually become used for direct in vivo imaging, the case is much clearer.

4.6. Biosensors, MEMS, microarrays and microfluidics

In this last section that describes the boundaries between traditional biomaterials science and medical technology I have included some examples that do not fit elsewhere, principally because they are based on different but disparate scientific phenomena. Even so, it has to be admitted that they do have some

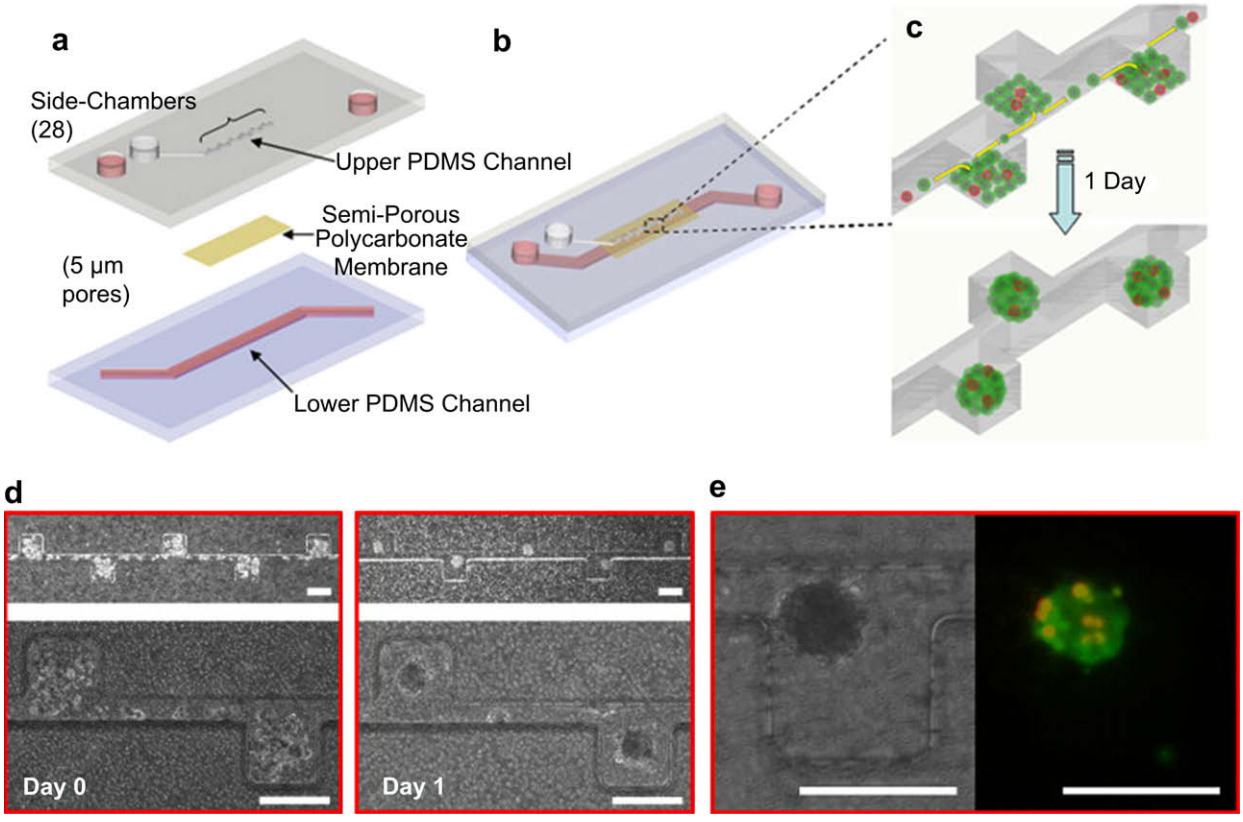

Fig. 9. Schematic illustrations of the microfluidic spheroid formation device design (a–b) and PC-3^{DsRed} co-culture spheroid formation process (c), reproduced from Hsiao et al. [55] with permission of Elsevier. The device consists of two PDMS microchannels separated by a semi-permeable polycarbonate membrane with 5 μm pores. The upper channel is a dead-end channel with 28 side-chambers to culture spheroids, and the lower channel has flow through capability for culture medium. Before seeding cells, the channel and membrane surfaces are rendered resistant to cell adhesion. The heterogeneous mixture of PC-3^{DsRed} and support cells (MC3T3-E1 and HUVEC) at 1:100 co-culture ratio are introduced into the upper channel as a confluent monolayer. The cells preferentially settle inside the side-chambers and self-aggregate to form PC-3^{DsRed} co-culture spheroids within 1 day of culture. (d) Actual time-lapse images of PC-3^{DsRed} co-culture spheroid formation within microchannel (side-chambers: 200 × 200 × 200 μm, central microchannel: 50 μm width, 200 μm height). Optical images were taken immediately after seeding and 1 day after introducing the cells. (e) Optical and fluorescent images of a PC-3^{DsRed} co-culture spheroid after 1 day of culture in the microfluidic device. Red = PC-3^{DsRed} cells, Green = Live cells. Scale bar is 200 μm.

similarities with other examples and this list is not meant to be a highly specific classification.

Let us start with microfluidic systems, which have many uses. These include the formation of 3D spheroids of cancer cells, that allow the exploration of the niche microenvironment of tumours and, potentially the development of cancer therapeutics. Hsiao et al. [55] have published work on microfluidic systems for the formation of PC-3 prostate cancer co-culture spheroids. As shown in Fig. 9, this has polydimethylsiloxane microchannels and polycarbonate semi-permeable membranes, both pre-coated with a Pluronic to control cell adhesion. A heterogeneous mixture of PC-3 cells and supportive pre-osteoblasts and human umbilical vein endothelial cells is seeded into one part of the system, separated from the culture medium. This allows the formation of uniform spheroids of metastatic prostatic cancer cells, where, in this niche microenvironment, there is high cell viability and a physiological growth behaviour. It is argued here that although this construct is not used directly in health care, the performance and beneficial characteristics of the spheroids is profoundly determined by the materials used and the interaction between them and cancer cells. I suggest that all of the engineered components here are considered as biomaterials.

This discussion moves forward to organ printing and the formation of tissue spheroids and macrotissues in general. Mironov et al. consider organ printing to be the layer-by-layer additive robotic fabrication of 3D functional living tissues and organ constructs [56]. Mironov argues, partly on the basis of the present author's statements about the inherent problems of scaffold biocompatibility [22], that tissue engineering may be better served by a solid biodegradable scaffold-free process. This position is predicated on the assumption that tissues and organs are self organising systems and that they normally undergo biological self assembly and organisation without any external influence in the form of instructive, supporting and directing templates or solid scaffolds. There is obviously some way to go before such a paradigm could be translated into a practical reality, but many steps have been taken. It might seem at first sight that if tissue engineering can be achieved by self assembly of tissue components without the need for conventional solid materials, biomaterials would have no further role. In line with many earlier statements in this essay, I would consider the self assembled tissue to be an engineered construct and, therefore, a biomaterial in its own right.

Much of the technology associated with tissue and cell manipulation *ex vivo* involves microwell arrays. For example, embryonic stem cells need to be manipulated very carefully if they are to be used in regenerative medicine, their differentiation being significantly affected by the microenvironmental stimuli. Moeller et al. have discussed the use of poly(ethylene glycol) microwell array

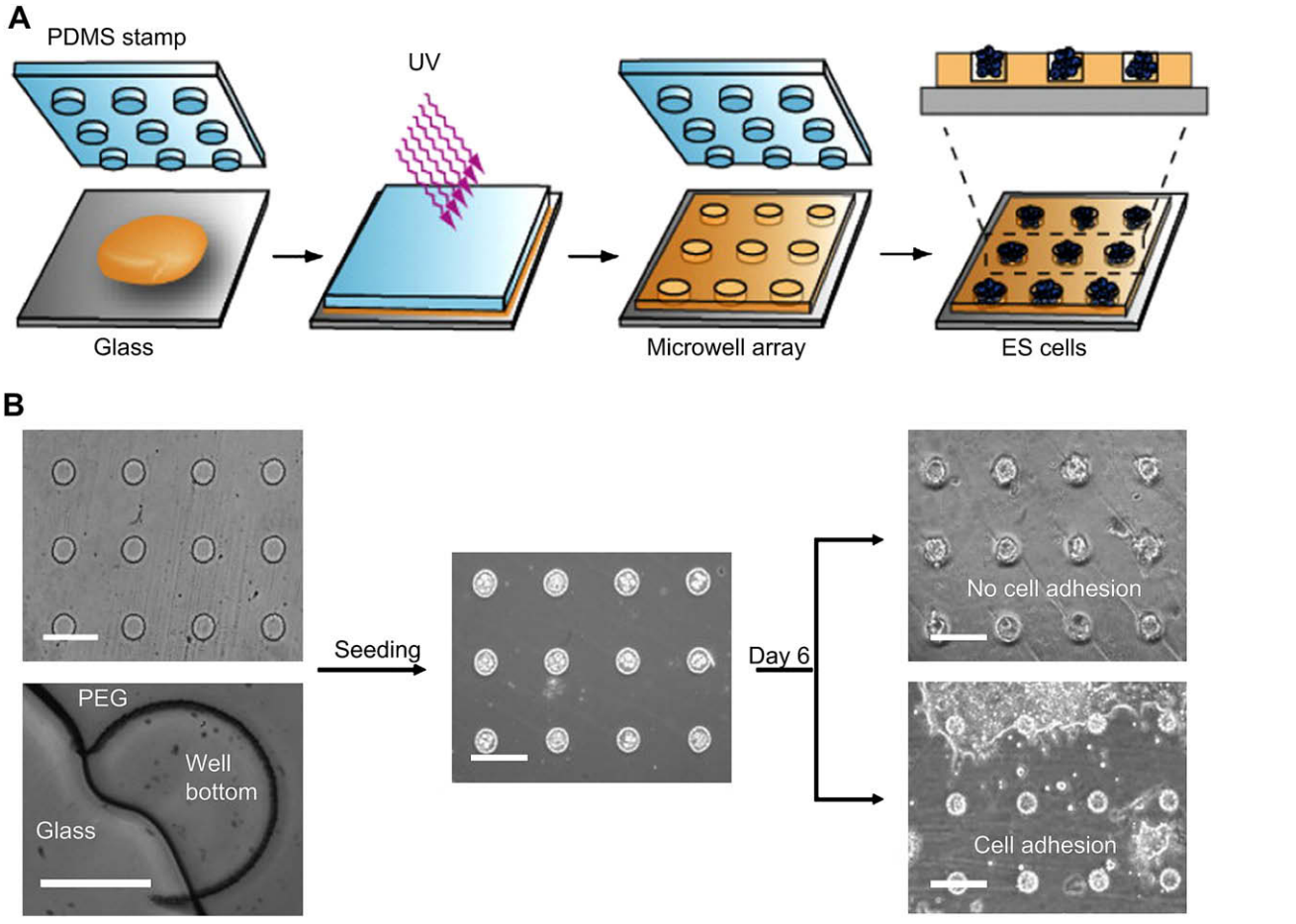

Fig. 10. Fabrication of a microwell array for EB culture, reproduced from Moeller et al. [57], with permission of Elsevier. (A) Schematic representation of the micromolding process to generate a PEG microwell array from a photocrosslinkable PEG-DA prepolymer solution (brown). PEG was molded using a PDMS stamp with protruding features and then photocrosslinked with UV light. The cross section shows a microwell array loaded with ES cells. (B) Phase contrast images show a 50 μm microwell before and after seeding. Higher magnification of a 175 μm microwell that was cut vertically shows that the entire microwell surface—including the well bottom—was made of PEG. In culture, EBs grew until they were constrained by the size of the well, yielding a homogeneous culture (upper image). In the previously developed platform, non-specific cell adhesion led to monolayer formation (lower image). All scale bars represent 100 μm.

systems for directing the formation of embryoid bodies, the structures that show the features of early embryonic development [57]. The schematic of this system in shown in Fig. 10. Although such microwells are only used transiently, they have to be considered as biomaterials in view of their profound influence on the process. Microarrays are used in many other situations, for example antibody arrays for quantitative immunophenotyping, as shown in Fig. 11 [58], and similar considerations should apply.

Electrochemical biosensor platforms have been under development for a number of years and these have led to some very exciting prospects. Wu et al. have described the formation of hairpin aptamer-based sensors for the detection of proteins, shown in the schematic of Fig. 12 [59]. Aptamers are stable single-stranded functional DNA or RNA molecules that can bind to targets with high affinity and selectivity. These have now been used for the detection of IgE with a very low detection limit. The electrochemical detection of DNA is itself important and a number of new materials platforms have been developed for this purpose. For example, as reviewed by Peng et al. [60], a series of conducting polymers, utilising several immobilisation and detection methods have been investigated, including polypyrrole – multi-wall carbon nanotubes. The interface between nanostructured materials and nanoelectronics in general has become very important, especially with relevance to medical technology. Chang et al. have described self assembled molecular magnets, involving magnetically aligned metallothionein containing Mn and Cd patterned onto silicon surfaces, with potential applications in sensing and nanostructured medical devices [61].

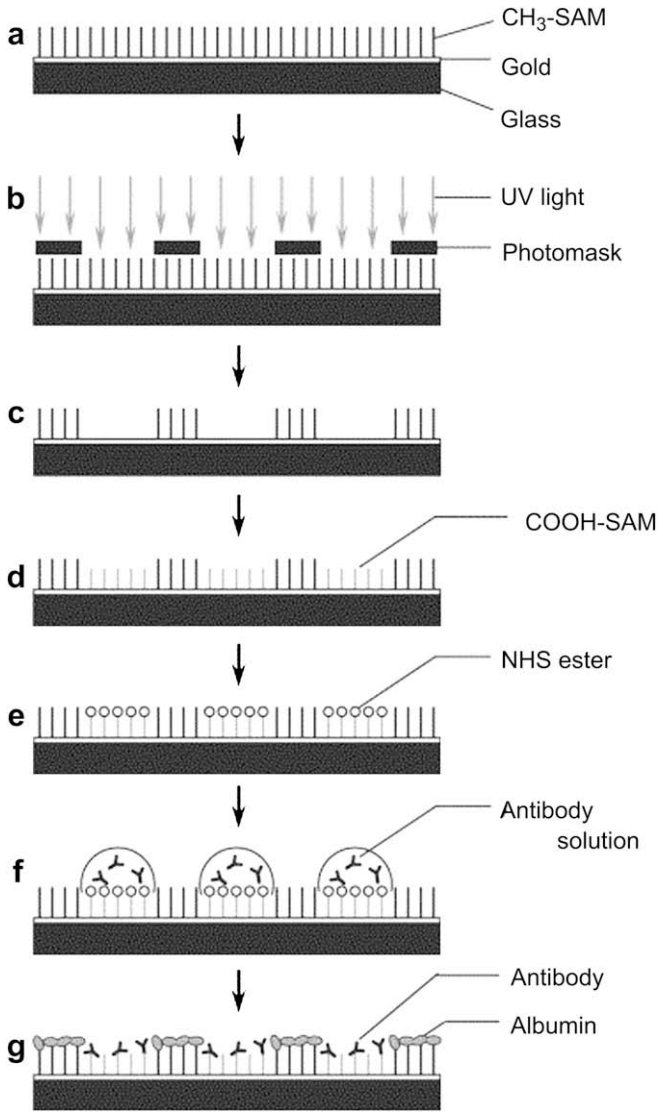

Fig. 11. Preparation of an antibody array, reproduced from Kato et al. [58], with permission of Elsevier. A methyl-terminated alkanethiol monolayer formed on a gold-evaporated glass plate (a) was irradiated with an ultraviolet light through the photomask having an array of transparent circular regions with a diameter of 1 mm (b). Photolytically-cleaved alkanethiols were removed by washing with ethanol, leaving spots exposing the gold surface (c). Then a carboxylic acid-terminated alkanethiol monolayer was formed within the spots (d), and the terminal carboxylic acid was activated with NHS and DCC (e). The solutions of antibodies and other proteins were micro-pipetted to the activated spots to allow covalent immobilization of these proteins within the spots (f). Finally, albumin was adsorbed to block non-specific cell adhesion (g). Molecular sizes are not scaled in the scheme.

5. The new biomaterials paradigm

In modifying the boundaries that control our understanding of biomaterials, we may return to the considerations of Sections 3 and 4.1.

One real barrier here is the concept of a material. We can no longer think only of the tangible, top-down manufactured, solid object. We have to encompass highly active nanoparticles, hydrogels, soluble contrast agents, self assembled biological systems, cells and viruses. The 'material' can be a single, well defined and characterised entity, such as a titanium alloy or hydroxyapatite ceramic, or it can be a virus coated with a layer of a cationic polymer, or an

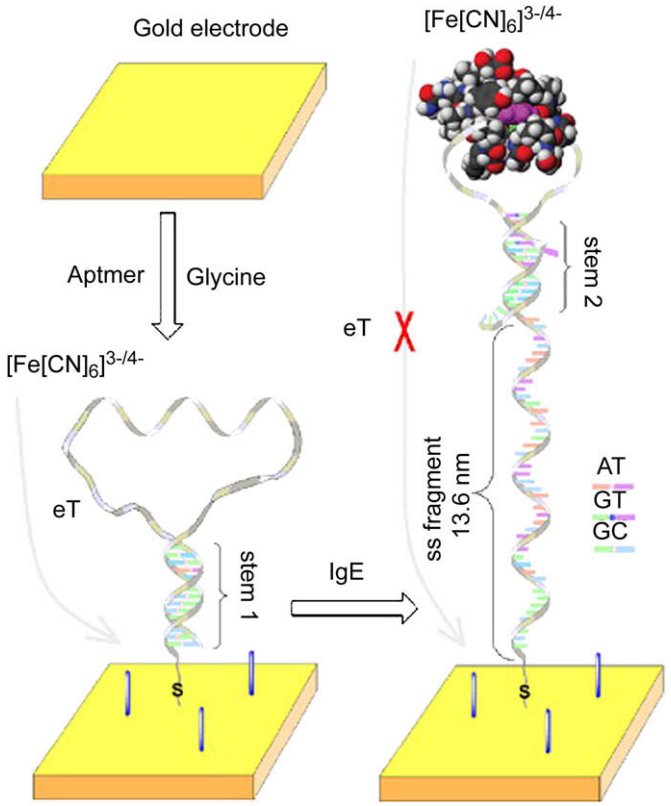

Fig. 12. Schematic representation of the construction of electrochemical aptamer-based biosensor and the principle of IgE detection, reproduced from Wu et al. [59] by permission of Elsevier. The aptamer probe, a 5′-thiolate DNA sequence, can fold into a hairpin structure and is immobilized onto a gold electrode surface. Short vertical lines denote glycine molecules used to block the bare region of gold electrode. The bases in the loop region are not shown. The target binding not only increases the dielectric constant of the bio-recognition layer but also induces the conformational change of the designed aptamer, suppressing significantly the electron transfer (eT) that triggers a current response.

engineered organ. Under these circumstances, I prefer to avoid conventional notions of materials and, instead think of biomaterials as substances or systems. In this context it is probably unhelpful to try to specify to rigorously what a substance is, and it is better to leave the concept of a substance, which may be equated to matter, simply as that which has mass and occupies space.

Starting with such an elementary concept, we are free to develop our thoughts of biomaterials in many different directions, away from the homogeneous monolith towards hybrids and composites, possibly with biomimetic hierarchical structures and multifunctional structures. It also leads us to embrace nanoscale materials without agonising about whether a collection of nanoparticles can be considered as a conventional material or where we draw the boundary between an active nanoparticle, such as a dendrimer or quantum dot, and a supramolecular assembly or crystallite.

The function of a biomaterial must be to direct the course of medical treatment, be that in diagnosis or therapy, and it must do so by specifically controlling the interactions with biological components of the patient being treated. It is tempting to believe that we will also know precisely how these interactions take place, but the truth is we do not fully understand the mechanisms of biocompatibility, and it is preferable not to insist that we always know how and why something works. To consider the interaction as being specific rather than general, or indeed completely accidental, is as far as we should go. It should be noted that directing the course of treatment through controlling the interactions with the living system can involve either promoting specific events, as in imaging procedures, or preventing specific events, as in antibacterial activity, or, as is often the case, a combination of both since positive biological activity may be compromised by cytotoxicity. Although this is a minor point, we should also take into account the fact that the technologies in which biomaterials play major roles are used in veterinary medicine as well as in humans. The intended outcomes may well be the same, for example when pet owners request therapies for their animals that are similar to those used in humans (for example fracture plates or intraocular lenses) but the details may well be quite different when considering engineered drugs and vaccines for livestock.

In all of the examples given in Section 4, the inevitable conclusion has to be that the critical factor is that the entity under discussion is engineered in some way. Provided there is no confusion over what constitutes engineering in this context (see Ref. [9]), this must control the differentiation between a normal tissue and manipulated tissues which we now consider as a biomaterial, or between a conventional pharmaceutical and an engineered drug, which is also a biomaterial, or between a virus and an engineered gene vector. These arguments are not those of pure semantics or academic musings. There are serious consequences to our understanding of the issues underlying the real nature of biomaterials, ranging from the way in which conceptual changes will assist in new developments through to the legal, regulatory and economic issues that are associated with redrawing this field of medical technology.

6. Conclusions

In line with these considerations, we should now be in a position to refine the biomaterial paradigm, and redefine the word ‘biomaterial’. Such a definition is presented here as:

> “*A biomaterial is a substance that has been engineered to take a form which, alone or as part of a complex system, is used to direct, by control of interactions with components of living systems, the course of any therapeutic or diagnostic procedure, in human or veterinary medicine*.”

The purpose of this Leading Opinion Paper has been to explore these concepts, in the hope that our understanding of what constitutes a biomaterial can change with the radically new types of substance that we are using, in many new ways, in medical technology. It is hoped that this will stimulate constructive debate about the biomaterials of today and of the future.

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