

Orthopaedic Implant Technology: Biomaterials from Past to Future

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Abstract

Orthopaedic implant technology is heavily based on the development and use of biomaterials. These are non-living materials (e.g. metals, polymers and ceramics) that are introduced into the human body as constituents of implants that fulfil or replace some important function. Examples would be prosthetic joint replacements and fracture fixation implants. For orthopaedic biomaterials to succeed in their desired functions and outcomes in the body, a number of factors need to be considered. The most obvious mechanical properties of the implants are that they need to suit their intended function, and various classes and types of biomaterials have been developed and characterised for use in different implant components depending on their demands. Less well understood but no less important are the interactions that occur between the constituent biomaterials and the living cells and tissues, both of the human host as well as pathogens such as bacteria. Biomaterials used for orthopaedic applications are generally considered to be biocompatible. However, adverse effects arising from interactions at the implant interface can result in various modes of implant failure, such as aseptic loosening and implant infection. This review paper uses the illustrative example of total hip replacement (which has been called the operation of the century) to highlight key points in the evolution of orthopaedic biomaterials. It will also examine research strategies that seek to address some of the major problems that orthopaedic implant surgery are facing today.

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Introduction

The orthopaedic implant sector forms a significant portion of the worldwide biomedical industry. In the US alone, the orthopaedic implant market was estimated at over US\$14 billion in 2008, and this is projected to rise to US\$23 billion by the year 2012.¹ Within this large and diverse field of orthopaedic surgical practice, there are 4 major implant applications: (i) reconstructive joint replacements, (ii) spinal implants, (iii) orthobiologics and (iv) trauma implants. The clinical need in all of these areas is anticipated to continue to grow for the foreseeable future, boosted by local and worldwide ageing populations, as well as increasing prevalence of physically active lifestyles and higher expectations of quality of life in older age groups.

Success in the application of an orthopaedic implant depends on the complex interplay of a number of factors. In broad terms, these can be grouped into surgeon factors, patient factors, and implant factors. The surgeon of course plays a crucial role in determining the success of a particular orthopaedic implant, not only through their

surgical technique and expertise, but also by the choice of implant type and design appropriate for a particular patient and condition. Patient factors are no less important, as the patient is not merely a passive recipient of the implant, but an active end-user as well. Patients can thus affect the outcome and long-term results of implant surgery not just by their medical status and physiological responses to the implant, but by their activities and compliance to medical instructions that can affect implant survivorship. Within the ambit of this review paper however, we shall be focusing on the third factor of this triad: the implant itself.

Orthopaedic implants are manufactured devices that have been designed and developed to fulfil particular functions when implanted into the living body, and usually for specific indications. The non-living materials that are used in their manufacture are termed biomaterials, as these materials are intended to survive and function as foreign bodies within a biological environment, i.e. in the living human system. Implants may consist of a single type of biomaterial

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such as in surgical stainless steel plates, or comprise a number of different biomaterials working together in modular parts, such as in a total hip replacement system which may contain up to 4 or more different materials such as titanium, cobalt-chrome alloy, polyethylene and polymethylmethacrylate (PMMA or bone cement). Prime examples of widely-used technology would include prosthetic hip and knee replacements for various types of arthritis affecting these joints, spinal fusion instruments for stabilising degenerate and unstable vertebral segments, and fracture fixation devices of various types such as plates, screws and intramedullary rods. Less common implants in which the technology may still be in varying phases of maturity, as well as those which are in development but may not yet be established in clinical usage, would include other joint replacements such as for shoulder, ankle, elbow and small joints, artificial vertebral disc replacements, and orthobiological implants such as artificial scaffolds for osteochondral defects and knee meniscal implants.

Whether well-established or not, there are some guiding principles that will have a general bearing on the ultimate viability of an implant. Firstly, the design of the implant has to be sound and takes into account all biomechanical and biological factors that may affect its success. Conformity to native anatomy, mechanical strength appropriate for the targeted function and environment, and suitable material properties of the constituents are just some examples of the considerations that come into play. One illustration would be that titanium, despite being an excellent orthopaedic biomaterial that is currently in widespread clinical usage, is never employed as part of an artificial joint articulating surface (i.e. the part that moves against another joint surface), as its material properties are simply inappropriate for this purpose: it does not have sufficient wear resistance, nor does it possess the desired low frictional characteristics. Instead, cobalt-chrome alloy is nearly universally used for this purpose, despite not being as friendly physiologically as titanium at the cellular level.² This leads to the second consideration, which is that the implanted biomaterial in its intended form must be biocompatible to an acceptable degree, and should not exhibit significant or unacceptable levels of toxicity or adverse physiological effects. Taken at face value, this seems simple enough; however the scientific research and clinical experience suggest that the reality is far more complex. An example would be the previously mentioned example of cobalt-chrome alloy (CoCr), which is ubiquitous in knee and hip replacement surgery. This alloy has been in clinical use for several decades now, which would seem to imply that its biocompatibility is well-established. Indeed, in its bulk form, the material is relatively inert and does not appear to excite significant tissue reactions, although in applications requiring contact

and bonding with host bone (osseointegration), it is certainly inferior to titanium. However, there have been recent concerns that the particulate form of CoCr, such as in wear debris generated from metal-on-metal joint articulations, may in certain patients stimulate certain tissue reactions (lymphocytic infiltrations and cell necrosis) that can affect implant success.³ Such phenomena still await further characterisation and clarification.

Even without the difficult and controversial issues of biocompatibility and host reactions, orthopaedic implant surgery is still not guaranteed success. Take for example joint replacements, where the implant longevity depends on its proper functioning in an aseptic environment, as well as stability of the parts bonded to the host bone. Two main problems that still confront the long-term success of these prosthetic implants are sub-optimal osseointegration at the biomaterial-host tissue interface leading to implant failure from loosening; and susceptibility of the inert implant material to infection by inoculated or circulating bacteria, leading to implant infection that can be impossible to eradicate without implant removal. These challenges still need to be addressed, and are currently the focus of a burgeoning area of research in biomaterial technology which shall be discussed in a later section of this review.

As can be seen from the above discussion, orthopaedic implants form a diverse group of applications and designs, compounded by the range of biomaterials available together with attendant issues affecting success and survivorship. Technology and research in this area thus need to consider all these complex factors in coming up with improved function and outcomes for the future. To illustrate the fascinating processes behind the evolution of such implants for successful clinical use, we shall now consider the development of one prime example: the total hip replacement, also known as total hip arthroplasty.

Evolution and Developments in Total Hip Arthroplasty

The total hip arthroplasty has been affectionately named the operation of the century.⁴ This moniker reflects the measure of success in which good, predictable long-term results have been achieved. Its current successes owe much to its modern orthopaedic implant design, the development of which is a testament to human ingenuity in melding medicine, materials science and mechanical engineering. Much can also be appreciated in understanding the processes of designing a complex biomechanical system that can survive and function in constant interaction with living human tissue.

Early attempts at hip arthroplasty using implanted material (both tissue-based as well as foreign substances) involved experimentation with a wide variety of different materials, including muscle, fat,⁵ rubber, decalcified bone

and pig bladder, to name a few.⁶ These early results were disappointing. Concurrently in Germany, Themistocles Gluck led the way in the development of replacement hip implant design. In 1891, he produced an ivory ball and socket joint that he fixed to bone with nickel-plated screws.⁷ Gluck originated orthopaedic implant concepts are still in use today, including stable fixation of the artificial joint, the use of bone cement, modular constructions of artificial joints assembled by the surgeon at the operating board, and the idea of biocompatibility. Meanwhile, Marius Smith-Petersen at Harvard Medical School provided the first synthetic interpositional arthroplasty, using a glass prosthesis. However, the glass moulds were prone to breaking, and Smith-Petersen then used Vitallium, a cobalt chrome alloy then recently introduced, to a mould prosthesis for the hip which provided the first relatively predictable results in interpositional hip arthroplasty.⁸

In the early to mid 20th century, many different combinations of materials were increasingly explored as candidate bearing surfaces for total hip arthroplasty. Metal-on-metal total hip replacements were first implanted in the 1930s, and later developed in the 1950s and 1960s by pioneering surgeons like McKee and Ring. In 1970, Boutin developed the first ceramic-on-ceramic total hip replacement. However, it was Sir John Charnley's hard-on-soft bearing concept that eventually dominated the other hard-on-hard bearing alternatives for the decades to come. Major contributions to the evolution of total hip replacement by Charnley were the idea of low friction torque arthroplasty; use of acrylic cement to fix components to living bone; and introduction of high-density polyethylene as a bearing material in the artificial joint. However, before reaching his ultimate design with polyethylene, Charnley had first experimented with Teflon as a low friction surface material, with spectacular failure: Teflon exhibited unacceptably high wear rates in vivo, and also provoked intense tissue reactions. By a stroke of luck, in 1962 Charnley was approached by a UHMWPE (Ultra high molecular weight polyethylene) salesman who had tried to sell him a sample for use in hip implants; originally the material was manufactured for automobile gearboxes. Initially rejected by Charnley, the idea was secretly tested by his technician Henry Craven, showing that UHMWPE had in 21 days exhibited less wear than Teflon after a single day.⁹ The importance of Charnley's subsequent development and popularisation of metal-on-polyethylene hip arthroplasty cannot be understated: first-generation results of his low friction arthroplasty show impressive long-term results of 77% to 81% survivorship at 25-year follow-up,^{10,11} with revision of any component as the endpoint.

However, a new complication was looming on the horizon. Presenting as insidious hip pain and appearing on

radiographs as massive bone lysis resembling metastatic malignancy,¹² an epidemic of periprosthetic loosening took the orthopaedic world by surprise. Tissue examinations revealed an inflammatory reaction around the implant border with macrophages displaying minute particles embedded in them.¹³ Initially these particles were thought to be bone cement, leading to the erroneous term "bone cement disease" being coined in 1987. Ultimately, it was ascertained that the problem was due to polyethylene wear particles stimulating a macrophage response, but not before the perceived problem with bone cement had given impetus to a new direction of development in hip arthroplasty: that of uncemented hip designs relying on biologic fixation through osseointegration, independent of bone cement. Implants were developed with porous coatings or a roughened surface which allowed bony apposition to anchor the implant. Thus did a mistaken idea give rise to the development of new concepts that are in widespread use today?

The identification of polyethylene wear particles as the implicated factor in periprosthetic osteolysis and aseptic loosening in turn led to further developments in polyethylene technology, as well as a resurgence in interest in alternate bearing combinations. Although the chemical formula for UHMWPE remains the same, individual manufacturing processes and subsequent post-manufacture modifications can lead to very different mechanical properties of the end product. Studies in the late 1990s established oxidative stress as the main cause of polyethylene degradation.^{14,15} Gamma radiation traditionally used to sterilise UHMWPE produces free radicals, which, when combined with oxygen, produce chain scission. When UHMWPE components are irradiated and stored in air, the mechanical properties of component begin to deteriorate on the shelf as well as further in the body after implantation.^{16,17} UHMWPE implants are now gas sterilised by ethylene oxide, which eliminates the formation of free radicals or are irradiated only in high vacuum. Gamma irradiation of polyethylene also results in polymer chains with stable C–C chemical bonds. Coupled with newer post production methods such as various annealing protocols,^{18,19} this form of crosslinking greatly improves wear resistance compared to conventional polyethylene,²⁰ reducing the number of biologically-active submicron wear particles generated. Thus far, clinical results for highly cross-linked UHMWPE have been promising,²¹ potentially addressing at least part of the problem of polyethylene-related osteolysis. Another direction of research in countering oxidative degradation in polyethylene is the development of vitamin E impregnated UHMWPE. Vitamin E is a natural antioxidant that known to be safe and biocompatible.²² Early reports are encouraging in suggesting that this new additive may be effective in decreasing oxidation and wear rates, but longer term results

are awaited as this is an additive with no clinical history in joint replacement.

Interest in alternate bearings to polyethylene has also been rekindled by the problem of polyethylene-related osteolysis. Younger, active patients as opposed to their older and more sedentary counterparts inflict as much as 40 fold greater wear on their hip joint bearing couples. Alternative bearing surfaces such as metal-on-metal or ceramic-on-ceramic (i.e. hard on hard) as compared to metal on UHMWPE (hard on soft) are being developed and assessed to address these issues. Metal-on-metal bearing surfaces were first used widely in the 1960s. The early generations suffered from poor fixation, inferiorly manufactured materials and generally had high failure rates. However, long-term follow-up of implants with polar (central head) bearings showed good survival and little wear without the difficulties associated with polyethylene-induced osteolysis.²³ Metal bearing surfaces have low wear rates in the region of 0.004 mm per year compared in contrast to 0.1 mm per year for polyethylene. Metal is also ductile, not brittle, unlike ceramics, hence, implant sizes can be kept thinner without risk of implant fracture. Thus, for a given acetabular shell size, a large head diameter can be used, which provides enhanced joint stability and a large range of movement before the neck impinges on the socket. Metal-on-metal bearings are also self-polishing, allowing for self-healing of surface scratches. However, although these bearings have the potential for low wear rates, they still generate of metal ions, which are detectable systemically as well as in blood and urine, and the long-term effects of such dissemination remains to be determined. Recent concerns have also arisen regarding the local tissue effects of CoCr particles³ and further clarification is needed. Ceramics have also been used as a bearing surface for several decades. Alumina ceramic has been used in hip replacements for more than 35 years, and it can be characterised into 4 distinct generations. First generation alumina (1970s) had a low density, a very coarse microstructure, and was not in compliance with specifications. Second generation alumina (1980s) had a reduced microstructure grain size. Third generation alumina (1990s) had improved mechanical strength, further reduced microstructure grain size, and was manufactured by using hot isostatic pressing. In 2000s (fourth generation, Delta), a new alumina matrix composite material with improved material properties was developed. The advantages of using alumina ceramic as a bearing surface in total hip arthroplasty are related to its hardness, wettability, fluid film lubrication, inertness, high level of oxidation of alumina ceramic which provides resistance to scratches, and high biocompatibility.

Developments and Research for the Future

Despite great advances in joint implant technology, the

holy grail of joint implant surgery has yet to be achieved: a truly long lasting implant in a young active individual. Current problems that contribute to implant failure include the major conundrums of failure of the bone-implant interface (lack of osseointegration) and implant infection.

Titanium and its alloys have been used extensively as implant materials in orthopaedic applications, and the naturally formed oxide layer on the titanium surface provides it with biocompatibility and bioactivity. However, the osseointegrative bioactivity is still often not sufficient to attain true adhesion between the implant and bone, which may ultimately lead to mechanical instability and implant failure.²⁴ Cobalt-chrome alloy is known to have much less potential for osseointegration. Strategies to enhance osseointegration include the use of newer biomaterials with enhanced osteoinductive properties, such as tantalum. Surface modification of metallic biomaterials may also prove to be a viable future strategy to enhance implant integration with bone and induce acceleration of bone healing phenomena. Many attempts to activate the surface have been made based on the control of surface topography²⁵ or surface energy²⁶ via either physical or chemical approaches.

The physical approach is focused on the modification of the implant surface morphology and topography using mechanical methods such as machining, acid-etching, plasma spraying, grit-blasting and anodisation to improve the microtopography of the surface. The rationale behind this is that an increase in surface roughness of the implant material would provide a higher level of surface energy which would improve bone anchorage, matrix protein adsorption, osteoblast functions and ultimately osseointegration.²⁷

The chemical approach is towards the creation of a bioactive implant surface via application of coatings onto the implant layer by biochemical and physicochemical techniques. In biochemical techniques, organic molecules such as growth factors, peptides or enzymes are incorporated to the implant layer to affect specific cellular responses.²⁸ While in physicochemical techniques, the incorporation is achieved with inorganic phases such as calcium phosphate which may increase the biochemical interlocking between bone matrix proteins and surface materials thereby enhancing bone-bonding.²⁷ Most implant modifications would involve a combination of both physical and chemical engineering methods, and in the following sections, we will discuss some of the current strategies used to enhance implant integration and bone-bonding.

Calcium phosphate coatings have been widely used in the orthopaedic field due to their similarity with the mineral phase of bone²⁹ and are well known for their bioactive properties beneficial in bone-bonding.³⁰ As calcium phosphate lacks the mechanical strength for use as a bulk

material under loaded conditions, it is usually deployed as a coating on the surface of metallic implants. There are several studies published which have shown the favourable use of calcium phosphate coatings in increasing bone-implant interface, implant anchorage and integration.^{31,32} The calcium phosphate layer functions as a physiological transition between the implant and the host tissues, guiding bone formation along the implant surface and the surrounding tissues. One of the most successful methods for the application of calcium phosphate is via the plasma-spraying method, which has the advantage of extensive coating capability and high deposition rate. However, despite a number of reports on the beneficial osteoinductive properties of plasma-sprayed calcium phosphate coatings,³³ there are still some concerns regarding its use. Plasma-sprayed coatings are not uniform, and there is poor control over thickness and surface topography, which may result in implant inflammation when particles are released from these heterogeneous coatings. To overcome these drawbacks, various other deposition strategies have been developed and employed such as biomimetic deposition, electrophoretic deposition and electrospray deposition etc. However care should be taken when comparing the efficacy of each of these methods which would require a comprehensive evaluation of both biological response and clinical performance. Although calcium phosphate coatings have been shown to be beneficial in enhancing bone-bonding, there is still no general consensus on the best form of coating systems.

Surface modification of implant materials with growth factors and peptides is gaining popularity in the recent years.^{34,35} Various therapeutic biomolecules of interest can be immobilised onto implant surfaces to enhance bone-implant interface interactions. Promising approaches would include the immobilisation of bone growth factors such as bone morphogenetic proteins (BMPs) onto biomaterial surfaces to enhance osteogenesis, and peptide sequences to induce

specific cellular functions. Growth factors immobilised on orthopaedic devices have been reported to enhance osteoblastic activity and favor implant integration.³⁶ The most commonly used growth factors in orthopaedics are members of the transforming growth factor beta (TGF- β) superfamily including the BMP family, especially BMP-2 and BMP-7. Growth factors may be physically adsorbed or covalently grafted onto the implant surface and various studies have shown that the functionalisation of implants with these factors can enhance interactions at the bone-implant interface and aid the remodelling process to improve implant integration.³⁷⁻³⁹

Critical factors in the successful use of growth factors in orthopaedic devices are the optimum dosage, exposure period and release kinetics. These have to be considered carefully to avoid the detrimental effects associated with growth factor use such as high initial burst rate, ectopic bone formation and short half-life. Our research group have developed biomolecular techniques to chemically attach bioactive molecules such as BMPs to biomaterial substrates, while retaining biological activity of the chemically bonded biomolecules.^{40,41} Our results showed that osteoblastic activities and bone formation can be stimulated by such surface-functionalised biomaterial substrates. As illustrated in Figure 1, osteoblasts seeded onto surface-functionalised biomaterial substrates developed by our research group were spindle-shaped and exhibited a healthier morphology, whereas the cells on pristine non-modified substrates were stunted and less elongated. Osteoblasts seeded on the modified biomaterials also showed greater capacity for bone matrix formation compared to the non-modified biomaterials (Fig. 2).

More recently, peptide sequences with the ability to target specific osteogenic cellular functions such as differentiation and mineralisation have been developed.^{42,43} These short

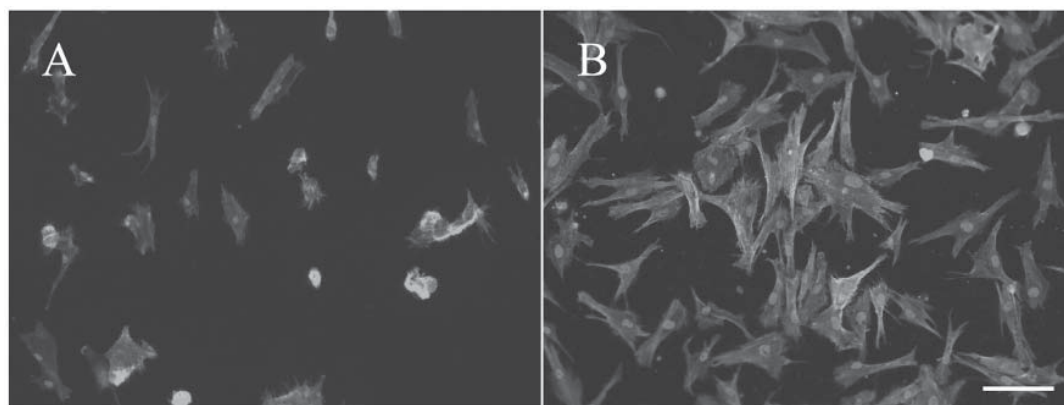


Fig. 1. Analysis of cell morphology of osteoblasts on surfaces of (A) pristine non-modified substrates, (B) substrates functionalised with osteoblastic moieties. The scale bar represents 100 μ m.

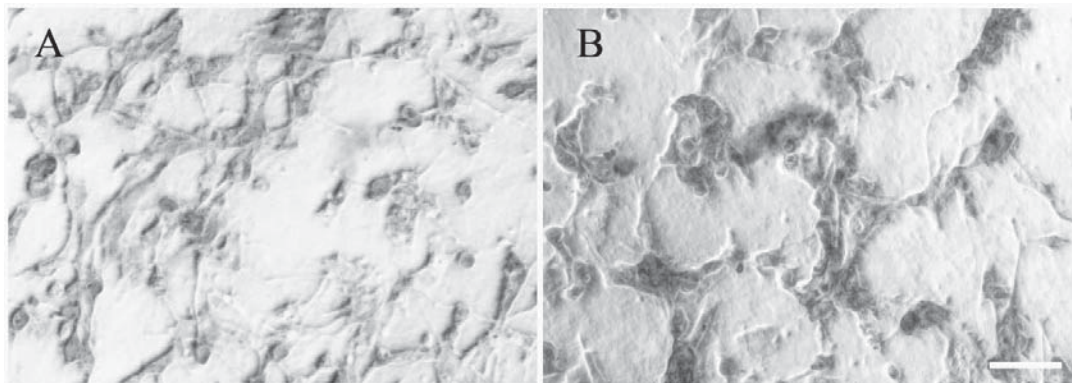


Fig. 2. Alizarin red staining for the presence of calcium deposits of osteoblasts on surfaces of (A) pristine non-modified substrates, (B) substrates functionalised with osteoblastic moieties. The scale bar represents 100 μ m.

functional fragments derived from the original protein have increased shelf life, can be synthetically produced and are more resistant to denaturising effects. Their usage would provide significant clinical benefits over the use of conventional proteins. They can be linked to implant surfaces to provide biological cues for bone formation. Peptide sequences in use include the BMP knuckle epitope, RGD, YIGSR, IKVAV and KRSR which have been used to improve cellular adhesion and bone matrix formation.^{44–46}

Techniques used for the modification of implants with growth factors or peptides would include physical adsorption systems, encapsulation systems and covalent grafting. Of these, covalent grafting is the usual preferred method, due to its advantages of having very high surface loading, low protein loss, and lack of undesirable effects at locations beyond the implant site in the body. However, this approach entails technically complex considerations. One of the problems encountered with biomaterials for covalent grafting is the lack of suitable chemical groups on the implant surface. The implant surface is derivatised into various reactive groups and for more versatility and applicability, the concentrations of the OH group and other reactive groups such as amino or carboxyl groups have to be increased. The initial organic layer immobilised on the biomaterials can then be used as a tether for the biomolecular moieties used to mediate cellular functions. In practice, the preferred immobilisation technique chosen would largely depend on the specific working mechanism of the biomolecules and their clinical viability after immobilisation.

A number of studies have also looked into the development of bioactive composite coatings to mimic the structure of the bone tissue. These composite coatings may combine calcium phosphate with growth factors, peptides and antibodies to enhance interactions at the bone-implant interface.^{47–49} Coating techniques that create gentle and sustained release kinetics are preferred to avoid the undesired high initial burst rate of biomolecules observed in some studies. A recent

study reported that a calcium phosphate coating combining slow release of factors aids in early success of bone cell recruitment.⁵⁰ Other studies have shown that depositing BMP-2 and TGF- β onto the implant surface would greatly enhance bone-bonding at the bone-implant interface.^{36,47}

Another aspect of biomaterial modification is the development of antimicrobial surfaces. As with all artificial materials in the body, orthopaedic implants act as foreign bodies within living tissues and hence are prone to infection. Adherence of inoculated or circulating bacteria onto implant biomaterial often leads to formation of a bacterial biofilm, which then protects the pathogens from the host immune defences.⁵¹ Infections are catastrophic complications to any joint replacement, often necessitating the total removal and revision of an implant with severe resultant morbidity. Much progress has been made in providing physical barriers in ensuring a sterile operating field, including developments in laminar air flow theatres, closed body suits and pulsatile lavage systems. Another approach is to imbue the components in an implant system with other active antimicrobial components, thus improving the local resistance to infection at the time of implantation. Antibiotic impregnated cement is widely used for this purpose. A recent meta-analysis concluded that the use of antibiotic-impregnated cement lowered the infection rate by approximately 50% in primary hip arthroplasty.⁵² However, persisting concerns regarding the adverse effect of antibiotics on the mechanical strength of cement⁵³ as well as the possibility of promoting resistant strains of bacteria⁵⁴ still limit the potential of this strategy. Also, the impregnated antibiotic leaches out with time and antibacterial activity is lost after about 2 weeks. In order to address these issues, our research group has developed various forms of selective biointeractive surfaces which inhibit bacterial adhesion without interfering with osteoblast functions, including immobilisation of antibacterial molecules dextran and chitosan on titanium.^{55,56} In combination with surface-functionalisation with osteoblastic moieties, our techniques

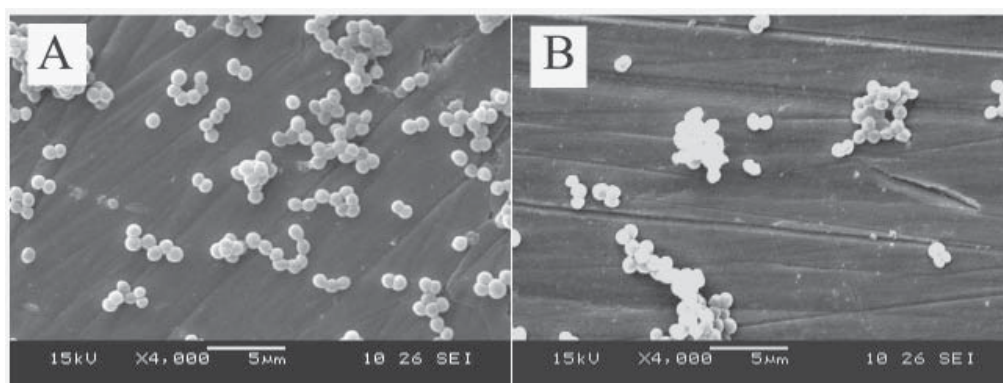


Fig. 3. Scanning electron microscopy of *Staphylococcus aureus* on surfaces of (A) pristine non-modified substrates, (B) substrates functionalised with antibacterial molecules.

were shown to confer the dual biological activities of enhancing osteoblastic activity as well as antibacterial activity simultaneously, leading to the potential for clinical application in implants of the future. As illustrated in Figure 3, the biomaterials functionalised with antibacterial molecules by our research group were able to inhibit the adhesion of bacteria as compared to the non-modified biomaterials.

In conclusion, orthopaedic implant technology has already achieved much in a relatively short span of a few decades, and we currently have implants that work well in many patients over reasonable periods of time. However, the current generation of implants are still not without problems, and long-term performance is still an issue particularly in younger high-demand patients. It is hoped that continuing breakthroughs in implant technology research will lead to translational clinical applications for improved implants of the future. The biological efficacy of orthopaedic implants can be improved greatly by both physical and chemical modifications. The use of a wide multitude of engineering techniques in the manipulation of surface topography, morphology and incorporating the use of various inorganic and organic components would directly influence the response in the local bone-implant interface and the apposition of new bone. With the development of new techniques and strategies on composite coatings to better mimic the human bone structure, this would result in a new generation of orthopaedic implants with improved implant integration and bone healing.

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