ENGINEERING IN REGENERATIVE MEDICINE

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There are few things more fascinating, and more difficult to recreate, than the natural processes involved in the growth and development of animal and human life. From the embryo, cells grow and divide, transforming into a myriad of different cells types defined by molecular and cellular signals and events (differentiation).

The goal of tissue engineering (TE) is to replicate some of these complex processes to replace and regenerate lost tissue. Decades of research now seem set to pay off in the treatment of a multitude of debilitating and deadly conditions such as myocardial infarction, spinal injury, osteoarthritis, osteoporosis, diabetes, liver cirrhosis and retinopathy.

The general strategy is to seed cells within a scaffold, a structural device that defines the geometry of the replacement tissue and provides environmental cues that promote tissue regeneration. TE skin equivalents have been in clinical use since 1997 and other TE devices currently in clinical trials or in use include those for cartilage, bone, blood vessel and pancreas. TE bladders and sections of the trachea have been successfully employed in humans.

Even without intervention from scientists, human tissue has a staggering capacity to self-regenerate. For example, a human liver can regrow to its previous size when as much as half of it has been removed. Bone, skin and several other tissues are also able to self-regenerate to fill injuries up to a critical size, often aided by stem cells present naturally in the body. These stem cells can be stimulated in the presence of the correct conditions to grow into multiple different cell types. Thus complex tissue can be produced by using and enhancing the body's own systems.

As well as requiring information from each other, cells derive information from their environments, including the material that surrounds them within tissues, namely the extra cellular matrix (ECM). A TE material scaffold must take on this instructive role to maintain cell viability and control cell behaviour. Mechanisms for such instruction can be both chemical and physical, and include the degree of physical support, geometry, and directional flexibility, as well as numerous chemical signals that lead to cascades of intra- and extracellular events.

THE VALUE IN TAKING A MULTIDISCIPLINARY APPROACH

Research in regenerative medicine within the Stevens group at Imperial College London includes the directed differentiation of stem cells, the design of novel bioactive scaffolds and new approaches towards tissue regeneration. We have developed novel approaches to tissue engineering that are likely to prove very powerful in the engineering of large quantities of human mature bone for transplantations in which the donor is also the recipient, as well as other vital organs such as liver and pancreas. Such targets have proven elusive with other approaches. To achieve these diverse aims we employ collaboration with numerous partners and have a multidisciplinary team consisting of members with backgrounds across:

- Biomedical Engineering
- Bioengineering
- Materials Engineering
- Chemical Engineering
- Electrical Engineering
- Mechanical Engineering
- Surgery
- Chemistry
- Cell biology
- Physics

With the combined knowledge from all of these diverse fields, successful development of tissue engineering is greatly facilitated.

REGROWING BONES

Bone tissue is of particular interest due to its highly complex architecture that contains many blood vessels and covers several length scales (macro to nano), important structural function, regulation role of calcium and phosphate levels within the body, and its high regenerative capacity. The majority of bone fractures heal themselves without the need for medical intervention, however in

some cases such as removal of tumours, this self-regeneration must be supplemented with grafted cells from elsewhere in the body. Harvesting of such autologous bone tissue is limited by supply and by negative effects on the donor site, which make TE of bone highly desirable.

Bone repair and replacement is also an important consideration in an ageing population. The number of age-related bone replacements such as primary knee arthroplasties is increasing rapidly; already 16% of the US population is over 65 years of age and this looks set to rise. Overall, globally, there are around 1 million bone defects annually that require grafting to repair.

Bone has specific requirements that differ from those of other bodily tissues, which must be considered in the engineering of bone tissue. Ideally, the template or scaffold for bone TE should be bioactive, contributing actively towards cell differentiation, encouraging directional bone growth and afterwards being reabsorbed or replaced by the body. Materials for such scaffolds used commonly include bioactive glasses, bioceramics, or polymers in the form of nanofibres or composite materials; they must be porous, functional, and, of course, biocompatible. Biological components from the ECM such as proteins that "switch on" certain cellular signals are often incorporated into the scaffolds.

SIMPLE MATERIALS CAN SOMETIMES REGENERATE EVEN COMPLEX TISSUES

Our developed concept that allowed the engineering of large volumes of bone in a predictable manner relied on the creation of an artificial space or "bioreactor" in the body between a bone and the periosteum (a membrane that surrounds all the major bones). A cavity is first created between the bone and periosteum by the injection of a salt solution. This cavity is then filled with a bioactive gel containing calcium to trigger the production of fresh layers of bone in the *in vivo* bioreactor. New bone tissue grows from stem cells in the periosteum into the bioactive gel and rapidly fills the bioreactor space. The new bone can then be easily harvested and transplanted elsewhere in the body without major trauma to the harvest site unlike with traditional bone harvesting from body sites such as the iliac crest. This reduces long-term morbidity and pain for the patient. Cartilage can also be produced using a similar concept using a different biomaterials gel formulation.

STRONTIUM – THE VITAL INGREDIENT

Bioceramics form a particularly strong bond with living tissue by formation of a hard bone-like layer on the surface, and they have been used to repair hard tissue in a variety of craniofacial, maxillofacial and periodontal applications. We have recently shown that if the bioceramic used contains strontium then it has the potential to combine the known bone regenerative properties of such glasses with the positive effects on the metabolism (anabolic) and slowing of tissue-breakdown (catabolic effects) demonstrated by strontium cations.

It is thought that this result is caused by a synergistic effect of strontium on the action of the bioceramics, which release calcium, silicon, and other vital bone-growing minerals to encourage bone growth. When implanted into a bone defect, the released strontium stimulates osteoblasts (bone cells) to make new bone and prevents it from being resorbed by osteoclast cells. The new bone is significantly stronger and of higher quality than if strontium is not incorporated into the material.

FROM BENCH TO BEDSIDE

Repregen™ Ltd, formerly BioCeramic Therapeutics Ltd until March 2010, is a spin-out company from Imperial Innovations plc co-founded in 2006 with Professor Stevens and headquartered within the Imperial College Incubator. RepRegen Ltd is a medical device company that uses patent-pending repair and regeneration technology platforms designed to mend and regrow hard tissue such as bone and soft tissue such as cartilage.

An ageing population and an increase of high risk sports have led to a surge of bone-related diseases and bone fractures. As a result, the use of bone graft substitutes has dramatically increased in the last decade. There are currently no synthetic products on the market with performance that is comparable to biologics such as Bone Morphogenetic Proteins and the gold standard autograft.

RepRegen Ltd's platform of strontium bone graft substitutes for hard tissue regeneration offers improved performance over conventional bone graft materials. The first product, StronBone™, recently received EU regulatory approval for orthopaedic, spinal and dental bone grafting indications. The company has a series of strontium bioceramic products in the pipeline which will build on this first product including a putty and porous bone graft.

RepRegen have shown that strontium is highly beneficial to bone cells and enhanced mineralisation and have also demonstrated this *in vivo* with rapid formation of high quality, mechanically competent bone. In fact significantly higher quality bone is formed with the incorporation of strontium into the biomaterial.

There are over 50 synthetic products on the market with little to distinguish them from each other. RepRegen's products offer a number of firsts which will clearly distinguish them in the market. If the NHS were to adopt these products, this would result in worldwide exposure and also result in the significant cost savings outlined above. RepRegen's StronBone™ is significantly cheaper to manufacture than biologics such as Bone Morphogenetic Proteins. Adoption of StronBone in the NHS would aim to result in faster patient recovery, fewer complications and implant failures due to infections, reducing costs to the NHS and burden on society and the economy in general.

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For more information go to www3.imperial.ac.uk/people/m.stevens and www.repregen.com

mHEALTH – MOBILE PHONES FOR HEALTHCARE

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INTRODUCTION

Developments in the last decade have led to mobile communications technologies becoming a new tool for the delivery of healthcare. It is only 25 years since the UK cellular telephony service, as it was called then, was launched. As recently as 10 years ago, the link between mobile phones and health was seen in an entirely negative light. Exposure to electromagnetic radiation close to the brain, through the use of a mobile phone, was perceived as giving rise to an increased risk of developing a brain tumour, and all mobile phones had to be switched off inside hospitals because of "possible interference with medical equipment".

What changed between 2000 and 2010? A number of studies, for example the report from Professor Sir William Stewart in 2000 as well as two reports from the World Health Organisation and a paper in the *British Medical Journal* in January 2006 (SJ Hepworth, MJ Schoemaker, KR Muir et al *Mobile phone use and risk of glioma in adults: case-control study)* showed that there were minimal health risks associated with mobile phone use, although children under the age of 16 are still advised to limit the time they spend on calls.

The introduction of GPRS (General Packet Radio Service), sometimes known as 2.5G, in 2002 made it possible to have two-way real-time transfer of data to and from a remote computer server. Today, mobile telephony, which includes voice, text messaging (SMS) and data services, has become the most widespread communication infrastructure in the world, with 80% of the world's population living within range of a cellular network. The mobile phone is both a data entry device with a keyboard and a data review device with a colour screen. Mobile phones have now become tools to facilitate the delivery of healthcare services, based on the secure exchange of medical data, and leading to a new term, "mHealth", the use of mobile communications technologies in health solutions.

LONG-TERM CONDITIONS

A 2010 report from McKinsey *(mHealth: A new vision for healthcare)* warns that, if current trends continue, spending on healthcare will consume an unsustainable proportion of the wealth of developed nations, up to 25% of gross domestic product (GDP), with the management of long-term conditions accounting for 80% of the growth in costs. Long-term conditions (also called chronic diseases) are defined by the World Health Organisation as health problems that require ongoing management over a period of years or decades. Innovative methods are required to address this challenge, and mHealth is highlighted in the report as having the potential to achieve significant reductions in the cost burden of long-term conditions.

In the UK there are 17.5 million people with a long-term condition. Some 12 million of these suffer from the most common conditions, namely diabetes, hypertension, asthma or chronic obstructive pulmonary disease – COPD. In the United States, long-term conditions affect 130 million people, generating healthcare costs of approximately $1.4 trillion per annum overall. Around 80% of GP consultations relate to long-term conditions and patients with these conditions or their complications use over 60% of hospital days. Type 2 diabetes is the fastest growing disease in the developed world as a result of poor diet and obesity, and the World Health Organisation has predicted that long-term conditions will be the leading cause of disability by 2020.

Improved self-management, coupled with regular education and support, is seen as the best means of slowing the inexorable rise of healthcare spending on long-term conditions, through a reduction in the number of unplanned hospital admissions, emergency visits to the GP surgery or days off work.

HOW ENGINEERING IS HELPING

The challenge today is to create sustainable, large-scale programmes that can support self-management of long-term conditions without being a drain on healthcare resources. Patients with a mild or moderate form of a long-term condition expect to lead a normal life and do not want to change their routine or be confined to one location for self-monitoring. The mobile phone can be used not only to transmit self-monitoring data and patient diaries to a remote server but also to provide real-time feedback, which increases patient compliance. Transmission of the encrypted data from the phone to the server using GPRS or 3G is a secure process. Algorithms running on the server can then prioritise patients for "telehealth nurses" to review and call on their mobile phone, whenever appropriate, without the costs of frequent visits to the patient's home.

Telehealth services (or "remote health monitoring") are focused mainly on two types of populations, with different economic cases. One type targets patients with COPD or chronic heart failure, for example, those who have a high risk of experiencing an expensive care episode, such as an unplanned hospital admission. The second type is more concerned with the long-term benefits of self-management for conditions such as diabetes. Here the target population is more likely to be younger, more active and early adopters of new technology.

The concept of mHealth can benefit both groups, although it has so far been mostly deployed among the second group. One of the main barriers to the adoption of mHealth by the first group has been the small and difficult-to-use keyboards of today's mobile phones, but this is being eroded by the introduction of the new generation of smart phones with large icons on touch-sensitive screens. It is essential that mHealth solutions are designed for the requirements of their target population, which can vary widely: an application to help teenagers manage their diabetes will be very different from one used by elderly patients to monitor their blood pressure following their discharge from hospital after a stroke. Both of these have been successfully developed at the University of Oxford and adopted by hundreds of patients (see http://www.ibme.ox.ac.uk/bsp and www.obsmedical.com/products/telehealth/).

OTHER APPLICATIONS OF MHEALTH

Other mHealth services are also being developed in markets outside the management of long-term conditions. For example, the automatic sending of text messages to remind patients of appointments is widespread within the NHS. Similarly, text-message reminders can help promote adherence to medication regimens, by prompting individuals to take their medication and encouraging them to complete their treatments. The Pill Phone, a mobile medication reminder from a US company, tells patients when they should take their medicine. Medication Tracker, MedsLog and Pillbox are among the most popular medication trackers in the iPhone store. Text messaging has also been used to improve success rates in smoking cessation programmes.

Recently mHealth has begun to have an impact in the developing world, albeit mostly through pilot projects at this stage. Three quarters of mobile phone users are in developing countries. Making sure that there is the right amount of malaria drugs at the hospital or the health centre where they are dispensed is a hard logistical problem in sub-Saharan countries, which mobile phone technology is helping to solve. Mobile phone applications have also been developed to empower community health workers, allowing them to record medical information in patients' homes and uploading it to a basic electronic health record.

FUTURE WORK

Before any new drug or medical device can be introduced into the market-place, evidence is required of its safety and efficacy. Because mHealth is a technology based on self-monitoring, there are no safety implications as it is generally accepted that the use of a mobile phone carries no health risks. There are now several thousand healthcare applications for the iPhone.

But the *sustained* use of mobile phones for healthcare will depend on evidence gathered in clinical studies demonstrating improved patient outcomes, for example an increase in the long-term control of blood glucose levels in people with diabetes or fewer exacerbations in people with respiratory conditions such as asthma or COPD.

The new generation of smart phones and tablets (iPads) based around either the iPhone Operating System (OS) or its open-source alternative, the Android OS, has the potential to provide a *generic* mHealth platform, usable across the long-term condition spectrum. With the computing power available on these new devices, mHealth will deliver software applications which can be optimised for the individual and integrated into care pathways so as to maximise the productivity of healthcare workers.

HOW ENGINEERING PROVIDES BETTER HEALTHCARE

MEDICAL ENGINEERING SOLUTIONS FOR "FIFTY ACTIVE YEARS AFTER FIFTY"

How can we be more active and live more healthily for the second half of our lives?

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Advances in modern medicine have led to increased life expectancy and we all expect to live longer. A fifty year old today may well live for another fifty years and may well walk up to another 100 million steps in the second half of their lifetime. Our musculoskeletal system starts to age and degenerate at around the age of fifty. As we age, we need to keep active in order to avoid other co-morbidities, remain healthy and continue to contribute to society and the economy. The ageing population, the so called "silver tsunami" is now one of the major societal challenges.

For example, it is estimated that the number of joint replacements implanted worldwide will increase fivefold to 5 million by 2030. These joint replacements will have to last longer and meet higher patient expectations and demand. Medical engineering can provide solutions for repair, restoration and replacement of tissues in the musculoskeletal and cardiovascular systems to help keep the ageing population healthy and provide "fifty active years after fifty". This paper summarises past medical engineering achievements, recent advances in longer lasting joint replacements and research into the future potential of regenerative biological scaffolds. The examples cited demonstrate the importance of integrating research, innovation and commercialisation, and partnership working between universities, industry and healthcare providers.

Total artificial hip joint replacements were invented in the UK in 1960 and have been manufactured here for over 50 years. The traditional designs, made from metal on polyethylene, provide pain relief and mobility for the elderly population, over 65 years. Our research has shown that when used in younger more active patients, the conventional design results in long term failure due to adverse reactions to the increased load of polyethylene wear products. This has defined the need for lower wearing and longer lasting joint replacements.

We have also researched and developed replacement heart valves. Chemically treated bioprosthetic heart valves which were researched, designed and developed in the University, were licensed to a local startup company and have been manufactured in the UK for over twenty years. These traditional medical devices have provided effective technology solutions for the elderly, but do not address the needs of the current ageing population.

Over the last twenty years, one area of our research has focused on reducing wear and improving the longevity of joint replacements. We have researched novel hard on hard bearings, and our unique ceramic-on-metal hip joint has demonstrated extremely low wear and extended life times. It has been licensed to a global company and is now sold worldwide for use in young active and high demand patients. In the knee we have redefined the scientific laws of the wear of polyethylene, and this has led to the understanding of lower wearing design solutions, which are now marketed worldwide. One example, the partial knee replacement, which allows early intervention and preserves natural tissue, has been shown to have tenfold less wear than conventional knee designs. During this period we have developed the largest simulation facility in the world for artificial joints, which allows us to study new materials and pre-clinically evaluate new technology solutions and designs, thus improving performance, reliability and safety of devices that are implanted in the body.

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Our current and future research is focused on regenerative biological scaffolds. These are scaffolds of biological origin, which uniquely replicate the structure and function of the tissue from which they are derived. When implanted in the patient they regenerate with the patients own cells. We believe that by replicating tissue specific architecture, structure and function, that the cells are subjected to the appropriate tissue specific environment, signals and strains, which will drive them to differentiate down the correct tissue specific lineages.

Research on biological scaffolds is being translated through University spin out company Tissue Regenix Group, recently listed on AIM and also through NHS Blood & Transplant Tissue Services. Current clinical products include the dCELL® vascular patch for blood vessel repair, a pulmonary valve replacement scaffold currently in clinical studies, and a dermal product for skin repair. Biological scaffolds for meniscus repair are currently under commercial development by Tissue Regenix Group. Unique biological scaffolds for ligament and bladder repair have been patented. Research work is ongoing for blood vessels, cartilage and bone and other soft and hard tissue composite grafts. This family of regenerative biological scaffolds represents a paradigm shift in medical technologies and tissue replacement, directly addressing the needs of the ageing population.

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The Institute of Medical and Biological Engineering and its partners in the WELMEC Centre of Excellence in Medical Engineering, the IKCRTD Innovation and Knowledge Centre in Regenerative Therapies and Devices, regeNer8 Centre for Translational Regenerative Medicine integrate multidisciplinary research, innovation, translation and product development, with 200 research staff, 50 industry partners and 50 clinical collaborators addressing the challenges of "50 active years after 50". With our academic, clinical and industry partners we are developing a novel approach to establishing a research led technology and innovation centre in medical technologies.

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