JRI for medical technologies

The Northern Research Partnership: overview: The University of Aberdeen, the University of Dundee and the Robert Gordon University have joined together to establish a research partnership in engineering and related disciplines, known as the Northern Research Partnership.

The purpose of this partnership is to pool research strength in areas common to partner universities, and to exploit areas of complementarity. It is the first time that the institutions have agreed to go beyond collaboration on an ad-hoc basis towards a convergence of research priorities in the area of engineering research. This will enhance research performance of the participating groups in all partner universities by creating critical mass, and increase significantly the competitiveness of research groups in the region. The proposal mirrors the establishment of similar regional partnerships in Edinburgh and Glasgow.

Research activity is taken forward through four JRIs and one overarching joint research group:

JRI for Civil Engineering (also to form part of the national Telford Institute)[1]
JRI for Computational Systems
JRI for Energy & Clean Technologies
JRI for Medical Technologies
Non-linear and Complex Systems Group

The partner universities have also set up a common Graduate School to support and enhance research student activities.

The partner universities have selected members for the JRIs with a view to international excellence, applying stringent criteria relating to research grants and contracts income and RAE submissible publications. The partnership represents a cluster of research groups in the engineering area, comprising 135 researchers, 160 research assistants and 286 PhD students.

JRI for medical technologies: Summary

Healthcare affects every member of the population and recent advances have fuelled a high level of expectation in terms of treatment quality and possibility. Whilst the field by definition is expansive, we are drawn to three particularly challenging areas to focus our initial programme of collaboration. The institutions involved each have a vested and prolonged interest in these areas of commonality, and more importantly, can offer strength in the breadth and depth of our complementary approaches and expertise. The three major challenges to be overcome involve:

- long-term practical interfacing of artificial, man-made devices with human tissues and organs especially via optimisation of surface coatings;
- the creation of practical living-tissue engineered prostheses;

1 This JRI will also involve a researcher from the University of Abertay, Dundee.

• novel technology-driven enhancements to minimally invasive protocols;

The triumvirate strategy thus involves the execution of research projects that address the above challenges via respective themed programmes involving:

• Biomaterials, Bioengineering & Biomechanics;
• Tissue Engineering and Regenerative Medicine;
• Innovative Surgical Technologies.

By necessity, this interdisciplinary proposal brings together existing research groupings consisting of physical scientists and engineers with expertise across Surface and Materials Science, Bioengineering, Tissue Engineering and Surgical Technology. Very close collaboration has also been developed with both academic, and active hospital-based (Ninewells Hospital Dundee & Aberdeen Royal Infirmary), scientists and clinicians from the requisite disciplines of Surgery, Orthopaedics, Radiology and Cardiology, many of whom are drawn from 5* RAE departments (e.g. Surgery and Molecular Oncology & Cardiology at Ninewells).

The deliverables from the research conducted by groupings of members of the JRI will include preliminary proof of concept insights, in depth scientific investigation with resultant high impact publications, as well as more tangible IP across a range of new medical devices, including implants, tissue engineered components and surgical devices.

1. Biomaterials, Bioengineering and Biomechanics

Biomaterials & Surface Engineering Background
The key to biocompatibility lies in manipulating the fundamental interactions which occur between the artificial and host biological systems. This requires control over surface properties of biomaterials/device coatings in order to achieve initial compatibility followed by long-term *in situ* stability to prevent bio-fouling. Success in this field requires an interdisciplinary approach involving the development of novel biomaterials, the modification of existing materials for enhanced compatibility, detailed surface studies and surface-driven processes, and a wide range of long-term viability and monitoring work, including studies in animal models. All three universities already have strong track-records in complementary areas relating to this field.

The Materials group at RGU are internationally recognised for their fundamental surface science, surface engineering and biophysics research. Over the past eight years RGU has invested heavily through capital equipment expenditure and associated technical support and the recruitment of academic research leaders to develop one of the leading UK centres for surface and interface science. A SHEFC RDG award (£0.83m) was granted in 2001, which has extended capability into the fields of biomaterials and bioengineering. Complementary to this, studies at UoD have focused on the development of non-fouling surfaces for implants and surgical instruments, an objective that hopes to overcome this pervasive problem with medical devices. This current research programme at Dundee is supported by Department of Health and EU funding.

Other notable complementary programmes that extend across the three universities involve the development of carbon nanotube (CNT) based systems as the basis for surface control of directed cell growth via electric fields (UoA), for more general self assembled electronic and bioelectronic structures (UoD), and as the templates for protein specific absorption (RGU). It is will be a focus of the present proposal to extend and enhance these individual programmes via the formation of a CNT collaborative group that will, amongst other things, attempt to develop this highly novel material into a functional drug delivery modality.

EXEMPLAR PROJECTS

Optimised Biomaterial Surfaces (Bradley[R], McCaig[A], Johnstone[R] , Abel[D], Keatch[D])

• Here, UoA and RGU will undertake collaborative experimental work whilst a computational and modelling approach will be adopted at UoD. We will study conformational properties of peptides during adhesion on surfaces with varied surface energies using different solvents to influence the degree of conformational change and cohesive interactions in peptides. This research, starting with small peptides, will be applied to the design of novel anti-fouling surfaces for surgical instrument applications (where disease transmission, especially vCJD, due to inadequate cleaning is of concern at UK and other national government level) and implant applications (where vascular implants particularly require early removal due to stenosis) and will provide more insight into the nature of the protein adsorption.

• RGU will also lead the development organic nanocoatings using plasma polymerisation[1,2] and deposition techniques which, in preliminary studies have been shown to lead to hydrophilic surfaces which have strong affinity for human primary osteoblast cells[3,4]. Such surface methods when applied to metal substrates, for example, in artificial hip joints, have potential for replacing the currently used ceramic coated joint components thereby further decreasing cases of aseptic loosening. These same coatings and treatments applied to the surfaces of other devices, for example polymeric artificial joints, can be used to directly adhere musculoskeletal and soft tissues selectively to different areas of the device.

Bio-engineering Tissue Scaffolds (Bradley[R], McCaig[A], Sharp[A], Abel[D], Slade[D], Keatch[D])

Controlled chemical patterning[1,2] has also been observed to act as a cue to cell mobility and migration[3,] which links directly with work being carried out by the UoA group in the areas of cell guidance cues. Cell migration, morphology, proliferation and differentiation can all be guided or stimulated using electrical[4], mechanical or chemical gradients and patterned substrates. These are very powerful guidance cues and their relative potencies and the ways in which they can be combined to promote and stimulate cell growth are a major focus. Using such electrical signals as a cue to guide cell behaviour is a relatively unexploited resource in tissue engineering applications and in clinical applications.

• There is a correlation between cell attachment and how cells respond to electric fields[5-8,10]: we will aim to study this correlation, both by using chemically-modified surfaces that will influence cell attachment[1-4], and also by disrupting/blocking the various surface integrin receptors on the cell surface[8]. This approach will be supported by collaborations within the proposed partnership. In addition, this group studies nano-engineered surfaces which act as contact guidance cues to direct nerve growth to facilitate connection to neuronal prosthesis. This work is directly relevant to attempting to discover improved methods to stimulate nerve re-growth following damage to the spinal cord and brain.

• Contact guidance using nano-fabricated surfaces combined with electrical and chemical guidance cues is important also in studies of vascular endothelial and smooth muscle cells using 3-D culture methods to determine how to grow and direct new blood vessels. We can already direct new blood vessel growth using electrical signals. This work is of particular importance in efforts to improve vascularisation of new bone growth, which is often a problem following bone composite implants. Knowing how to stop new vessel growth into tumours would also be a crucial step in the battle against cancer, since tumour growth and the development of secondary tumours depends entirely on directed angiogenesis of new vessels into the original tumour. Revascularization and collateral vasculature growth in occlusive artery disease can be further targets. This work links directly to the work of the Dundee Angiogenesis group.

Bioengineering related Enhanced Imaging Modalities (Bradley[R], McCaig[A], Sharp[A], Abel[D], Melzer[D])

• Interactions of imaging with particular regard to Magnetic Resonance Imaging (MRI) is an existing strength at UoA and will be a new and collaborative research focus in DU[9]. Through the use of coatings in different layers with different electromagnetic characteristics undesired intercations with MRI can be reduced and on the other hand a combination fo conductive, insulating and capacitive layers allows the integration of resonant circuits into implants to improve MRI imaging e.g. of the stent lumen. The electromagnetic function provides a variety of other options such as controlled drug delivery, improved cell interactions and adhesion as well as coupling as an antenna to monitor sensor and actuator elements e.g. for continous blood presure measument or stress/strain sensing at bone implants.

• UoA has a world-leading group studying electrical control of wound healing[6-8,10]. Endogenous wound-induced electric fields have been measured at wounds in animals and humans and in animals the strength of the electrical signal correlates with wound healing. We plan to use two novel techniques to measure the endogenous electrical signals from patients in a clinical setting and correlate the measurements with healing rate. This will directly test the hypothesis that all wounds generate endogenous electrical signals which determine wound healing rates in patients.

• We have measured the electric currents at wounds in humans and plan to extend that work using a new device (Bio-electric Field Imager). This multiple probe, hand-held device also is able to map an electrical profile at a wound without contacting the wound. Both devices are non-invasive and do not require direct surface contact. We shall map the electrical profiles of a variety of clinically important and intractable wounds such as the endogenous electric currents at skin wounds in animals but also, and perhaps most importantly, the multitude of surgical and non-surgical wounds that arise in treating problems associated with the cornea[10,11].

2. Tissue engineering and regenerative medicine

Recent studies in Dundee of adhesion of protein residues on different diamond-like carbon surfaces have shown that modification of diamond surfaces by Si can reduce adhesion of the residues. Electrostatic interactions of point charges created on the surface by atomic substitution have the largest contribution in such reduction. We are proposing to use computational methods to design novel surfaces which promote bone material growth and adhesion to use as bone implants. As bones are built from collagen and hydroxyapatite, a successful bone-friendly material would show high adhesion to both of these components. Currently, most vascular implants are made of stainless steel, cobalt alloys and Nitinol and polymer and ceramic coating with drug eluting function. The majority of bone implants are made off titanium with a polymer cement or ceramic coating that may disintegrate in the body affecting the fitting of the implant. More recently, implants promoting bone growth by means of interpenetration of bone into highly porous materials synthesised from powdered metals by laser sintering have appeared. These materials, however, may have reduced mechanical strength compared to usual titanium-cast implants. A surface coating either in the form of adsorbed self-assembled monolayer or obtained from chemical modification of the titanium surface may considerably increase the implant integration with the bone and thus reduce the risk of implant loosening and increase serving time of the implant. The proposed research will use computational chemistry methods to design different modifications to titanium surface and to screen their properties in terms of protein and hydroxyapatite adhesion. Hydroxyapatite is the important building material of the bone and it has the ability to interact with protein components of the bone structure as well as other tissue cells.

Similarly, investigations have been developed at UoA aimed at designing bone-like compositions that can stimulate bone cell growth. Correlating the new chemistries that have been produced with the behaviour of cells grown on their surfaces will require interfacial studies to be made to correlate how different surface chemistries affect cell growth. Preliminary studies have shown that the contact angle and surface charge of these materials can be altered as a result of their final chemical compositions. In order to produce better implants, and understand better the behaviour of existing implants, establishing the correlation between the surface properties and cell behaviour is a priority and will be a major part of future research and will involve specific focuses for developing artificial cornea from lens epithelial cell behaviour following cataract.

EXEMPLAR PROJECTS

Optimised Bone and Bone Substitutes (Bradley[R], McCaig[A], Abel[D], Johnstone[R] Keatch[D])

• We are developing synthetic scaffold materials (on the back of pilot research funded by ApaTech Ltd and EPSRC) that can be used clinically as bone substitutes, or as support structures on which to grow cells and tissues. As well as the aforementioned approaches, co-culture with endothelial cells and/or fibroblasts will be explored to develop a nascent vascular supply to assist integration with surrounding tissue on implantation.

• At RGU, and as a direct result of previous collaborations with UoA, similar work to that described above, but utilising organic surfaces and chemical guidance cues will be carried out[1-5]. This will be based on the long term culture of viable human osteoblast cells and other connective tissue types. In addition, and in very recent work, a number of tissue culture support materials have been developed which have surfaces with superior proliferation and cell-viability properties than many existing materials. These materials rely on either direct chemical functionalisation of a pre-existing polymer substrate or the application of an organic nanocoating to the substrate. In either case, there is huge potential for both the *in vitro* culture of soft tissue, for example for use in burns treatment and also for the 'activation' of other growth and scaffold structures. Indeed, optimisation of cell attachment, adhesion and proliferation at these new surfaces coupled with EMF[5-8] and/or chemical-gradient driven cell motion, offers a completely new and world leading approach to fabricating 3-D cell specific populated scaffolds for a variety of implant applications. The UoD component of this research area will apply computational methods to design novel short peptides, similar to the natural bone peptide, which can co-crystallise with hydroxyapatite.

Practical Connective Tissues (Bradley[R], McCaig[A], Abel[D], Keatch[D], Melzer[D])

• The development of tissue engineered cartilage, ligament and tendon is a major objective. Development of 3-D matrices is a major goal for workers at both UoA and RGU as de-differentiation and phenotypic changes can occur when cells are grown on 2-D surfaces. The influence of applying shear by fluid flow, tension, hydrostatic pressure, or direct compression will be investigated and compared. A rapid prototyping machine will be used to lay down patterned surfaces of bio-resorbable materials on which we shall grow ligament and tendon fibroblasts and stem cells derived from synovium, as this is the main source of cells in growing implanted ligaments. The UoA group will also apply tensile strains to these constructs to simulate the strains experienced in vivo and further investigate the effects of introducing doses of growth factors into the 3-D supported cultures. Controlled environment micromechanical test facilities are available at RGU to assist with this work. Further applications are controlled growth of cells on vascular implants such as heart valve prosthesis, venous valves and stent grafts, and neuronal engineering for spinal cord repair. In this latter context, the proposal has distinct added value in that UoA have just been awarded a Framework 6 EU grant (1.5 million euros) to develop a spinal cord implant device that will use a modified surface, contact guidance and electrical stimulation to promote nerve regeneration and spinal cord repair. Finally, the conversion of both adipose and bone marrow stem cells into cardiomyocytes has recently been described at UoD and developing a functional cardiac patch[12] will also represent a focus for activity under this remit.

Engineering and directing new blood vessels (McCaig[A], Harris[D], Chaplain[D] Keatch[D])

• Creating a functional, properly patterned and directed blood supply for regenerating tissues is a major obstacle in tissue engineering. Nanofibres that stimulate vascular endothelial tube formation when injected as a gel into experimental animals offer exciting new opportunities. We have shown that electric fields control[5-8,10] and direct growth of new blood vessels in 3D culture and we are translating this to animal models. We shall develop new combinations of electrical signals[13], injectable nanofibres, fixed protein gradients, micro-topographies and biomaterials with different electrical properties to engineer functional and spatially patterned blood vessels.

• The UoD Angiogenesis group has a major focus on new blood vessel growth and in ways of improving the clinical management of patients with impaired wound healing. Expertise[14] in the group includes microengineering, polymer chemistry, cell biology, biochemistry and molecular biology. There are strong ties with the mathematical biology group in Dundee, including the mathematical modelling of endothelial cell migration and angiogenesis[15], and Life Sciences, involving the modelling and synthesis of migratory stimulating factors (MSF) peptidomimetics. Working in close collaboration with clinical staff in hospital units (e.g. Diabetes Centre, Plastic Surgery, Vascular Surgery and Dermatology), we anticipate that the research activities of the Centre will ultimately drive translational studies designed to improve best practice in wound management strategies. A major development from this JRI bid will be the drawing together of the UoA and UoD angiogenesis research in formal collaborations.

3. Innovative Surgical Technologies

Through earlier research undertaken by Professor Johnstone (UoA and RGU) and his team, they have identified several growth factors that have differential effects upon aspects of human meniscal fibrochondrocyte metabolism both in primary cell cultures and explants, resulting in considerably enhanced cellular proliferation, collagen and glycosaminoglycan synthesis. By combining their research findings with those of the Materials Research Centre, RGU, they plan to create novel drug delivery systems by modifying existing materials that are currently used to surgically repair injured menisci. The perceived advantage of this approach is that new surgical techniques will NOT need to be developed to obtain a significantly improved clinical success rate following meniscal repair, which instead will have been achieved through the controlled addition of specific growth factors. Through its relative simplicity, it is anticipated that this approach will facilitate the rapid inclusion of these ‘drug enhanced’ materials into the surgeons’ armamentarium and lead to the creation of similar solutions for repairing other tissues that have poor intrinsic healing potential e.g. articular cartilage, tendons and ligaments.

EXEMPLAR PROJECTS

Novel Devices and Implants (Cuschieri[D], McCaig[A], Sharp[A], Johnstone[R], Abel[D], Melzer[D], Zhao[D])

We have considerable experience in designing novel implants and surgical/interventional equipment. RGU has focused on devices for the Orthopaedic Surgery market which is a substantial - $5.61 billion globally - and continues to grow at 4-5% per annum. Projects in association with three multinational implant manufacturers, but are also the main source of patented ideas licensed to a newly created Grampian based spin-out company owned jointly by RGU, UoA and NHS Grampian. Their research covers many aspects of Orthopaedics including; trauma, small joint arthritis, spinal degeneration, and surgical navigation. They have successfully modified the surfaces of new and existing implants using deposition techniques, aimed at enhancing the mechanical stability of implants in bone by increasing their biocompatibility, while reducing the tendency for bacteria to colonise the exposed sections of implants that, by necessity, exit through the skin.

• The next obvious stage in this research is to undertake *in vivo* projects using small animal models in collaboration with researchers based at UoA. In addition, the RGU group will develop protocols for testing the mechanical properties of new biomaterials, such as metals, ceramics and plastics that have undergone surface modification, to check their performance prior to undertaking *in vivo* experiments.

• The Biomedical Engineering Research Group at UoD is researching the fundamental properties and the applications of smart materials and structures in surgical and interventional instruments and, of particular future interest, in functional implants[16,17]. The group is researching four main categories of smart material; shape memory alloy, piezoelectric materials[16] and structures, electroactive polymers and magnetorheological fluids. For example, two way shape memory alloy is difficult to produce, its properties are not well researched, yet it has considerable potential in miniature implanted actuators. As another example, electroactive polymers (EAPs) have the potential of functioning as artificial muscles and other structural components in the body. UoD and St Andrews University (Dr R.T. Baker) are developing new materials for EAPs. Parts of the structures from which future devices will be made contain materials that will need to integrate with body tissues. Both examples illustrate where research into surface processes will complement the development of implants made from these materials.

• In carbon nanotube (NTs) technological applications, a focus for present interest lies in the incorporation of NTs in bioengineering materials and in the functionalisation of these materials for use in controllable drug delivery applications. In particular, the use of surface treatments and existing surfactant methods to aid the dispersion and interfacial properties of the NTs in polymer based composites along with other processing considerations such as mixing and extrusion are being addressed. All three universities have active complementary research strengths in this area and a major aspect of the present proposal will be to exploit the potential for innovation through technology transfer and the extension of present programmes.

Minimally Invasive Therapies (Cuschieri[D], Campbell[D], Robertson[R], Lawton[R], Johnstone[R])

UoD in collaboration with St. Andrews are developing new modalities and technologies for both image guided therapy and therapeutic imaging for treatment of cancer and other diseases whereby the cell membrane is manipulated through ultrasound (Sonoporation) or Laser (Photoporation) so as to allow an increased uptake of medication, or transfection of the cell with genes. This strand of investigation has significant added value as it has recently been bolstered by a substantial research grant under the ***Basic Technolog*****y 5** call (**£1.04M**) to Dr Campbell at UoD. A focus for that study will involve the development of microbubble systems that will be injected into the circulation and can then be activated by ultrasound once sufficient numbers have accumulated at the site of interest (nominally a tumour).

• Whilst that grant largely seeks to modify FDA & EU approved [contrast agent] microbubbles, the plan with the present undertaking is to develop newer more versatile microbubbles that have distinct chemical targeting strategies optimised for both drug delivery and tumour ablation. We have recently demonstrated the fundamental mechanism whereby microbubbles interact with biological tissues[18] Further, we have covered all the intellectual property arising through that study via three filed UoD patents that can be exploited in the present context. A specific focus will involve the close interaction of the RGU materials group and especially their expertise in polymer oxidation and surface chemistry control, in order to develop a range of microbubbles (solvent extracted and UV crosslinked albumin based) that exhibit the correct shell stiffness to achieve well defined bioeffects such as straightforward lysis or, preferably apoptosis in the tumour cells[19]. Moreover, the effective hydrodynamic 'blast radius' of individual microbubbles can be measured using the somewhat unique chemical patterning facility at RGU so that pre-positioned cells can be examined on target substrates and their post-insonation level of poration ascertained using fluorescence microscopy. This experimental approach represents a typical synergy that will arise directly from facilitating the pooling of laboratory resources at the RGU Materials group, with the expertise available in optical trapping and ultrasonics at UoD (Physics).

• One other such exciting synergy involves the development of more effective physics and chemistry based antibiotics. This is of particular importance in the present context given the prevalence of MRSA related infection to a rising number of post-operative subjects. Particularly ground-breaking work by Robertson & Lawton[20] at RGU has demonstrated the potential for TiO2 based photocatalysts to kill several strands of microbe outright. We propose to develop microbubbles systems that incorporate the correct level of photocatalyst to achieve this bioeffect but that are automatically microinjected into the tissues at large during ultrasound mediated sonoporation. By following up with laser irradiation at the optical wavelength we will effectively provide a contingency antibiotic dose within the surgical protocol. This will be developed in an in-vitro exemplar strand and effectively bring together the Engineering and Applied Science staff expertise from RGU with the laser and ultrasonics expertise at UoD. The potential of this particular strand to make an impact to the NHS, from both an improved protocol and resultant decrease in morbidity, as well as the possibility of pre-empting or at least reducing the risk of MRSA/septic onset, could have significant (and positive) intellectual and financial ramifications.

References

1. Davidson MR, Mitchell SA, Bradley RH; Surface studies of low molecular weight photolysis products from UV-ozone oxidised polystyrene ; SURFACE SCIENCE 581 (2-3): 169-177 MAY 1 2005
2. Mitchell SA, Davidson MR, Emmison N, et al.; Isopropyl alcohol plasma modification of polystyrene surfaces to influence cell attachment behaviour ; SURFACE SCIENCE 561 (1): 110-120 JUL 10 2004
3. Mitchell SA, Poulsson AHC, Davidson MR, Bradley RH; Orientation and confinement of cells on chemically patterned polystyrene surfaces; COLLOIDS AND SURFACES B-BIOINTERFACES 46 (2): 108-116 DEC 10 2005
4. Mitchell SA, Poulsson AHC, Davidson MR, et al.; Cellular attachment and spatial control of cells using micro-patterned ultra-violet/ozone treatment in serum enriched media; BIOMATERIALS 25 (18): 4079-4086 AUG 2004
5. Lubarsky GV, Browne MM, Mitchell SA, et al.; The influence of electrostatic forces on protein adsorption; COLLOIDS AND SURFACES B-BIOINTERFACES 44 (1): 56-63 JUL 25 2005
6. McCaig CD, Rajnicek AM, Song B, et al.; Controlling cell behavior electrically: Current views and future potential ; PHYSIOLOGICAL REVIEWS 85 (3): 943-978 JUL 2005
7. Wang ET, Yin YL, Zhao M, et al.; Physiological electric fields control the G(1)/S phase cell cycle checkpoint to inhibit endothelial cell proliferation ; FASEB JOURNAL 17 (1): [doi:10.1096] JAN 2003
8. Zhao M, Bai H, Wang E, et al. ;Electrical stimulation directly induces pre-angiogenic responses in vascular endothelial cells by signaling through VEGF receptors; JOURNAL OF CELL SCIENCE 117 (3): 397-405 JAN 26 2004
9. Kivelitz D, Wagner S, Schnorr J, Wetzler R, Busch M, Melzer A.; A vascular stent as an active component for locally enhanced magnetic resonance imaging: Initial in vivo imaging results after catheter-guided placement in rabbits.; INVEST RADIOL 2003; 38 (3):147-52.
10. Reid B, Song B, McCaig CD, et al.; Wound healing in rat cornea: the role of electric currents; FASEB JOURNAL 19 (3): 379-386 MAR 2005
11. Shanley LJ, McCaig CD, Forrester JV, et al.; Insulin, not leptin, promotes in vitro cell migration to heal monolayer wounds in human corneal epithelium ; INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE 45 (4): 1088-1094 APR 2004
12. Baar K, Birla R, Boluyt MO, et al. ;Self-organization of rat cardiac cells into contractile 3-D cardiac tissue; FASEB JOURNAL 18 (15): doi:10.1096/fj.04-2034fje DEC 2004
13. Cui XD, Primak A, Zarate X, ..Harris G & Lindsay SM; Reproducible measurement of single-molecule conductivity; SCIENCE 294 (5542): 571-574 OCT 19 2001
14. S.L. Schor, A.M. Schor, R.P. Keatch,; The Cloning and Molecular Characterisation of MSF, a Novel Cell Activation Molecule involved in Wound Healing; INT. J. ARTIFICIAL ORGANS, 26(9), 845, Sept. 2003

15. J. Valenciano and M.A.J. Chaplain; Computing highly accurate solutions of a tumour angiogenesis model; Math. Modell. Meth. Appl. Sci. 13 , 747-766 (2003)
16. Wang ZG, Abel EW, Mills RP, et al.; Assessment of multi-layer piezoelectric actuator technology for middle-ear implants; MECHATRONICS 12 (1): 3-17 FEB 2002
17. Zhao Q, Liu Y, Abel EW; Surface free energies of electroless Ni-P based composite coatings ; APPLIED SURFACE SCIENCE 240 (1-4): 441-451 FEB 15 2005

18. Prentice P, Cuschieri A, Dholakia K, Campbell PA; Membrane disruption by optically controlled microbubble cavitation; NATURE - PHYSICS 1 (2): 107-110 NOV 2005
19. Feril LB, Kondo T, Cui ZG, et al.; Apoptosis induced by the sonornechanical effects of low intensity pulsed ultrasound in a human leukaemia cell line ; CANCER LETTERS 221 (2): 145-152 APR 28 2005
20. Robertson JMC, Robertson PKJ, Lawton LA; A comparison of the effectiveness of TiO2 photocatalysis and UVA photolysis for the destruction of three pathogenic micro-organisms; JOURNAL OF PHOTOCHEMISTRY AND PHOTOBIOLOGY A-CHEMISTRY 175 (1): 51-56 SEP 30 2005