Introduction

Biomaterials have seen exceptional growth and development over the past decade, translating into a major, worldwide market of over $36bn. Projected growth is up to 10% per annum, for particular clinical applications, but even as a proportion of total healthcare costs, biomaterials are set to gain in significance. They play a key part in the delivery of radical surgery based, clinical interventions, and often provide the only viable basis for repairing major tissue and organ structures. Though originally developed for life-threatening and serious debilitating conditions, they are now increasingly being used to correct minor structural and functional defects. It is now recognised that the failings of current biomaterials make them inadequate for the management of serious clinical conditions, particularly over the longer term.

Despite the importance of this application area, the paradox is that the majority of biomaterials have not been developed specifically for clinical use, but selected and adapted from other materials sectors. Partly for this reason, there is as yet no ideal clinical material able to guarantee either complete functional replacement of tissues and organs, or to sustain functional performance within the body over extended periods. The challenges facing biomaterials reside mainly in the host of complex reactions set up around the implant site which range from rejection, complement activation, clot formation, fibrous encapsulation and surface infection through to more generalised whole body reactions.

An important basis for advancing biomaterials research and for reducing the risk of clinical device failure is for biomaterials research to be set in a fully multidisciplinary context, encompassing both material/physical and biological sciences. This will be true much more than in the past in view of the escalating international commercial competitiveness in this field. Proper coordination and input of key interconnected disciplines, including Clinical Medicine, will be critical to a competitive edge, and these will preferably be involved at initial rather than just the later stages of research programmes. The increasing direct personal and societal healthcare impact of biomaterials is too great and the market too important for continued reliance on past organisational models for biomaterials research; analogous pressures in the pharmaceutical industry have already led to radically altered pathways for drug development.

Current Trends

Current research developments in biomaterials certainly reflect the influence of multidisciplinarity with moves, in particular, towards bioactive implants. Here, biologically active agents, (natural or synthetic), are incorporated within a biomaterial and used to modify the local tissue response to the implant. More ambitious developments in tissue engineering which seek to fully reproduce tissue structures through integration of cells with scaffold materials are also well advanced. Our greater understanding of the fundamental biophysical processes involved in the body's response to artificial implant surfaces regardless of their metallic, ceramic or polymeric origin, has also helped to create linkages across traditional materials boundaries. The highly complex biological environment within which implanted devices are expected to operate place unique demands on their constituent materials, and these will continue to provide a driver for more unified approaches across the spectrum of different material sub-classes.

The biomaterials industry is highly regulated and end users (i.e. clinicians) extremely conservative, themselves constrained by issues of cost, patient well-being and uncharted risks associated with new therapies. There has, therefore, been a past tendency towards incremental improvement using existing materials with emphasis on materials with an established history of clinical use. These more traditional materials are likely to continue to be the mainstay of future R&D effort, not least because commercial and legislative barriers to new materials will become greater. The problem is compounded by performance criteria often limited to very basic comparisons with existing products. New evaluatory perspectives are needed which better reflect clinical efficacy; this will be more readily achieved in emerging technologies with standards now likely to be implemented throughout the innovation process. Advances in new forming and characterisation methods, including those from other sectors, will also open up new opportunities for innovation using classical materials. In the case of polymers, greater control over molecular/supramolecular design and self-assembly should allow fine-tuning of selected properties, with structural gradation and anisotropy, for example, leading to a better match with natural tissue.

Developments in nanocomposites will further pave the way for diversity in biomaterials using existing materials. Nanocomposites are likely to be of particular value in regard to the replacement of load bearing structures. Advanced nanoforming techniques will also enable integration of self-diagnostic and actuating functions into the bulk of a biomaterial. Smart nanostructures could also provide distributed sensing elements and self-healing agents within a single material, possibly avoiding surgical retrieval in the event of failure.

Structural complexity, multi-functionality and sensor-actuator combinations are all of potential value in the quest for fully biomimetic materials. Moreover, they will acquire much greater importance in the case of future specialist implants to support the function of complex neuromuscular and endocrine tissue.

The Challenge of the Interface

Though there has been a considerable body of work on the bulk properties of biomaterials, their surfaces are the key determinant of the host response. Improved understanding about surfaces from a physical science perspective has enabled mechanistic rather than purely descriptive studies, and much more is now understood about the biophysics of cell and protein behaviour at biomaterials. The outcomes will be radically new surface designs, but within the domain of existing biomaterials. Control of the interface might be channelled to specifically avoid any cell and protein attachment (vascular implants) or to augment cell interactions (orthopaedic implants, neuroprostheses).

A new emphasis on surface and interfacial phenomena would have wider implications in biomaterials; stabilised surfaces could, for example, allow more controlled drug delivery, avoid catheter-blockage and reduce microbial attachment. Furthermore, in the case of membranes used for say filtration and dialysis, more efficient solute transport might be achieved through reduced fouling. Improvements in performance might in future be mediated by bioactive or externally addressable surface layers, able to mimic the interfacial and separation functions of major organs, at least on a short-term basis. Integration of addressable biomaterial layers with electronics could open up wider possibilities for in vivo devices including inherent switching and logic functions.

Future advances in surface design, allowing for self-renewing surfaces, could enable replacement of an existing, contaminated surface, or allow it to react to local environmental change, in particular to a common cause of clinical morbidity and implant failure, as that associated with surface microbial contamination and biofilm growth. Such films are often refractory to systemic antibiotics, so self-renewing and self-disinfecting materials offer a potent alternative. There are likely to be many new opportunities for fundamental studies of the biological-physical interface to translate into direct clinical benefit.

For miniature structures, surface interactions acquire a much more important role. A particular example is where microcapsules are used to deliver drugs or cells, viz insulin secreting pancreatic islet cells. Here, reliable function depends almost entirely upon low surface contamination with controlled interfacial transport.

The Nano-Scale

Polymeric structures coupled to therapeutic drugs for their selective delivery to tissues also fall within the domain of biomaterials. Through appropriate polymer design (e.g. informed by cell receptor modelling), it would be possible to direct drugs to specific tissues. Future nanostructures may also accommodate such functions, so leading to a direct linkage between biomaterials and therapeutics. Interfacial properties will be of exceptional importance for nanoparticles used clinically. Practical use of nanostructures could include the delivery of drugs across natural body barriers such as skin, mucosa and the blood brain barrier, and with appropriate switchable properties new possibilities for non-viral gene therapy may open up. Advances in the clinical use of nanoparticles would, of course, add new insights into the mechanisms of nanoparticle toxicity.

Chemical sensors and biosensors are essentially interfacially active structures, and require, in turn, protective materials barriers to stabilise performance and control in vivo sensing performance and biocompatibility. Their development demands a convergence of materials science, biochemistry and biology, incorporating other key domains such as biomechanics, physical sensors. They thereby utilise principles from a wide range of disciplines, which if suitably integrated could allow for more effective diagnostic systems both for clinical use and screening. Such devices when used in bioreactors can also help optimise the growth of tissue engineered constructs as part of intelligent bioreactors.

Resorbables and Tissue Regeneration

For full physiological replacement of tissue function, there is a need to develop resorbable implant materials. The area has seen substantial growth in recent years, with more challenging applications now targeted, including hard tissue replacement. Composites may prove to be particularly valuable here, subject to radical design changes, e.g. extended fibres used instead of particulates. Whether polymeric or ceramic, such structures are likely, in future, to incorporate a cocktail of slow release growth factors and drugs. Future design, will therefore need to take into consideration the complex dynamic between degradation, drug release and tissue integration. The ultimate challenging, goal would be a fully regenerated tissue or organ, the degradable biomaterial providing an important but transient growth controlling function. Degradable scaffolds loaded with stem cells, could furnish a more potent vehicle for tissue regeneration cell-based therapies.

Cell loaded scaffolds with 3-D structures matching natural tissues could also offer in vitro analogues of tissues for testing drugs. Such a development could contribute to the reduction and replacement of in vivo testing. Such a strategy could be further supported by in silico models of biochemical and immunological processes; benefits from modelling have already been derived using biomechanical and flow models used for the design of musculoskeletal and cardiovascular biomaterials. There will be more data input from high throughput screening (HTS) and combinatorial materials libraries tested against specific cell systems, and greater relevance to the in vivo biological response achieved through identification of more robust biological markers. Microfabrication technology will open up new HTS possibilities, and possibly allow precision fabrication of tissue scaffolds.

Biomaterials Production

Advances in the research laboratory will need to be transferred more effectively to scale-up production. Even with existing materials, this will demand high levels of engineering innovation. Materials incorporating biological components, moreover, will have special processing requirements, e.g. low temperatures and near-physiological reaction conditions. So new synthetic routes, using say enzymes and avoiding organic solvent are likely to be of greater interest in the future. One lower risk option is to develop biologically derived materials; such advances, however, will depend upon better understanding of natural materials, and through this the informed selection of natural structural motifs and biomimetic structures. Natural biopolymers, typically produced in bioreactors, will thus have an important role in extending biomaterials design.

Key Issues

Commercial

Existing clinical needs, many the outcome of chronic, degenerative disease, will expand because of population demographic changes. The dominant areas will remain musculoskeletal and cardiovascular, but with important shifts in emphasis within these, for example in response to the greater incidence of osteoporosis and diabetes. Materials costs will not be an issue with high value added biomaterials, especially if these help offset downstream healthcare costs. However, the threat of litigation and the stringent demands of the regulatory authorities will create problems, possibly on a scale of that of the pharmaceutical industry; biomaterials pricing is unlikely to compensate for this. This will be a particular problem for SMEs who are important drivers of biomaterials for innovation in the UK. Governmental support for a common framework to help SMEs steer through such hurdles and to create a critical mass would UK help competitive growth.

Societal

Patient preference will drive many of the developments in biomaterials. Real, as well as perceived, risks vs. benefits and quality of life issues will all dictate future public acceptance. There is a parallel here with the growth in cosmetic surgery, where lifestyle and generational differences in attitudes have been clearly in evidence. Public education and the effective use of the media will be especially important in the future, including highlighting “good news” stories and the benefits of implants. This will condition a critical vs. positive response to new advances. With public opinion increasingly averse to animal testing, and even possibly to clinical trials, greater investment in improved predictive models based on non-animal testing will be vital. The general context within which Medicine is practiced will also change because of greater use of international treatment facilities. One factor conditioning the perception of risk will be the nature of the required surgical procedure; minimally invasive surgery may change the outlook here.

Additional background considerations

Biomaterials continues to be an attractive area for undergraduate students, suffering rather less from the image of materials associated with traditional engineering disciplines. The future workforce is, thus, more likely to be sustained, but there will be a greater responsibility to include teaching of fundamentals whilst sustaining attractiveness. The diversity of biomaterials exploited may, however, conflict with the need for in-depth technical knowledge and skills.

Whilst the area has been successful in attracting UK government funding and is perceived as being strong, the actual level of spend as a percentage of GDP is less than many industrialised countries. A comparison with the US demonstrates a considerably lower volume output of biomaterials, but one not necessarily of lower quality and which, moreover, provides a platform for future healthcare gains. Competitiveness, however, will require, first, a critical evaluation of UK

strengths and a coordinated effort between academia and industry; IPR ownership issues are a potential barrier to enhanced collaboration. A more balanced UK research portfolio also needs to be achieved with clarity over long term national goals. Short-term, initiatives to help pull laboratory research through to clinical trials could overcome a critical bottleneck in the supply chain. Central initiatives also need to take account of, and address more directly, the lack of UK companies with the size and resources to exploit new biomaterials technology. Smarter procurement for clinical use targeting those best able to achieve innovation would help underpin UK competitiveness.

Recommendations

- Enhanced research effort on bioresorbables and bioactive materials, and novel manufacturing routes to achieve new properties in existing materials.
- New interfacial structures for control of biomaterial-tissue interactions including emphasis on biomimetic approaches to forming processes and end stage structures.
- Integration of sensing systems into biomaterials for in situ implant monitoring.

Key Point

An organisational framework to help SMEs address regulatory barriers and skills gaps.

The growth and overall dynamism of the SME sector will depend critically upon the successful handling of a broad range of regulatory and healthcare issues. The limited resources which SMEs can bring to bear on such challenges may delay entry into the marketplace. The generic nature of such challenges means, however, that a common framework of support could have a high impact and offer substantial returns on the investment required.