Designing materials for biology and medicine

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Biomaterials have played an enormous role in the success of medical devices and drug delivery systems. We discuss here new challenges and directions in biomaterials research. These include synthetic replacements for biological tissues, designing materials for specific medical applications, and materials for new applications such as diagnostics and array technologies.

Biomaterials have been defined as substances other than foods or drugs contained in therapeutic or diagnostic systems[1] and, in some cases, have been described as materials composed of biologically derived components (for example, amino acids) irrespective of their application. Throughout history, biomaterials have played an important role in the treatment of disease and the improvement of health care. Early biomaterials include metals such as gold that were used in dentistry over 2,000 years ago. Other early examples of biomaterials include wooden teeth and glass eyes[2]. However, with the advent of synthetic polymers at the end of the nineteenth century, these materials became increasingly used in health care. For example, polymethylmethacrylate, PMMA, was used in dentistry in the 1930s[1] and cellulose acetate was used in dialysis tubing[2] in the 1940s. Dacron was used to make vascular grafts; polyetherurethanes, the materials used in ladies' girdles, were used in artificial hearts; and PMMA and stainless steel were used in total hip replacements[1,2]. Naturally occurring materials such as collagen have also been used as biomaterials[3]. However, in nearly every case, these materials were adopted from other areas of science and technology without substantial redesign for medical use. Although these materials helped usher in new medical treatments, critical problems in biocompatibility, mechanical properties, degradation and numerous other areas remain. To this end, scientists are creating new materials including those with improved biocompatibility, stealth properties, responsiveness (smart materials), specificity and other critical properties. Modern biomaterials science is characterized by a growing emphasis on identification of specific design parameters that are critical to performance, and by a growing appreciation of the need to integrate biomaterials design with new insights emerging from studies of cell–matrix interactions, cellular signalling processes, and developmental and systems biology.

Biomaterials are already having an enormous effect on medicine. Controlled drug delivery systems that largely involve polymers[4] are used by tens of millions of people annually[5]. Recent examples are polymer-coated stents, which have recently been approved both in Europe and the United States. Hundreds of thousands of lives are expected to be saved each year[6]. In addition, various controlled release systems for proteins, such as human growth hormone, as well as molecules decorated with polyethylene glycol (PEG), such as pegylated interferon[4–7], have recently been approved by regulatory authorities, and are showing how biomaterials can be used to positively affect the safety, pharmacokinetics and duration of release of important new drugs. Another area where biomaterials have recently had an impact is in tissue engineering. By combining polymers with mammalian cells, it is now possible to make skin for patients who have burns or skin ulcers, and various other polymer/cell combinations are in clinical trials, including corneas, cartilage, bone and liver[8]. Biomaterials have also had a major impact as the central components of dental implants, sutures, and numerous medical devices[2].

Here we describe novel material concepts that are shaping future directions in biomaterials science. In particular, we discuss (1) creating synthetic replacements for biological tissues using naturally occurring building blocks, (2) synthesizing materials using man-made building blocks for specific medical and biological applications, and (3) design concepts for new *in vitro* applications such as diagnostics and array technologies.

Synthetic replacements for biological tissues

Materials composed of naturally occurring (biologically derived) building blocks, including extracellular matrix (ECM) components, are being studied for applications such as direct tissue replacement and tissue engineering. The ECM, a complex composite of proteins, glycoproteins and proteoglycans, provides an important model for biomaterials design[9]. ECM-derived macromolecules (for example, collagen) have been used for many years in biomaterials applications[3], and it is now possible to create artificial analogues of ECM proteins using recombinant DNA technology[10]. Through the design and expression of artificial genes, it is possible to prepare artificial ECM proteins with controlled mechanical properties and with domains chosen to modulate cellular behaviour. This approach avoids several important limitations encountered in the use of natural ECM proteins, including batch-to-batch (or source-to-source) variation in materials isolated from tissues, restricted flexibility in the range of accessible materials properties, and concerns about disease transmission associated with materials isolated from mammalian sources.

Elastin-based systems have been of special interest in this regard. Urry and co-workers have shown over many years that simple repeating polypeptides related to elastin can be engineered to exhibit mechanical behaviour reminiscent of the intact protein[11]. Crosslinking can be accomplished via radiative[12] or chemical[13] means, and electrospinning has been used to prepare fibrous forms of engineered elastins[14] (Fig. 1). Incorporation of cell-adhesion ligands allows attachment and spreading of cultured cells, and in the specific case of materials for vascular grafts, retention of endothelial cell adhesion in the face of shear stresses characteristic of the normal circulation[15].

The promise of biosynthetic approaches to biomaterials design must be weighed against the fact that very little is known about the *in vivo* performance of systems prepared in this way. Animal experiments on elastin-like polypeptides prepared by chemical synthesis have shown these materials to evoke relatively mild tissue reactions, but the range of materials investigated to date has been small[16]. As more is learned about the mechanical properties of such materials and about their interactions with cells in culture, the groundwork will be laid for more extensive evaluation in animal models. Recent progress in the development of methods for incorporation of non-natural amino acids into recombinant proteins points the way to an alternative strategy for preparing artificial ECM proteins with diverse chemical, physical and biological properties[17].

Substantially more experience has been gained in evaluating the *in vivo* performance of engineered biomaterials based on polysaccharides. Alginate hydrogels bearing cell-adhesion ligands have been used as scaffolds for cell encapsulation and transplantation, and have yielded promising results in experiments directed towards the engineering of bone tissue capable of growth from small numbers of implanted cells[18]. The prospect of growing tissues from small numbers of precursor cells is an attractive alternative to harvesting and encapsulating large cell masses before transplantation.

Molecular self assembly of peptides or peptide-amphiphiles may also lead to unique biomaterials. A number of self assembled peptide systems have been developed, including systems that can potentially be used in tissue engineering and nanotechnology[19,20].

An alternative to synthesizing polymers composed of natural components is the synthesis of biomimetic polymers, which combine the information content and multifunctional character of natural materials (such as a particular amino acid sequence that might be desirable for cell attachment) with the tailorability of a synthetic polymer, such as control of molecular mass or polymer degradation, and the ability to impart appropriate mechanical properties. An example of this concept has been the synthesis of polymers composed of lactic acid and lysine. Like polylactic-glycolic acid, these polymers can be made to degrade at desired times. However, by adding lysine as a co-monomer with lactic acid, a free amino acid is provided, which allows coupling reactions to take place and does not affect the overall biocompatibility of the polymer[21]. By coupling specific amino acids (such as the tripeptide sequence RGD) to this polymer, cell adhesion can be regulated[22].

Another strategy that has been used in modifying a variety of natural and synthetic polymers has been the inclusion of PEG into the material to reduce non-specific effects of protein adsorption and colloidal aggregation. The molecular origins of these phenomena are not yet thoroughly understood. One example of the effects of the PEG can be seen in the creation of polylactic-glycolic acid (PLGA) PEG diblock polymers that, when formed into nanospheres, can, like cells, circulate in the body for long time periods. For example, in mice, only 30% of PLGA-PEG nanoparticles were cleared after 5 h whereas 66% of non-PEG-containing PLGA nanoparticles were cleared in only 5 min (ref. 23). Halstenberg *et al.*[24] have adopted a related approach in engineering protein-based biomaterials, by grafting poly(ethylene glycol) diacrylate onto an artificial protein that contained multiple cysteine residues. The protein was designed to serve several functions, including cell adhesion, heparin binding, and degradation by plasmin to facilitate penetration by invading cells. The mechanical properties of the material were controlled by photopolymerization of the pendant acrylate units.

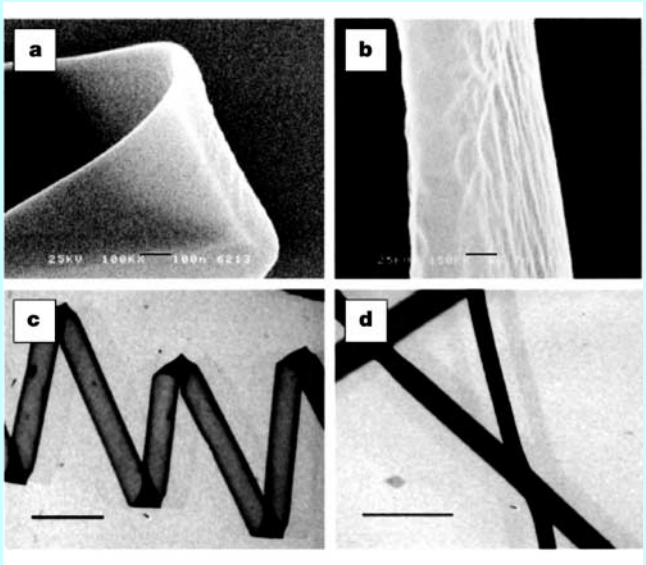

Figure 1 Electrospun fibres of elastin-like artificial proteins made by expression of artificial genes in bacterial cells. **a**, **b**, Scanning electron micrographs. **c**, **d**, Transmission electron micrographs. Scale bars: **a** and **b**, 100 nm; **c**, 3.3 μm; **d**, 2.0 μm. Images from ref. 14.

Another approach to creating a biomimetic reversible system is the creation of an antigen responsive hydrogel. Corresponding antibody pairs are used to form reversible non-covalent crosslinks in a polyacrylamide system. In the presence of excess free antigen, the hydrogel swells, but in its absence, the gel collapses back to a crosslinked network. Swelling does not occur when foreign antigens are added, showing that the system is antigen specific. Release of a model protein such as haemoglobin has been demonstrated in response to specific antigens[25].

Materials for specific medical and biological applications

A variety of new materials are being synthesized from man-made building blocks, and being used to create devices for specific medical applications. One area of increasing attention has been the development of shape-memory materials that have one shape at one temperature and another shape at a different temperature[26]. Such materials might permit new medical procedures. For example, current approaches for implanting medical devices often require complex surgery followed by device implantation. However, with the development of minimally invasive surgery, it is possible to place small devices inside the body using laproscopes. These types of surgical advances may create new opportunities to enable a bulky device to be implanted into the human body in a convenient way.

Shape-memory materials might provide such an opportunity, because they have the ability to memorize a permanent shape that can be substantially different from an initial temporary shape. Thus bulky devices could potentially be introduced into the body in a temporary shape, like a string, that could go through a small laproscopic hole, but then be expanded on demand into a permanent shape (for example, a stent, a sheet, and so on) at body temperature (Fig. 2). New polymers have been synthesized with this concept in mind, including phase segregated multiblock copolymers whose starting materials are known biocompatible monomers such as ϵ-caprolactone and *p*-dioxanone. Generally, these materials have at least two separated phases, each with thermal transition (glass or melting) temperatures. The phase with the higher transition temperature is responsible for the permanent shape, whereas the second phase can act as a molecular switch and enable fixation of a temporary shape. By regulating temperatures above and below the second phase's transition temperature, shape can be shifted from one form to another. In addition to permitting new opportunities for implanting devices, these polymers have been developed into sutures that are able to tie themselves on demand, triggered by a temperature change[27] (Supplementary video 1).

Materials that are liquids at room temperature but that harden in response to a change in temperature or an external stimulus, such as light, are also being studied[28–30]. Such systems offer an opportunity to inject materials containing drugs, for example, into the body through a small needle, but still enable the formation of an implant.

A variety of smart gels have also been developed. These gels can respond (and swell, for example) to triggers such as temperature or pH, or even specific molecules in the body such as glucose. Such systems may, with further study, be valuable in the treatment of disease: in the case of diabetes, for example, smart gels could provide direct feedback control, allowing more insulin to be delivered in response to excess glucose[31].

It may be possible to change not only the bulk properties of materials but also their surface properties, using a simple 'switch'

such as temperature or electric charge. For example, alkanethioates such as 16-mercaptohexadecanoic acid, which has a hydrophobic chain capped by a hydrophilic carboxyl group, forms self-assembled monolayers on gold surfaces. These chains have an upright equilibrium conformation presenting the carboxylic groups to the surrounding medium. But when these alkanethioates are placed on gold at the correct density, application of an electric potential causes the carboxyl groups to be attracted to the gold surface electrostatically, causing the molecules to reversibly rearrange and expose the hydrophobic chain (Supplementary video 2). Such surface switches might offer new opportunities in such areas as drug delivery, microfluidics and biosensors[32].

The development of high-throughput approaches to create novel biopolymers and screen them for various applications is garnering increased attention. For example, Kohn and co-workers have created polymer libraries and then screened them for different applications[33,34]. This type of high-throughput approach has also been used in the creation of gene therapy agents. For example, poly-β-amino esters can be synthesized in a high-throughput manner, and a number of these new polymers have been shown to have higher DNA transfection activities in cell-based assays than existing materials such as lipofectamine[35,36].

Gene therapy represents an area where appropriate molecular design is critical to achieving a successful outcome. Although viral vectors are highly effective, their use has raised serious safety concerns. This has motivated research on synthetic gene therapy vectors, which, although safer, have thus far been much less effective than viral vectors. To be effective, there are a number of attributes that the material must possess, including the ability to condense DNA to sizes less than 150 nm so that it can be taken up by receptor-mediated endocytosis, the ability to be taken up by endosomes in the cell and to allow DNA to be released in active form, and to enable it to travel to the cell's nucleus[37]. An interesting example of the design of such new materials is provided by the cationic-cyclodextrin polymers developed by Davis and co-workers. Cyclodextrins are relatively non-toxic and do not elicit an immune response. When Davis and co-workers initially used cyclodextrins for packaging DNA they found the resulting complexes to be relatively unstable. To address this, they added adamantane-conjugated polyethylene glycol to the surface of the cyclodextrin particles. This enabled the development of uniformly sized nanoparticles that resisted aggregation. By modifying the surface of the particles in this way, chemical groups could be exposed that could attach other molecules and allow the particles to be targeted to, and deliver genes to, specific cells[38]. Another novel approach for gene therapy involves creating a triplex where low-density lipoprotein is used for targeting and stearyl polylysine is used for DNA complexation. This approach has been used to deliver vascular endothelial cell growth factor to heart muscle to aid in treating blockage of blood vessels[39]. With the advent of new gene therapy agents such as RNA interference[40], the ability to design improved materials to deliver these agents will have increasing importance.

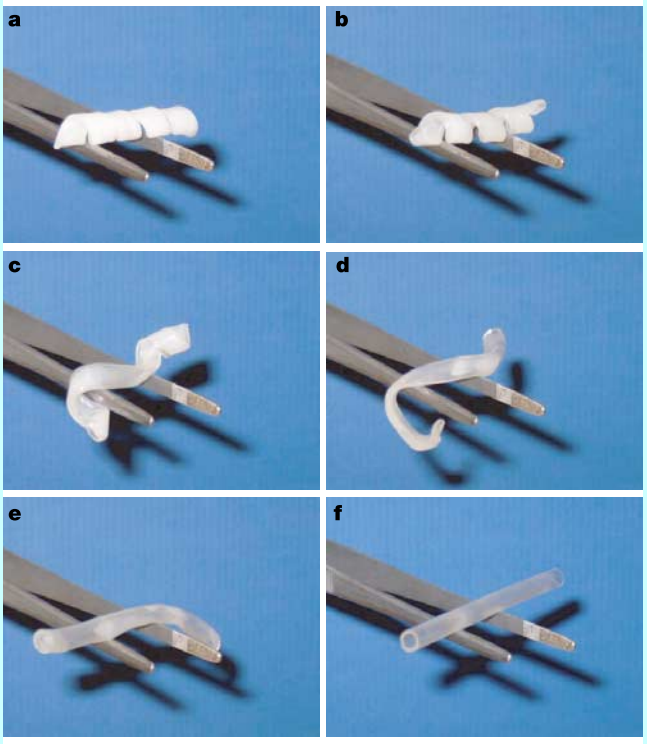

Figure 2 Time series of photographs showing recovery of a shape-memory tube. **a**–**f**, Start to finish of the process; total time, 10 s at 50 °C. The tube was made of a poly(ϵ-caprolactone)dimethacrylate polymer network (the M_n of the network's switching segments was 10^4) that had been programmed to form a flat helix. Images courtesy of A. Lendlein.

Biomaterials are also being used to affect bioadhesion in novel ways, even enabling materials to be used to potentially deliver complex molecules orally. It appears that polymers with high concentrations of hydroxyl groups bind with the intestinal mucosa. For example, Mathiowitz and co-workers[41] have designed polyanhydride nanoparticles (which can encapsulate DNA or other molecules, and which expose carboxyl groups on their exterior as the polymer erodes), and have shown that they can attach to mucous membranes and bind to the intestinal wall. Poly(fumaric-co-sebacic) anhydride showed greater adhesive forces than other materials tested, had a longer contact time with cells in the intestine, and was able to pass through the intestinal wall with a protein inside it. Peppas and co-workers have developed polymers that are not only bioadhesive, but also swell in response to a pH change. These polymers are able to protect proteins from the acidic pH of the stomach, and release it in the more basic pH of the intestine. These materials also appear to temporarily open connections between intestinal cells, allowing the proteins to pass through[42].

Microfabrication-based devices may also provide a novel approach for creating a variety of new biomaterials and delivery systems. For example, silicon microchips have been engineered to contain over 100 nanometre-sized drug-containing wells covered with gold on a chip 1 cm × 1 cm. By applying approximately 1 V to individually addressable wells, the drug in any of these wells can be released[43]. These types of systems have also been recently made with degradable materials (Fig. 3)[44].

Microfabrication has also been used in the creation of sensors. For example, small sensors are being used to measure intraocular pressure for glaucoma patients[45], and silicone microstimulators have been developed that can be controlled by telemetry[46] and are being used for retinal stimulation to aid in photoreceptor generation to treat diseases of the back of the eye that cause blindness. Prausnitz and co-workers have developed microneedles that are able to penetrate into the skin to depths far enough for drugs to enter the circulation, but shallow enough not to reach skin layers that contain nerves: therefore they do not cause pain[47]. Microfabrication has also been used to create polymer scaffolds containing an intricate vascular network[48]. All of these represent important ways of using micro- and nanotechnology to create potential new medical devices.

New applications: diagnostics and array technologies

Much of the preceding discussion has focused on the development of materials that display biological information, often in the form of peptide or protein domains, for the purpose of controlling cell and tissue behaviour. A related challenge arises in the engineering of

materials for diagnostics and array technologies, in which large numbers (typically hundreds or thousands) of nucleic acids[49] or proteins[50] are presented in a format that allows rapid and highly parallel read-out of information concerning gene expression or protein function. Analogous technologies are being pursued with peptides[51], carbohydrates[52] and other small molecules, as well as with cells and tissues[53].

The role of materials science in array technologies was demonstrated in striking fashion by Fodor and co-workers[54], who used photolithographic techniques to prepare an array of 1,024 peptides in just ten sequential operations. Similar methods have been used to create oligonucleotide arrays[55]. Brown and co-workers introduced an alternative approach to DNA arrays by high-speed robotic spotting of complementary DNAs on treated glass surfaces[56]. Both techniques yield 'DNA chips' characterized by high densities of biological information.

Although these technologies are now highly developed and widely used, they are far from optimized. Hybridization of DNA arrays typically requires many hours[56], precluding their use in circumstances that demand rapid diagnosis or detection of pathogens, and limiting the possibilities for high-throughput screening of large numbers of samples. Array technologies that allow local application of electric fields (to enhance DNA migration)[57], ultrasonic mixing, or acoustic microstreaming[58], have all been shown to reduce substantially the time required for read-out of microarray data. Thermal-gradient DNA chips have been developed to allow local (site-to-site) control of the hybridization temperature[59], which can be important in distinguishing perfect sequence matches from single-site mismatches, and microporous arrays have been used in flow systems to speed up hybridization[60].

Additional challenges arise in the fabrication of protein arrays. Unlike nucleic acids, which share a common physical chemistry that is largely independent of sequence, proteins are highly diverse in terms of charge, hydrophobic character, and so on. So whereas robotic printing of DNAs on a common substrate can be done reliably, similar treatment of a complex protein library is unlikely to result in uniform retention of protein structure and function. The potential importance of protein arrays in the direct determination of protein concentrations in cells and tissue fluids, in the identification of protein–protein interactions, and in the study of drug-binding behaviour, has prompted substantial effort directed towards the development of reliable methods for array fabrication[50].

A successful fabrication method must be applicable to diverse protein libraries, and must achieve robust attachment of each protein to the surface of the array device. The attached proteins must not denature (unfold), and at least some fraction of each protein must be presented in an orientation that is consistent with retention of function; the site(s) of interest cannot be blocked by the array surface or by the linking groups used to achieve surface attachment. The substrate should not be prone to non-specific protein adsorption, because non-specific adsorption can give rise to high background noise and false positive signals.

Brown and co-workers examined the simple approach of printing proteins (either antigens or antibodies) on poly(L-lysine)-coated glass microscope slides[61]. They examined 115 antibody/antigen pairs, and found that approximately 50% of the printed antigens yielded signals that were quantitatively consistent with the known concentrations of the corresponding antibodies in the analyte solutions. Antibody arrays performed at a significantly lower level. This study is especially instructive because it provides a careful analysis of the quantitative reliability of the technology, and because it illustrates the challenges involved in fabricating protein arrays. The fact that fewer than 50% of arrayed antibodies yielded reliable signals is particularly striking given the structural uniformity of antibodies. More diverse protein libraries are likely to be substantially more difficult to array.

Alternative approaches to the fabrication of protein microarrays have used aldehydic surfaces to capture protein-bound lysine side chains[62], polyacrylamide gel pads to entrap proteins and to immobilize antibodies via reaction with oxidized carbohydrate substituents[63], and 'capture ligands' that react covalently and specifically with a single 'capture protein' that can be fused to each of the diverse proteins in the library to be arrayed[64]. The most ambitious experi-

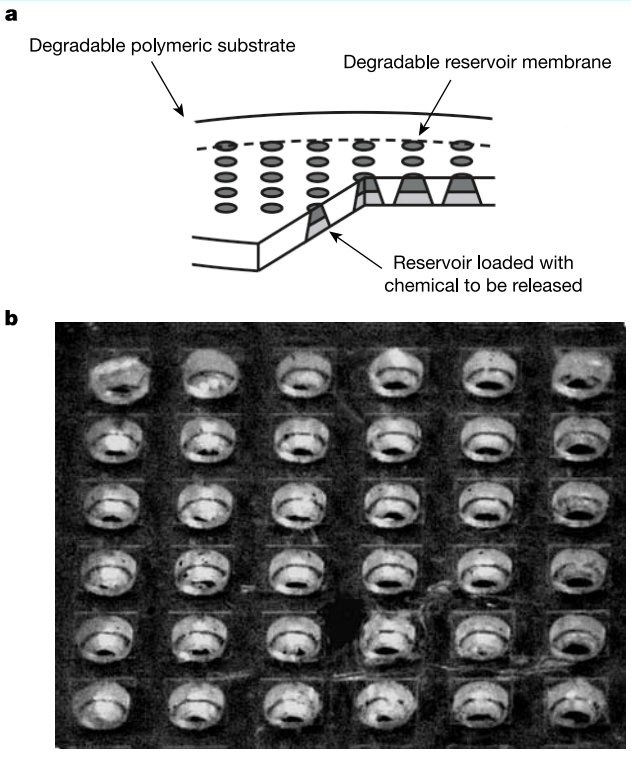

Figure 3 Degradable polymeric microchip. **a**, Cut-away diagram. **b**, Close-up photograph of reservoirs on a degradable microchip composed of polylactic-glycolic acid. Image courtesy of A. Richards-Grayson.

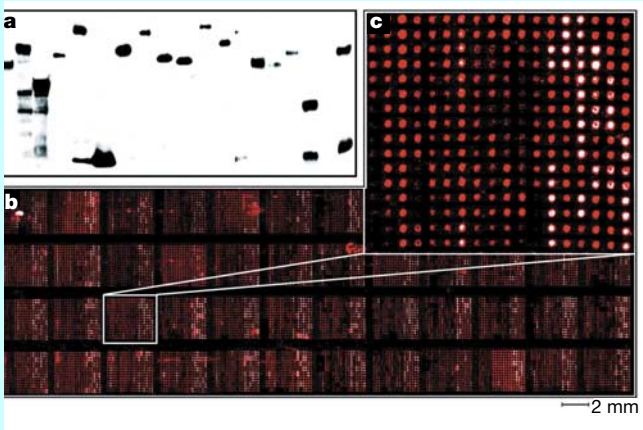

Figure 4 Miroarray of 5,800 yeast proteins, each fused to a hexahistidine sequence that facilitates immobilization on a nickel-coated glass slide. A second fused sequence, that of glutathione *S*-transferase (GST), allows visualization with anti-GST antibodies. Arrays of this kind have been developed by Snyder and co-workers, and used in global analyses of the yeast proteome. **a**, Immunoblot analysis of 19 representative fusion proteins purified in 96-well format; proteins were visualized with anti-GST. **b**, Protein samples spotted on nickel-coated glass slide and probed with anti-GST. **c**, Enlarged image of a portion of the protein array. Image from ref. 65.

ment to date[65] has used a polyhistidine tag to immobilize more than 5,000 yeast proteins to the surface of a glass slide functionalized with Ni^{2+} (Fig. 4)

Arraying of membrane proteins presents special challenges. Membrane proteins are especially difficult to isolate and to maintain in active form. A promising approach to membrane protein arrays has emerged from studies of supported lipid bilayers, and from the discovery that supported bilayers can be partitioned into 'corrals' that do not allow lipid intermixing via lateral diffusion[66]. Partitioning can be accomplished by microcontact printing, by deposition of molecular barriers, or by a variety of photochemical methods. The supported bilayer stabilizes membrane proteins with respect to denaturation, and the lateral mobility of the system facilitates protein–protein interactions that are critical to many biological processes.

There is as yet no consensus regarding the preferred method(s) of array fabrication, and further development will be required before protein arrays become widely available for use in research and clinical practice. Materials that reduce non-specific adsorption and protein denaturation, that allow further reduction in feature size, that facilitate address of individual array features, and that enable signal amplification and enhanced sensitivity, will constitute an important part of such development.

Concluding remarks

Biomaterials have already had an enormous impact on health care, and are already widely used in prosthetic and drug delivery devices. Much of this success has been achieved through judicious selection of existing materials, with little real design for biomedical use. Current work is laying the foundations for a much richer application of biomaterials through elucidation of the fundamental design considerations that determine the success or failure of biomaterials systems.

Numerous challenges remain in biomaterials development. These challenges include targeting materials (containing drugs), for example, to specific cells; designing materials that can sense biochemical signals in the body; and developing materials with improved biocompatibility. The ability to address these challenges will be facilitated by advances in biology and materials science. Understanding more about extracellular matrix biology, cell receptors, and immunology will help, for example, in understanding how the body responds to specific materials. Analogously, advances in nanomaterials will create new opportunities to mimic entities in the body (such as cells), and advances in materials characterization will aid in understanding how materials interface with cells and tissues. Finally, we note that many significant recent advances in biomaterials occurred at the interface of clinical medicine and materials science and engineering. Creating opportunities and training programs for cross-disciplinary research for individuals engaged in these areas could significantly accelerate the advancement of biomaterials and create new applications for these materials in medicine. □

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