The Biomedical Applications Division is a division of The Institute of Materials, Minerals and Mining (IOM3) which is a professional engineering institution whose activities encompass the complete materials cycle from exploration, energy and ore reserve evaluation, mining and extraction, refining, processing, forming, finishing; applications, product recycling, waste management and land reuse.

The Biomedical Applications Division represents materials engineers and other related technical disciplines with interests across biomedical applications. For more information, and additional copies of this report, visit: www.iom3.org/biomedical-applications-division
Members of the Biomedical Applications Division of the Institute of Materials, Minerals and Mining have reviewed the current status of biomaterials and tissue engineering research, development and clinical translation in the UK. The current needs, new directions, opportunities and constraints to commercialisation and areas for future research have been identified. Overall there appears to be huge potential for growth with the change of emphasis toward “prevention rather than cure” and the NHS offers key, enabling advantages in the UK. However, there is a perceived funding gap between in-vitro laboratory research and in-vivo validation of results which may limit the translational impact of both university- and industry-based research and development. It is concluded that, with suitable funding and support mechanisms involving co-ordination between the Government, research councils, charities and industry and through enhanced multidisciplinary communication links and careful control of regulatory pathways, the barriers to innovation can be minimised.

EXEUCIVE SUMMARY

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Collagen scaffolds
BACKGROUND

There have been several reports published recently in the general area of “needs in the healthcare sector” (1–4). However, none of these has focused specifically on the current status and future needs in the areas of biomaterials and tissue engineering. This report seeks to provide information about the status and future directions of the field of biomaterials from academic-, regulatory- and industrial perspectives.

Simultaneous with developments in design for orthopaedics and tissue systems more generally, the need for scaffold materials with appropriate architectures for tissue regeneration is now understood to be a key, underpinning requirement in tissue engineering and regenerative medicine. The importance of the development of materials with the appropriate composition and structure for tissue grafting and blood compatibility is also becoming clear.

The origins of the field of biomaterials were in materials “borrowed” from other technologies. The focus was, until relatively recently, on the optimisation of bulk properties and attempts to find solutions to macro-structural mechanics-based problems often for orthopaedic and dental applications. However, in the last 10 years there has been a marked shift in emphasis in biomaterials R&D. The importance of a suitable infrastructure in the area of device regulatory approval was recognised (including for example USP Class VI or ISO 10993). The essential role of medical device regulation has been highlighted by recent issues including the failure of the ASR Metal on Metal (MoM) Hip design and improper use of non-medical grade silicone in breast implants. The need for an effective combination of design and materials selection in the biomaterials field has been put under the spotlight and it is clear that many materials science-based problems are still to be solved.

2. RAEng summary report “Establishing High-Level Evidence for the safety and Efficacy of Medical Devices and Systems Biomedical Engineering Panel meeting on Safety and Efficacy”
Hip implants
CURRENT STATUS

There has been an extremely rapid growth of interest in characterisation of the biological response to materials and this has occurred in combination with a recognition of longer time horizons needed for research and development. Recently, the potential for nanotechnology in drug delivery and gene therapy has been identified and the potential impact of this new class of materials in regenerative medicine is becoming clear. There has been increasing recognition that small particles behave differently to their macro-scale counterparts in terms of their cellular response, e.g. cellular interaction with particles at the nanometre scale. The greater awareness of the biological consequences of materials at the cellular level has stimulated research in nanometre-scale engineering, interfacial properties and molecular biology.

CURRENT NEEDS

There remain a number of areas that need investment and further development. For a range of areas, an unmet clinical need exists, and these can be categorised both by application and material type. Further technological gaps encompass drug delivery, regenerative medicine and structural materials.

There is still potential for a major step forward in drug delivery (both in terms of acute or short term delivery and for long term delivery from scaffolds) for application to conditions ranging from cancer through to infection control. However, biological strategies are also needed for the controlled delivery e.g. cytokine modulators to treat degenerative diseases. Overall, it is essential to gain relevant knowledge of the pathophysiology of the biological system to increase the likelihood of successful treatment. There is a pressing need for devices to assist patients with brain injury and neurodegenerative disease (including applications ranging from cranial plates through to nerve conduits, localised drug delivery and devices aiding independent living). In clinical practice the majority of recurrent problems, costly in terms of resources and quality of life for the patient tend to be considered too mundane, unglamorous and not 'worthy' of involving academia. The problems of the long-term catheter are a very good example of that, yet the fundamental biological and mechanical issues relating to their pathophysiology are extremely complex. With the changing demographics and disease susceptibilities of the populations, it will also be necessary, with increasing frequency, to repair and reconstruct tissues associated with the cardiovascular system. For this same reason, orthopaedics and also dentistry continue to demand the development of novel materials and with issues surrounding microbial antibiotic resistance, there is a need for new methods to treat and prevent wounds, including those associated with diabetes.
POTENTIAL WAYS FORWARD / NEW DIRECTIONS

There are a number of ways in which improvements and prioritisation can be encouraged. These include:

- Engagement between clinicians and the materials R&D community
- IP profit-sharing incentives
- Availability of clinicians for involvement in joint industry collaborations
- Streamlining of regulatory approval and patient recruitment processes
- Improvement in understanding of the funding mechanisms to support industry-academic links.
- Improved access to clinicians by (UK) SMEs

The HealthTech and Medicines (HTM) KTN has taken a leading role in identifying unmet clinical needs in close collaboration with leading clinicians in several areas such as orthopaedics, cardiovascular disease, regenerative medicine and cancer. With existing and new initiatives, e.g. Healthcare Technology Cooperatives (HTCs) (launched early 2013), it is hoped that there will be much better ways of addressing unmet clinical needs with the assistance of the HTM KTN.

In terms of clinical work, a close working relationship between clinicians “working at the coal-face” (identifying common recurrent clinical problems but carrying heavy clinical responsibilities) and university clinical appointments that are appraised by their academic productivity, should be encouraged.
There are a number of novel materials and structures that are under development with potential for near and mid-term translation and these mark another change of emphasis in the UK approach to biomaterials. Opportunities include:

- Biomanipulative structures
- Bioactive solid state constructs
- Bioequivalent mechanical properties
- Controlled degradation
- Self interrogation
- Self-healing materials
- Controlled surface chemistries
- Temporal control of bioactivity (cf research on controlled drug delivery in pharmaceutical research)
- Carriers for cell, gene and bioactive molecules in challenging clinical applications (e.g. pathologies of the myocardium)
- Integration of nanoscale materials and devices, magnetic and electroconductive materials.

Another goal for the future would be Personalised materials design reflecting individual patient genetic makeup; this is already a feature of pharmacogenomics and the way cancer treatments are being tailored.
ABOVE
Cell response to porous bioceramic

LEFT
A bioactive glass scaffold for bone regeneration, with streak lines showing the path of cell migration and potential blood vessel growth.
While the UK is probably the world leader in biomaterials research and innovation, the translation of research from the bench top to clinical application has many challenges, requiring careful gearing of regulatory control and the provision of sufficient support and investment. There are a number of hurdles to competitiveness, and sometimes materials developments are not addressed, simply because they are difficult to design and engineer. However, increasingly now, new ideas are based around functional convergence with the behaviour of natural tissue, though this can be exceptionally difficult to understand and even harder to mimic. Other barriers include scale-up manufacturing, sterilisation, packaging and industrial sustainability. Added to these problems is also the lack of sufficient investment, both public and private, in particular to cover the costs of clinical tests/trials.

There are still significant problems faced in the translation of laboratory ideas into the clinic. One issue is that new developments often occur ahead of the changes required by the regulatory framework. Even now the regulatory framework is relatively cumbersome – and it is likely that future developments will add further complications with, potentially, negative implications for novel biomaterials, particularly in the field of Advanced Therapy Medicinal Products. Another major issue is the funding gap between in vitro laboratory research and in vivo validation of results. This places significant constraints on the move from innovative biomaterials science through to clinical evolution.

A need has been identified for increased connectivity between the Research Councils (e.g. EPSRC and MRC) in order to co-ordinate funding sources for pre-competitive research. Although currently there are improving numbers of clinician representatives advising the Research Councils, their relatively small number coupled with a high turnover can lead to reduced levels of continuity. Funding is also required to leverage and encourage interactions between different disciplines (ranging from fundamental materials science, through surface chemistry to biological sciences) and ideally investment is required for universal access to major investigative tools (the Diamond Light Source being a notable exception to this).

The strong science base in the UK does not yet appear to have the ideal balance in terms of funding and support mechanisms to translate commercialisable ideas into products. This gap between concept and clinic is in part due to companies who are unwilling to take financial risks. Some large device companies are focused on cost saving rather than product innovation. A lack of continuity in funding, especially for innovative ideas to take them beyond the concept stage, causes delays in industrial uptake and therefore eventual patient benefit. The emergence of new funding opportunities (such as the Biomedical Catalyst) which support different stages of innovation from concept to application in patients will give the UK a major advantage in these areas. It seems that this is an opportune moment to instigate a national debate to allow a formative assessment of whether the current balance between fundamental science and translation is correct.

Therefore, in summary, there is an urgent need for a review to identify appropriate directions for funding and the establishment of a comprehensive translation model to ensure that the next generation of exciting new products is moved swiftly towards clinical application. This will, for example, provide for healthy ageing which has, potentially, a huge market and opportunities.
THIS PAGE
DC Bead vials

OPPOSITE
Screw/anchor for tendon/ligament repair
RESEARCH OPPORTUNITIES FOR THE FUTURE

Some areas that have been identified for the future include:

- Therapeutics through design of nanostructures
- Human wellbeing, early diagnosis and preventative medicine (with the promotion of “prevention” rather than “cure”)
- Advancement in applying cell-based therapies and regenerative medicine
- Advancement of diagnostics tools to detect the early signs of diseases and also for disease prevention
- Designer polymers with controlled mechanical and chemical properties/motifs; convergence of the nanoscale with chemistry; smart (reactive) materials; nanostructures for controlled delivery and theranostics; stealth polymers; oligomers and polymers for gene transfer
- Development of synthetic biomedical materials with the ability to mimic the physiological extracellular environment, for tissue repair and regeneration
- Nanoscale, biomimetic, biohybrid structures, membrane technology for improved separation systems (renal, liver, lung function support) and for cell encapsulation

For the next ten years, the major developments are expected to be in the area of regenerative medicine, stratified medicine (which includes the development of new drugs, diagnostics and imaging tools requiring materials), as well as remote sensing and monitoring, especially applicable to the ageing population and those suffering from chronic conditions. There is no doubt that there will be significant pressure on the healthcare providers due to the increasing number of people living well beyond 65. It is also important to note that there are many new challenges in preventative medicine, associated with major issues such as obesity which can make a significant contribution to a number of diseases such as diabetes, cardiovascular disease and cancer. Since healthcare is a global issue, it is also essential that any proposed innovation or research activity will consider its global, rather than national, utilisation. Therefore, it is important to remember that research is likely to prove cost-effective, especially when adapted for global healthcare.
A pit on the surface of a medical-grade polyurethane, which was injection moulded and cured in air. The image was obtained via an optical interferometer, used to measure roughness of these materials.

Image Scale: The plane dimensions are 0.34 mm x 0.26 mm.

LEFT
Screw/anchor for tendon/ligament repair
MECHANISMS TO ENABLE TRANSLATION

What is required to make these developments happen? Clearly, sufficient Government funding is essential, but alongside this, industrial investment should continue to be encouraged. Public investment should be maximised through the model proposed by the Technology Strategy Board (TSB) to facilitate collaborations between research organisations and industry. However, the rules set out for TSB-based funding can be restrictive and do not necessarily promote investment in micro- and spin-out companies. Capital investors should be attracted towards this field through a more co-ordinated and inclusive approach. A survey of the activities of universities in the sector might be highly instructive and the results might usefully be made available to capital investors and biomedical companies. It is clear is that education and training are also essential for 21st century healthcare.

To address these points, it is recommended that future Grand Challenges are identified to assist in focusing the UK effort. A survey of successful European models might reveal new research strategies for the UK. The possibility should be explored of funding a National Centre providing access to world leading facilities to researchers across the UK community, to reduce resource duplication.

From the clinical perspective it is proposed that "co-ordinators" should be appointed to liaise between young consultants, academics and industry. In an era when specialist languages (and acronyms) are developing rapidly, these individuals might help to identify the priorities in healthcare as well as encouraging greater interdisciplinary collaboration. Emphasis should continue to be placed on medical research to advance professional careers, but should also have increased focus on improving palliative non-operative care and comfort for the patient with the introduction of more surgical implants.

There will necessarily be new challenges in the conversion of the areas described earlier in this document from the laboratory to the clinic (and hence into the NHS) and these include:

- Ensuring appropriate connectivity between the supplier, the notified bodies, the MHRA and NICE, based on experience from drug technological advances.
- Ensuring an efficient and effective process of regulatory approval (with consideration of classification of new categories of device as the emerging field develops).
- Availability of more evidence-based information through preclinical/clinical trials to support the assessment of the effectiveness of new technologies.
- Provision of opportunities for effective exchange of understanding and information between clinicians and materials scientists in the development of new technologies.
- Working towards improved methodologies for handling, storage and scale-up production of cells in clinical applications.
CONCLUSIONS

This report highlights the fact that there are a number of medical conditions and major diseases suffered by the ageing population. However, a change of emphasis is required to allow focus on “prevention rather than cure” and hence research is required to characterise pre-clinical states right through from the neonatal stage to diseases currently associated with old age. There are several very exciting areas coming on stream and it is important that the current levels of support are continued to ensure that multidisciplinary research collaborations are fostered, focusing on new biomaterials that can regenerate tissues or deliver therapeutic molecules (e.g. cancer treatment using nanoparticles).

Hence, the development of highly innovative materials designed for specific applications should be funded and financing should ideally cover not only the costs of R&D, but also industrial feasibility studies and eventually clinical studies where commercialisation potential is clear. The major funding organisations need to encourage joint industry/academia/clinician collaborations to ensure the most effective use of skills and capabilities in the UK in order to support innovation and commercialisation. This includes the training of suitably qualified personnel for the development and implementation of new technology. Investment in materials science should be targeted to strategic disease areas, with focus on translation and clinical application, integrating other disciplines to ensure that a holistic or platform solution is developed.
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