

The Royal Academy
of Engineering

**FROM ENGINEERING RESEARCH
TO PRACTICAL HEALTHCARE**

**3 Carlton House Terrace
London**

Monday 29 October 2007

Chair: Dr Sue Ion OBE FREng

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Keynote Speaker: Professor the Lord Darzi of Denham

Speakers: Professor Sir Alfred Cuschieri
Professor Christofer Toumazou
Professor Tony Unsworth
Professor Chris Taylor
Dr Glenn Wells

Welcome and Introduction

Dr Sue Ion: A very warm welcome to you all, and particularly to our speakers, at this important event. Before I begin my introduction proper, let me tell you a little about the housekeeping arrangements. Although many of you are Fellows of the Royal Academy, this may be your first visit to our new and prestigious headquarters. We are happy that you are able to join us here at our new home here in Carlton House Terrace.

[Housekeeping: Exits; Fire evacuation procedure; cloakrooms]

The Academy has long realised the potential for improvement in healthcare and in wealth creation which is brought about by advances in biological and engineering research. We were very pleased last year to join with the Academy of Medical Sciences, in developing our report on systems biology, which was published and received a lot of good press and was taken significant note of by people like Phil Willis, the Chairman of the Parliamentary Select Committee on Science and Technology. It recognised how important it is that systems and control engineering, modularity, increasing computing capacity and natural sciences are all linked and are critically important to taking the field forward.

Interdisciplinary work, beyond the traditional field of engineering, embracing life sciences and natural sciences, will be important, as well as engineering disciplines themselves, encompassing the full spectrum of activity from biomaterials, to imaging, to joint replacement, to informatics, regenerative medicines, advanced diagnostics, innovative devices and vaccines. All of these will play a very important role, going forward.

We are particularly pleased to join the Wellcome Trust, who picked up interest following publication of the Systems Biology report.

I am sure that this event will provide you with the opportunity to hear from those who have successfully negotiated the tortuous path of translational research, and its journey into commercial application, and also to learn about the funding that is available through the Wellcome Trust. I would like to suggest that brief clarifying questions are taken at the end of each of our speakers' talks, because we will have a full Q&A session at the end of the day.

I am very pleased that our keynote address is to be given by Professor the Lord Darzi of Denham. Unfortunately, since he is very much in demand, as you would expect, and he will be jetting off to Washington later this afternoon, we have a car at the ready with its engine going as we speak. He has agreed to take a few questions after he has spoken.

He is the Parliamentary Under Secretary of State for Health and he holds the Paul Hamlyn Chair of Surgery at Imperial College. He is an honorary consultant at St Mary's Hospital and the Royal Marsden. Most importantly for us, he is an honorary fellow of our Academy and he is also a fellow of the Academy of Medical Sciences. Lord Darzi and his team are respected internationally for their innovative work in the advancement of minimally invasive surgery and in the development and use of allied technologies, including surgical robots and image-guided surgery. He actively pursues and relentlessly campaigns for improved interdisciplinary research of the type that we have highlighted and are interested in.

His innovative work is globally recognised. Many prizes have been awarded to him, including the Queen's Anniversary Prize for Excellence in Higher and Further Education in 2001. This prize was given in recognition of the new pioneering technologies to address training requirements for trainee surgeons and surgeons in post, as well as professionals.

The Prime Minister and Health Secretary sensibly announced that Lord Darzi would lead a review of the NHS that would advise on how to meet the challenges of delivering healthcare over the next decade. He was knighted by the Queen in December 2002 for his services to medicine and surgery. Without further ado, Lord Darzi.

KEYNOTE ADDRESS

INNOVATION: FROM ENGINEERING RESEARCH TO PRACTICAL HEALTHCARE

**Professor the Lord Darzi of Denham KBE HonFREng FMedSci
Parliamentary Under Secretary of State
Department of Health**

Thank you very much, Sue, for that introduction and for inviting me here, to the first meeting of the Royal Academy at these premises.

My relationship with engineering goes back a long time. I come from a very strong family of engineers and in fact I was the rebel in my family when I decided to become a doctor, until I realised, in my medical training career, and certainly in my postgraduate training career, that I probably was a failed engineer, until I arrived at Imperial. What that shows is the wonderful culture and the multidisciplinary teamworking that exists at Imperial which has really underpinned my research and I will share you some of the work in relation to that.

I have always said, with reasonably strong belief, that a failed engineer is one thing, but something I definitely am is a failed politician, since I have started over the last three months. I shall also share with you the journey of the last three months as far as the *NHS Next Stage Review* is concerned because innovation is a very strong theme in that, and where the NHS needs to be as far as innovation is concerned in the next decade.

In large measure, healthcare is engineering and always has been

Human nature, in all aspects of healthcare, not uncommonly tries to systemise the way in which we deliver healthcare. It is not uncommon to create so-called virtual boundaries and certainly, being in public service for the last three months, it is not uncommon to talk about these boundaries when it comes to primary care, secondary care or even tertiary care, and the boundaries that exist between health and social care. It is not uncommon to talk about boundaries when it comes to engineering and healthcare.

Most of us know that engineering has had a tremendous impact on where we are, as far as 21st century medicine is concerned. You can see, on the diagram on the left of this slide, the first prosthetic device, dating from 300 years BC, and the impact of biomedical technologies on healthcare, whether that happens to be in the acute sector or in the primary sector and, certainly more importantly in the future, the impact of health technologies in the

provision of care at a home level. So engineering is about technological solution to health and human problems.

Improving patient lives requires innovations to be developed and harnessed by the NHS

As far as innovation goes in healthcare, we all know that this is a fairly long and interesting journey, starting from the discovery – and certainly the most challenging, from the NHS perspective – is the adoption of that innovation, whether or not it happens to be a technological innovation. It is not uncommon that we have tried to fix the problems in one area of this pathway rather than actually trying to fix the whole of the pathway from the start to the adoption. I will come to these different points throughout my talk – whether these are ideas in research, products in trials, or approval or adoption.

For the NHS, the innovation challenge is broader than medical devices and pharmaceuticals

Interestingly enough, when we talk about innovation, certainly from an NHS perspective, most of the thoughts are about new medical devices or new pharmaceutical drugs. In actual fact, however, we forget that one of the major challenges facing the NHS is innovation in clinical practice. How do you change clinical practice to improve the outcomes for patients? That has been the main drive of the NHS Next Stage review.

If you look at the number of different reviews in the NHS over the last decade, we had the big NHS Plan in the year 2000, which was described as the most quantitative investment that the NHS had seen in its history. It was mostly around capacity building. We then went through an interesting phase, a so-called systems reform, reforming the system as an NHS. The whole purpose of the Next Stage review is to refocus the mind on what matters most, which is the quality of care that we provide. Re-designing and introducing innovation in clinical practice is one of the challenges facing us.

We should also not forget the delivery models. We have seen examples of this in London, where the delivery model is at a primary care level, in the creation of – my favourite word – polyclinics, or certainly at the more extreme end, which is the organisation in which I work, which is Imperial's leadership in bringing the NHS under its wing in the form of an academic health sciences centre.

However, if you are really to ignite innovation in the NHS, then you need to look at the NHS management. I will share with you some of the issues that could have an impact in the uptake of innovation, and certainly a more cost-effective way of taking up innovation – one of which is long term condition. This is probably the most challenging thing the NHS is facing as, with the demographics and certainly the aging population, you can see the impact of technology in managing disease outside of a hospital setting.

And getting it right is absolutely central to the future of the service

Innovation needs to be better, certainly for patients. It needs to improve the outcomes and the experience, and technology has a role to fill that gap that exists currently. It certainly needs to be better for staff, constantly pushing the edge of innovation, whether this is acquiring new skills in the application of new technologies, and certainly better from a public perspective and better value for money.

Britain has a long and distinguished history of developing medical technology ...

British science, certainly when it comes to the area in which most of us in this room have an interest, has had a distinguished history in the development of medical technologies. Although the first patent was described in the US when it came to MRI, it was Peter Mansfield in Nottingham who actually developed MRI as a diagnostic tool as far as the clinical pathway is concerned. That was back in the 1960s but it took until 2003 to acknowledge his contribution, in winning the Nobel Prize.

... but over 20 years after its widespread introduction, the NHS had below average ...

If you look at the use of such technology within the health service, you form a different view. This is the number of MRIs per million of population, looking at Japan – certainly well out of the context there, with 35 MRIs per million of population. Where are we in relation to the OECD average of 7.3? We are significantly behind. Our investment in diagnostics, and certainly our investment in translating these technological innovations, has certainly not been as good as it could have been.

MRI is just one example ...

If you look at health globally, we are behind the rest of the sectors, whether that is the technology or the business sectors. That is not unique to England: it applies across the globe but, in the UK, we have more of the challenge when we are talking about the uptake or the adoption of new technologies.

Historical emphasis on cost containment in the NHS

You can explain this in a number of different ways. First, there is the expenditure. This is the spend on medical devices per capita, showing the UK versus some of the Western European countries, which we always use as a benchmark. You can see some of the quotations on the right hand side here – we are significantly behind when it comes to investment in and uptake of medical devices. This has been a challenge in the past and, although we have systems like the National Institute for Clinical Excellence, which constantly make recommendations on the uptake of new technologies, for some reason or the other, we have failed to police the recommendations. This was one of the main drivers for the

announcement which was made by the Prime Minister about four weeks ago at Imperial College, about the creation of the so-called Innovation Council. I will come back to that.

The sector suffers from the so-called “valley of death” in technology transfer

Within the spirit of the Innovation Council, there was also an announcement made of an innovation fund. This really brought the leadership of the Wellcome Trust and convinced the Department of Health in making an investment to the tune of £100 million. Most of that innovation fund is to support the concept of discovery to development. The area is the so called the ‘valley of death’ which is commonly recognised in the healthcare technology sector. This is an extremely exciting project which will probably kick itself off in May of next year. It will be jointly managed and funded between the Department of Health and the Wellcome Trust. It will be peer-reviewed and we will be trying to achieve excellence in stimulating that medical device technology innovation, mostly around the diagnostics but even in other areas. I will come back to my own specific interest in this field.

Some clinicians have always believed there is nowhere new to go

We also need to tackle one other challenge with the clinical community. How do you make innovation part of the culture of every clinician working in the health service? The best example to use is perhaps that of Lord Moynihan. I am sure Alf (Sir Alfred Cushieri) is here – he was certainly one of my mentors and innovators in the field of minimally invasive therapy – and he will probably agree that Moynihan was the godfather of surgery. Interestingly enough, however, if you go back to the 1930s, this was the foreword of his book, where he said:

“We can surely never hope to see the craft of surgery made much more perfect than it is today.”

We have seen some of the revolutionary aspects of surgery, most of which will have been underpinned by technological advance, such as minimally invasive therapies.

Laparoscopic surgery is ‘disruptive change’

It is not uncommon, within the clinical communities, and certainly within the NHS, that when a new technology is introduced – certainly in the laparoscopic area, which is an area in which I have had an interest – it comes in very much like a disruptive technology. Most of us are not ready to translate that technology into clinical practice and most of us remember some of the disastrous outcomes we had with the introduction of laparoscopic surgery in the early 1990s. Being more receptive, and certainly smarter in predicting some of this change, and also having the right guidelines through which such technology is introduced, is very important.

While those in the healthcare system were resisting surgery, those outside welcomed it

This is another interesting study that we looked at – laparoscopic cholecystectomy, which is the removal of the gallbladder. This was the interesting driver of change in the era of the minimally invasive therapies. Most of that was actually driven by patients, and patient demand, which led to a major change in clinical behaviour. However, if you look at the advantages from a laparoscopic cholecystectomy, you can see that it was mostly patient driven and the surgeons eventually accepted it – although there are still, and I am sure Alf will agree with this, some centres in which open cholecystectomy is still performed significantly more frequently than it should be. It was certainly pushed by the hospitals, who saw the advantages of shortening hospital stay, and by purchasers, who saw the advantages of reducing cost. However, there was an interesting story behind that in that, although the unit costs of laparoscopic cholecystectomy dropped, the number of laparoscopic cholecystectomies that we are doing now is significantly greater than it was in the open era, because the threshold of patients dropped significantly.

If you translate that into a more advanced procedure, which is a colorectal resection, you can see that with the concept, although it was accepted by the patients, there was a significant lobby not to change practice within the clinical community. Fifteen years down the line, we are still talking about how we can increase the number of laparoscopic colorectal resections. So it is a matter of taking on and bringing on the clinical community and making innovation a part of their culture, and putting the right incentives in the system, which I am sure will only be resolved if we have an empowered population of patients who will demand and push for these technologies.

Much of the surgical resistance was related firstly, with laparoscopic surgery - if I could just give you some of the basic challenges from a surgical perspective – that you have lost the 3D image, so that you are operating in a 2D environment. You have lost the tactile cue, which was a very important attribute in surgery, being able to feel what you are operating on.

[Slide]

That was the main driver in bringing so-called robotics into surgical practice. This is the da Vinci robot, which is probably one of the first generation robots that actually allowed you to do a full surgical procedure. Most of you here are engineers. These are not robots, but they are master/slave manipulators. You can see where the surgeon sits on the master station and this blade, which is attached to the operating theatre, started off with three arms but it now has a fourth arm – and you can add as many arms as you wish. The unique point about this, however, is the introduction of the 3D image. As you can see, the surgeon is fully

immersed in the console of the operating theatre, looking at a 3D image and, at the same time, the interesting point is the development of the instruments which have six-degree freedom of movement, which essentially simulates a human wrist.

This was developed initially for cardiac surgery but, at the same time, there was another technological revolution – angioplasty and stenting – and so it was interesting to see how the technology was shifted, mostly to be used in areas of radical prostatectomy, but also in other areas of pelvic surgery, where anatomical areas were important.

Advanced robotic systems

This slide brings you back to my own area of interest. This work goes back to the Imperial laboratories, mostly led by my colleague, Professor Guang-Zhong Yang and others. One of the challenges we saw with the introduction of robotics was the issue of motion compensation, the concept of image guidance and certainly active constraint, which is Brian Davies's interest, and how you introduce that, in enhancing safety in robotic assisted surgery. I will share with you some of the work in augmented reality and in integrating other visual cues intra-operatively.

The unique point about this platform is that it is not just a master/slave manipulator, the mechanical aspect, but there is the ability to bring computer-assisted surgery in its entirety into the operating theatre, capturing all kinds of different visual and other data, to create certain cues during operative surgery.

Beating heart surgery

Just to explain what we mean by 'motion compensation', this is a robotic assisted TCAB, which is a coronary artery bypass graft of a single vessel. You can see that, despite having a stabiliser, which is this fork-shaped instrument, you still have a significant movement of the pericardium during that. If you are doing a microvascular suturing and, in some cases, using 6-0 or 7-0 sutures, you can see the difficulty – even with that fine movement, and the impact on that.

Virtual motion compensation

The initial work was funded by the MRC and the EPSRC – one of the few funds in biomedical technologies and this is one of the Hopping awards – looking at the possibility of compensating for motion, using different salient features from the heart. By doing so, that is actually measuring the X, Y, Z co-ordinates of that movement and trying to synchronise the movement of this scope with the same movement of the beating heart. The whole ability here is to get a static image and to display a static image to the operating surgeon. That is an interesting concept: the Hopping award was looking for a wacky idea and you certainly

could not get wackier than this. Although we got that through, if you went down and analysed the accuracy of our motion compensation, you would have some serious concern about this.

Binocular eyetracking

This is where the next piece of work came in, which is using some of our research in binocular eyetracking. There is the ability that, by tracking the two eyes and measuring the focal point or the fixation point that you are looking at, you can actually measure the depth of the tissue that you are looking at. In other words, you could use the surgical brain, if there is one, to measure the depth of the tissue that the surgeon is looking at, intra-operatively, and in a dynamic way.

Gaze-contingent motion stabilisation and depth reconstruction

The result of that piece of work was quite exciting. This is the stereo image from the robot. It can show you the left camera video and the right camera video and there, we are measuring the fixation point, which is inserted using laser light which is inserted in the actual console. By doing that, we are actually measuring the fixation points and looking at the depth – we are creating a virtual depth recovery of the organ that the surgeon is looking at and then, at the same time, using some complex algorithms, we are moving the 3D scope and the robot at the same frequency as the beating heart. This displays to the surgeon a static image.

Improving outcomes in robot-assisted surgical treatment of prostate cancer using augmented reality guidance

This is where we were, earlier on this year and, interestingly enough, where we will be taking this work to will be quite exciting in the future. There is the ability to bring back the computer-assisted platform and the ability to manipulate some of the images that we have pre-operatively and display those intra-operatively to the surgeon. This piece of work was funded by CRUK and you can see the pre-operative MRI images, which have been reconstructed in virtual organs and displayed on top of the prostate.

Most people having a urological resection or a radical prostatectomy would expect the surgeon to know where the prostate is, and I could not agree more. What we are trying to display here, however, is the pelvic side walls, and trying to reduce the impotence rate following radical prostatectomy because I am sure that you know that, even in the best hands, there is a significant impotence rate, which has a detrimental and obviously huge impact on the quality of life of those patients undergoing radical prostatectomy.

Non-photorealistic rendering augmented reality

Our next challenge is to try, with image augmentation, to give the surgeons some form of a depth recovery. This is the non-photorealistic rendering of augmented reality and this is in lung tissue, where you are trying not only to display on the lung surface where the tumour is, but also to give the surgeon an idea of the depth of that small lesion. The whole idea here is to reduce the trauma by actually doing as minimally invasive a lung resection as possible.

Application of i-snake robot

More recently – and this was a grant that we have just received from the Wellcome Trust, and their interest in this field of robotics has been on the back of the creation of the so-called i-snake robot, very much compatible in our vision certainly in minimally invasive therapies, we are moving from intra-cavity surgery, into a ‘natural orifice’ surgery. In other words, incisionless surgery – this is the ability to undertake surgical procedures, trans-oral, trans-gastric, into the peritoneal cavity. You probably heard, six or eight weeks ago, about the first trans-vaginal cholecystectomy was carried out in Strasburg. The whole idea is to have a smart instrument like the snake robot – although snakes are not new when it comes to technology in other spheres – with the ability to insert and have different working channels, either to do image mosaicing, which I shall return to, or to do certain MEMS controlled instruments.

We are working with Chris Toumazou and others at Imperial, to develop some of the instrumentation that will complement this. The whole idea, as shown on the left hand graph, is to do either a natural orifice trans-endo-luminal surgery, or to have the ability to use some of these instruments to go behind the heart, to allow you to do more triple vessel disease, rather than single vessel disease, as we have it at the moment.

Fixing the problems we face on innovation requires a perspective on the whole NHS system

How do you bring this innovation into clinical practice? How do you make the change happen in the NHS? This was certainly my challenge when I received that interesting phone call. You might be innovators in your clinical practice, or you might be innovators in your scientific practice, but how do we make that happen from the NHS perspective? That is our biggest challenge.

Most of us will know that we have made a significant investment in research and development with the creation of biomedical research centres, when it comes to the NHS. There have been a few announcements in recent times on biomedical research units.

We need to be smarter in our approval – it should not take 18 months to get a drug or a medical device through NICE (National Institute of Clinical Excellence). If we really want to adopt innovation, we need to be smarter in relation to that.

We certainly need to have better commissioners and commissions in which clinicians, on behalf of the patients, where innovation, whether that happens to be a medical device or a pharmaceutical drug, are very much a part of that commissioned model of care. We certainly need to be smarter in procurement and we are doing all sorts of activity in that arena. We need to put the right incentives in the right place, whether that is at a primary care level – let us not forget that innovation does not start in secondary care but innovation needs to start at the gateway of healthcare, which is primary and community services.

We need to stimulate management. If the management do not have innovation as part of their culture then how do you expect clinicians to lead innovation in clinical practice? Finally, and probably most importantly, there is the culture. How do you put the culture of science and innovation at the heart of what we do? Academic health sciences centres may be one way but let us not forget, why should we not have academic primary care centres in which innovation is in the heart of primary and community services?

These are the challenges that I am bringing in and this is the result of the creation of the so-called Innovation Council. This is a joint venture between academia and industry and the clinical community. This is not another quango, but the best way to describe it is as the guardian of innovation that will scrutinize the NHS executive in changing and meeting the expectations in relation to this important pathway.

Promoting innovation in the NHS – making sure change happens

The whole idea of the Council is to provide the leadership, the overview and the action on behalf of the NHS, to meet the aspirations of the clinicians who use technology but, more importantly, of the patients who benefit from its use. Thank you very much. [*Applause*]

Questions & Answers

Sue Ion: Thank you for that absolutely super presentation to start the afternoon. Are there any questions?

Professor Sir Alfred Cuschieri: I am now the scientific adviser of a new Institute for Medical Science and Technology between the Universities of Dundee and St Andrews. I have known Lord Darzi for a long time and, in fact at one time, although you may not believe it, I was his mentor.

I would like to know more about this innovation fund. How will it be used, and what sort of peer review will there be? I think it is a giant step forward.

Lord Darzi: Thank you. I will try to give you an overview of it because, at the moment, both are designing the way this will be launched. It will be launched next year and it will certainly be peer reviewed with scientific vigour. It will be based on an assessment of need and it will be between discovery to development – that gap is what we fill. It will not be on adoption. I do not think we should be spending taxpayers' money and charitable money on adoption. Adoption is a completely different challenge of culture, commissioning and the NHS getting that together. Hopefully in May of next year there will be the announcement. I know that colleagues are here from the Wellcome Trust and they may give you a better brief. I am keeping away from it, for all sorts of reasons.

Professor Ian Young (Imperial College): I lived through about three introductions of major technologies, the last and the most spectacular being MRI. That required clinician lead. It is all very well to talk about Peter and Paul and so on, but the people who made it happen were four radiologists, without whom nothing would have happened. It seems to me that what you do not have is the solution to the question, how do we get past NICE? How do we get the data for NICE? That will be the key.

Lord Darzi: I agree with that. We need to scrutinize and that is one of the areas I am looking into. NICE has delivered in a number of different areas and we must acknowledge that, because it is important that we acknowledge what we have. It is actually the envy of many other European countries. On the other hand, we could be smarter in relation to NICE, in getting some of these approvals more quickly. More importantly, let me

just say that in my own area of robotics that there are no guidelines coming out of nice to say that robotic surgery should be part of your activity when it comes to a radical prostatectomy.

The only way you will change that will be by bringing in the leadership that is required in the clinical community, put the right incentives in the clinical community to take up innovation, and also find the right platforms in which to do that. Hammersmith was a good example many years ago of where, in actual fact, there was a true integration between the NHS and the university. We seem to have lost that framework within the NHS, and that is the framework that we need to revive within the NHS. That is where leadership and cultures come in, and that is why we have all supported the Academic Health Sciences Centre concept. We need a few more of these across the country, in which that translational work and leadership will be part of disseminating change.

Professor David Hughes (The Business Innovation Group): Lord Darzi, thank you for that. It was rather interesting for me to see somebody describe innovation in a very wide sense, as you have. If more people did that, then we would have a better shot at creating wealth out of what we are doing.

You highlighted one area which you called management. I would like to encourage you to really push this very far in your studies. If we go back to the basics of management, going through the gurus with people like Taylor, Sloane, Drucker and so on, what we were really talking about is how to manage a process which, frankly, was of the last century? How do we replicate, in increasing scale, with increasing efficiency and so on? The challenge for the 21st century, not only in the medical world but elsewhere, is how to harness globalization of the technology.

We need to encourage the skills, capability and creativity of all of our workforce, so that we are no longer trying to find ways of managing a workforce to do what the organisation wants, but we are trying to organise things in a way that enables people's creativity to come to the fore. I do not think this has had nearly enough attention in terms of management and so the innovation management side seems to be particularly important. I wonder whether that figures with you, and what else we can do about it.

Lord Darzi: Absolutely. You have raised what is probably *the* most important challenge, not only as regards the management of innovation but also in how to engage the workforce and train them, in providing that leadership.

I probably failed to refer to the fact that the Innovation Council will be making sets of recommendations in relation to that in the spring of next year when I publish my Next Stage

review. There will be two deliberative through events which, hopefully, we will capture people who are sitting in this room but, more importantly, across the NHS, the academe and industry sectors. They will try to design ways in which, certainly from a workforce perspective, going back to the innovation culture will be part of your everyday life when you come to work. How do we get rid of the tremendous amount of boundaries that currently exist? In everything we do, we never look at healthcare from a patient perspective, but we actually look at it from the perspective of the clinician or the scientist. We never actually look at it from the perspective of those who are actually going through that journey.

Thank you. [*Applause*]

Sue Ion: Thank you very much, Lord Darzi. We wish you a speedy trip to Washington. [*Lord Darzi leaves*]

Sue Ion: Our next speaker this afternoon will be Professor Sir Alfred Cuschieri, who will talk to us about Newer Disruptive Biotechnologies: the Opportunities and the Challenges. He is currently Professor of Surgery at the Scuola Superiore Di Studi Universitari E Di Perfezionamento S. Anna, Pisa, Italy, and he is Clinical Director of the Cuschieri Skills Centre at Ninewells Hospital and Medical School at Dundee.

He was recently appointed Chief Scientific Adviser to the Institute for Medical Science and Technology, which is a joint initiative between the universities of Dundee and St Andrews in Scotland. He was formerly Professor of Surgery and Head of the Department of Surgery and Molecular Oncology at Ninewells Hospital and Medical School at the University of Dundee, and Reader in Surgery at the University of Liverpool between 1970 and 1975.

He has of course received many international and national awards for his pioneering work on the techniques and the technologies for minimally invasive surgery. He is a fellow of the Royal Society of Edinburgh and also a fellow of the Academy of Medical Sciences. A warm welcome, Professor Cuschieri.

**NEWER DISRUPTIVE BIOTECHNOLOGIES:
OPPORTUNITIES AND CHALLENGES**

**Professor Sir Alfred Cuschieri
Universities of Dundee and St Andrews**

Disruptive technologies

I shall talk about 'disruptive technologies'. This is not my term – it was first described by Clayton Christensen and I would recommend his book, *The Innovator's Dilemma*, as excellent reading for those who are interested in this field of human achievement.

Disruptive technologies are those which change the way we live and work and, more importantly, make value, and you become rich as a country. More often than not, they do not emanate from basic, new findings, but they emanate from gathering together useful information from existing technologies. These are brought together in an effective way. A typical example is of course the mobile phone, which has revolutionised life.

In the medical context, disruptive technologies require a long period of time to mature. Initially, they are less effective than the technologies which they ultimately replace. This is because medical technologies require very demanding use, particularly in terms of patient safety. I shall give you some examples of this.

Present situation

In terms of challenges to disruptive technologies, the way I assess the system is that, up to very recently, the interaction in the UK between life sciences research and development, and the physical science and engineering, has always been fortuitous. My view is that this is a paradigm that we need to change and I will dwell on this topic at some length in this lecture.

Interface medical science and engineering research

In fact, my concept is that of an interface. We have to introduce a new paradigm of interfaced medical science and engineering research. This is a stage beyond multidisciplinary research but it is research carried out in shared laboratories, between biologists, physicists, engineers, chemists and so on. It also embraces the new resources that have been introduced with the introduction of nanotechnology.

These scientists interact on a daily basis and learn each other's scientific language. As a surgeon, and as a medic, I found that it took me a long time to understand what the physicists and engineers were saying – and I have been working with engineers and physicists for at least 30 years.

I shall give examples, as Brian Doble asked me to, of what I consider to be disruptive medical technologies, both from Pisa, where I have been professor for the last three years, and also from the new institute that I referred to in Dundee. The three examples on which I shall touch are sonoporation, bio-magnetism and the NINEVE nanotechnology project, which is a European project.

[Slide]

This is the difference, as I see it, between interdisciplinary and interfaced research. In interdisciplinary research you have a big project which is farmed out to a number of different departments, very often in different universities, where they do parts of the research within the programme and then they ultimately get together and produce the whole. This is a very ineffective way of R&D, in my view.

A much better system is to set up, within universities and allied institutions interfaced laboratories, with a mix of cell biologists and cell engineers, physicians and so on, working together. This is exemplified by the new centre that is being opened by two universities in Dundee at St Andrews.

Emerging interventional technologies for cellular surgery

I shall address certain aspects of, in my view, emerging technologies for cellular surgery, which will have implications for stem cell research and regenerative medicine in particular.

Optison albumin microbubbles filled with octofluoropropane gas

The first relates to sonoporation, which is simply energising microbubbles – usually of albumin but they can be lipid, by low powered ultrasound, to induce the process of cavitation, during which these microbubbles release a very significant amount of energy which can be controlled and used for medical purposes.

Experimental set-up

To study this system, the IMSaT group, headed by Paul Campbell, on EPSRC funding, set up what is in Europe certainly, in my view, the only experimental set up to investigate the cellular interaction of sonoporation. The set-up includes the creation of a hologram for optical tracking. It contains an ultrasound transducer system for delivering energy to cultured cells in a solid chamber, and an ultra-high-speed camera. We can grab the bubbles – the microbubbles – and put them adjacent to living cell cultures and study the interaction there.

Laguerre-Gaussian optical trapping of microbubble

For those of you who are optical physicists, you can see that optical trapping is a very efficient way, in this case, of trapping one of these albumen 5-micron bubbles of this stone, which we can place exactly where we want in relation to a cell culture. On exposure to ultrasound energy, you see the cavitation system being processed, or being evoked [*shows animation*], in close contact with the cell.

AFM on jet exposed cell

If you then take an electron microscope picture, an atomic force microscopy picture of these cells, you see that you have made a perforation in the cell – you have created a sonopore. In other words, we can invade this cell for a period of time, so that large molecules can enter. Provided this permeabilisation is graded, the cell itself can recover. We have a process of repairable sonoporation. This is a physical technique, which can have tremendous applications to chemotherapy – *targeted* chemotherapy – and also to gene therapy.

Perforation/injection of cell...

This is a photograph showing how these punctures by this cavitating burrow is delivering its contents into this cell.

Double bubbles

What is interesting is when you trap more than one microbubble and sonicate them with low power ultrasound. You then have a situation whereby not only do you get this micro-jetting phenomenon which you will see here [*shows animation*], but you also generate light, giving sono-luminescence. This has further applications, in my view, in relation to photo-chemotherapy, photodynamic therapy, intravascular photodynamic therapy.

Optically trapped double bubble ...

This slide shows the microjets that these bubbles produce. Of course, this is in cultured cells that we have transfected with the growth hormone gene with this technology.

Biological effects of US-induced cavitation of microbubbles

The biological effects of ultrasound-induced cavitation of microbubbles has considerable medical applications. These microjets have penetrating power and in fact you can use them to kill cells – which, in my view, we really do not want. However, you can grade the energy and use it for repairable sonoporation and this is what I call cellular surgery, to enable targeted high-dose cellular chemotherapy or transfection of DNA plasmids in gene therapy. Of course, there is tremendous scope for that in stem cell biology and tissue engineering research. The bubble-bubble interaction produces sonoluminescence and opens the way to technology-based endogenous targeted photodynamic therapy.

[Slide]

More recently, we have been contacted by a company, CapsuTec, that synthesizes amino-acid nano-drug carriers. We have put cytotoxic agents in these carriers and the insulation actually releases this non-covalently bound drug from these nanocapsules. At the

same time, of course, we have increased the permeability of the cells. I think we have the potential here for some very refined nanosonics targeted drug delivery system.

Nano/micro-technologies based on tissue ferromagnetisation ...

The other aspect that I have been involved with at IMSaT is the ferromagnetisation of tissue. I hope this video will work.

[Shows video]

This is a pig's stomach that has been ferromagnetised. As I bring a magnet to this explanted porcine stomach [*demonstrated on video*], I can attract it, and that is not a party trick - it is a system of localised ferromagnetisation of tissues, with microparticles, such that it opens a new avenue for surgical instrumentation. We can have the development of retractors with the right sensor systems, which will enable even non-contact retraction as a technology.

Biomagnetics ...

This is a whole list of systems that we are developing.

Approaches for targeted ferromagnetisation ...

Ferromagnetisation of tissue is possible by surface, using glue-based ferromagnetic media, or by injection or by incorporation – actual cellular uptake – by transfection technologies using special biochemical techniques.

Ferromagnetic conduits

This, of course, has resulted in the development of ferromagnetic conduits. These are stable colloidal suspensions of sub-domain nanoparticles, with surfactant to prevent agglomeration in the case of a strong magnetic field. These are the fluids that you can inject into cells, or media. This time, we have suspensions of biological glues, also with a surfactant.

Simulated surgical procedures

As an example, this is a drop of glue on tissue. I have a 3mm magnet in these forceps. The tissue is adhering to the palate and I can lift it and resect the area.

Force vs media volume

More effectively, you can see the good retraction force that we can obtain, even with instruments based on small magnets – in this instance, 3mm and 6mm.

Retraction by injected ferro-fluids

If you inject the solution as ferro-fluid, then of course your retraction can actually lift an entire liver. I do not have a slide here with me to show you that.

Loading colorectal ca cells with magnetic particles

You can also load tumour cells.

Magnetocaloric effect of gadolinium assays

The interest here is to develop a system based on the magnetocaloric effect of incorporating gadolinium nanoparticles. This is what the St Andrews group are currently interested in. As you probably all know, if you expose gadolinium to a magnetic field, it heats up. This is the principle of magnetic refrigeration. We are reversing that principle for a medical application, to destroy tumours by endogenous heating following the uptake.

NINIVE – FP6-STRP 033378

The third example of nanotechnology is the NINIVE project, and this is my work with a group in Pisa. NINIVE is a pan-European programme, very well published, which involved a British university as well.

Carbon nanotubes – a new carbon allotrope

It is basically looking at the use of carbon nanotubes as vectors of both gene therapy and targeted chemotherapy. Nanocarbon tubes, of course, were discovered a long time ago. We are working with multi-lumen nanocarbon tubes for this project.

NINIVE tool for gene therapy: technical specifications

The NINIVE tool is as shown here. The idea is to coat the nanocarbon tube and then put ligands onto the carbon axons as a transporter into cells in a targeted fashion.

Translocation of an anticancer

This has been reported previously, as you can see in the published work on this slide, using nanocarbon tubes as carriers. The cytotoxic drug, methotrexate, is used as a cytotoxic agent and shows the incorporation of large amounts of this cytotoxic drug into the cell.

Cell transfection: by phagocytosis

The studies so far have relied on the process of cell phagocytosis of these nanocarbon tubes, which are tiny, of course – from 1 Angstrom to about 100 nanometers in diameter.

Cell transfection by electroporation

The NINIVE project is exploiting the dielectric properties of nanocarbon tubes. It has explored the hypothesis that, by exposing the tubes following injection to external electromagnetic field, we can induce a voltage on the nanocarbon tube and therefore use effective cell electroporation. Electroporation has been around for a long time and it is used clinically to get cytotoxic drugs into tumours, but it requires very high voltages, in the kilovolt range. The prospect of this new technology is that it will considerably reduce the voltage necessary for electroporation, which therefore makes it much safer and more effective.

Vector development: problem of bundling (conglomeration) of CNTs

One of the major problems that we had to resolve in using these carbon nanotubes as vectors for chemotherapeutic drugs and genes, is to prevent the problem of bundling, which is basically conglomeration, because they tend to form these clumps of nanotubes. They are therefore formed into bodies that are hazardous because, effectively, they will end up as microemboli, blocking the vessels.

CNT functionalisation

However, you can treat this, and this is a successful demonstration, by specific coating, to ensure that they remain dispersed. We have found, in fact, that the best coating is PEI and, for our experiments, this is the coating we have used.

Electroporation method

To cut a long story short, we have found that you can certainly electroporate cells efficiently by using two static electric fields.

The mechanisms of CNT-enhanced EP ...

The first one aligns the nanocarbon tube along the cell membrane. This is the electroporation field, and it aligns along the outer wall of the cell, this bi-lipid cell membrane.

Transfer mediated by cell ...

If you then supply another electric field, the A field, at right angles, you can considerably enhance the electric field in the membrane, as shown on this slide.

Experimental assays

These are the latest results of the projects. In assay 1, we are using two fields; in assay 2, we are using a single, static electroporation field and, in assay 3, this is just with EP wave plus A wave as well.

Experimental results: repairable EP

As you can see from the results of the experiments, it is only when you have the two fields at right angles that you have this very effective electroporation. We are using tritan blue, to see the increased permeability of the cell that we can obtain, or large molecules, in this way.

[Slide]

What is important is that the viability of the cell is not disturbed.

Changes in strategy

My final comments relate to the changes in strategy that I think are needed, particularly in universities and allied institutions.

Education and research are symbiotic and the two, graduate education and research, are inseparable. We should shy away from research universities as being separate from teaching universities. The training of the next generation of scientists and innovators – in that order – is best done in a university, with an interface science setting. Universities excel at technology transfer, simply because they transfer people – not ideas. On graduation every year, the youngest and the most promising and most ambitious talent leaves, but let us make sure that they are suitably trained and skilled. Technology transfer, in my view, should be a prime function of at least some UK universities.

Successful translation – multifactorial

Successful translation to new technology is multifactorial. Technology breakthrough is just the seed. We have certain deficiencies in this respect. We have low university entrants for science, engineering and technology subjects. I was reading Lord Broer's lecture yesterday and, apparently, the number of graduates in science, engineering and technology has remained static, despite the fact that the overall number of graduates has more than doubled. The number of A level students doing science and technology subjects has remained static, too, and has fallen in relation to other subjects.

In the UK, we do not have the ingredients of the fertile soil needed to translate the existing and new technologies into production. We are not good at access to venture capital. We are not good at access to engineering challenge – in fact, we are relatively under-skilled, compared to our competitors

We have limited access to management talent, both technical and general. Our manufacturing capability, too, is in my view not what it should be. There is a low level of entrepreneurial drive, generally speaking, amongst UK scientists.

Changing playground – altered needs

The playground is changing. We need to address the proposition of stimulating interface science approaches, which are needed for complex challenges – including effective research in nanosystems, regenerative biology and so on.

Universities need to become multidisciplinary institutions. I know that this poses organisational challenges but these can surely be addressed and overcome. We also need to have research and development support for applied physics and engineering, in translating existing basic research into technological devices – but, in my experience, that does not happen now.

Interface science and engineering ...

This is my view – that the sum of the two put together, the interface, will be greater than the sum of the individual parts in terms of output and productivity.

Thank you for your attention. [*Applause*]

Sue Ion: Thank you very much, Professor Cuschieri. Unfortunately, Professor Cuschieri also has to leave us now – these experts are in big demand internationally. However, he has agreed to take a few questions now, before leaving to catch his flight.

Questions & Answers

Tony Unsworth (Durham University): Thank you for your very interesting presentation. Could I go back to the start, where you distinguished between interface research and interdisciplinary research – and you showed those dots overlapping. In your view, what are the characteristics of the interface research over an above interdisciplinary research?

Alfred Cuschieri: Interface research is topic-orientated, where you have a mixed team of cell biologists, cell physicists and engineers, working in a specific area, in shared laboratories. It is a facility, not a department. It acts as an extra resource in the context of research and development, to bring together the expertise. In terms of the development of an applied protocol, they work together in shared laboratories. There is a flow from departments to such a facility.

Dr John Egan (BITECIC Ltd): I am representing the Health Technologies, KTN. In the Interface Research Centre, what role if any do you see for actual clinicians? If there is a role, how would you engage them to be productive within this environment?

Alfred Cuschieri: That is very important and clinicians have to be involved. In terms of medical technologies, interface science has to have very strong, clinical, academic involvement. I function, together with my colleagues at Ninewells hospital, as advisers to the group – there is no question about it.

The interface science relates to a specific area of need, for a medical technology. It then uses or builds a team with the necessary broad range of expertise to address the problem and develop the necessary technology and device. This is then taken by the clinicians involved in the project, for evaluation. The clinicians are there as advisers, but also as evaluators. In my view, it is becoming so complex now that you need this broad range of expertise.

The average development time, from concept to product, is about 20 years – for various reasons, some of which are regulatory, I know. However, one of the main reasons for this is that very often, because there is so little overlap between the life and physical sciences, they do not know what is happening on the other side of the divide. If you bring the right component expertise to a team, dedicated to develop a specific medical technology, for diagnosis or treatment or whatever, then you should have the facility which brings expertise from the partners in this interface lab. For a period of a year, they will develop this system, in consultation with the eventual users – the medics, of course - who will then take it and evaluate it. The interface is not a substitute for departments or whatever, but it is extra to that. However, in my view, unless you have scientists from the two divides, rubbing shoulders and working on a problem, then it will always take a very long time to mature.

Sue Ion: Thank you very much indeed, Professor Cuschieri. We wish you a safe journey to your next port of call. [*Professor Cuschieri leaves*]

Sue Ion: Our third speaker this afternoon is Professor Christofer Toumazou, the Research Director, Bionics, at the Institute of Biomedical Engineering at Imperial College. He will talk to us about disposable healthcare devices.

Chris Toumazou has been Professor of Circuit Design in the Department of Electrical and Electronic Engineering at Imperial College and Executive Director of the Institute of Biomedical Engineering there. He has co-authored or authored around 350 publications in the field, which encompasses low power electronics, and he has 20 patents to his name.

Chris is the founder of three technology-based companies with applications spanning ultra-low power mobile technology and wireless medical monitors – that is Toumaz Technology Ltd UK; digital audio broadcasting, Future Waves, which is a Taiwanese company; and DNA sequencing, DNA Electronics Ltd UK.

He is an adviser to many healthcare panels, including the Singapore Government, in the field of medical devices. It will be interesting to know whether the advice that he gives to them is similar to the advice that he might give here in the UK. Over to you, Chris.

TOWARDS DISPOSABLE HEALTHCARE DEVICES: A PARADIGM SHIFT

**Professor Christofer Toumazou
Imperial College, London**

I am rather an imposter because I am not a biomedical engineer, although I run the Institute of Biomedical Engineering. In fact, I would like to begin by saying that I am an example of someone who comes from one core discipline and has translated the technology to another discipline. I spent the first 15 or 20 years of my academic life developing mobile phone technology and radio frequency chips.

My honeymoon in this whole biomedical area happened seven or eight years ago, when I was approached by a company in Canada who were very interested in cochlear prosthetics, particularly for born-deaf children. I wondered why they were approaching me, a mere radio frequency, low-power radio engineer. The reason they approached us was because they had read some of the work we were developing on very low power semiconductor technology.

They developed this beautiful electrode array – and here is the example of the implant that we ended up designing for them [*shows example*]. This is an electrode array that wraps round the back of the membrane in the inner ear and makes physical contact to

the eighth nerve. This meant that the power consumption of the electrodes went down enormously. Instead of relying upon the viscosity of the fluid to make an electrical connection, there was a physical connection to the nerve. This made the surgical procedure really efficient because the surgeon would insert a little needle with the array, pull the needle out, and this would spiral around. The array worked very much like the proboscis of a butterfly or the trunk of an elephant – you can unravel it but, if you let go, it ravel itself around. It made physical contact to the eighth nerve and the power consumption went down enormously. What they were left with, however, were these whacking great wires and a big battery pack – as big as a car battery – outside the patient's ear.

They read some of this low power radio frequency work that we were developing and, to cut a long story short, we just supplied a fraction of the technology from this space and created one of the world's lowest power cochlear chips. So it is not all about inventing new technologies.

I then became very interested in applying these technologies to other applications. We looked at cochlear and we looked at retinal prosthetics, nerve implants and so on. I was thinking about titling this presentation, 'The Bionic Man' – but I thought that would be rather nerdy. I expect you remember the old American \$6 million man, but this business has actually become a \$6 *billion* dollar business now. This whole area of taking away primitive health technologies and, as the gentleman said earlier, trying to disrupt in a very positive way the NHS and the medical bodies around the world, is very important. It will take a giant to make it happen. It will take the Intels or Cardinal Healths of the world, who understand distribution, and who understand consumables, to bulldoze these new devices into these sectors.

Health on the go!

The space I am very much into is health on the go, looking at 24/7 monitoring, out of the hospital and into the home technology. We entering this fantastic new wave of technology supplied by lifestyle, personalised healthcare, quality of life – and it is not just a matter of making sick people healthy, but it is making healthy people healthier as well. It is that well-being technology that we are very interested in now.

The bad news is that I might bore you for the next 20 minutes but the good news is that, for every five minutes I speak, you will live one more second – so you will have four more seconds after this presentation. That is what is happening. We are living longer and you heard about the demographics earlier from Ara Darzi. People are applying technologies now and you will see that we go to the gym more often and we measure our ECGs more

often, and we are more interested in our blood pressure. We will go and buy our own blood pressure monitors and so on.

Large scale biomedical research ...

As was said earlier, it is all down to interdisciplinary research. Some traditional universities still work with silo departments – you have the department of physics, department of electricals. There is no problem with departments, because they incubate the core ingredients and that is what departments are for, but it is the next layer that we are very interested in – the mixture of those ingredients to make the cake. That is where we need to foster the interdisciplinary activity.

Academic and commercial success requires that we work together

How do we make that happen? Ten years ago, Imperial College did not have a faculty system and so we needed to bring in somebody like a Richard Sykes, who is used to merging things. We were then able to create a Faculty of Engineering, a Faculty of Medicine – and it is great that Leszek Borysiewicz is here, because he was one of the pushers of the big Faculty of Medicine that we now have at Imperial College. There is also a Faculty of Life Sciences and a Faculty of Physical Sciences. Once you have these faculties, then you have a layer of management that will allow this interdisciplinary research to take place. The gentleman mentioned interfacing earlier and it is at that level that we need to create these neutral institutes that allow members from all these different faculties to work together.

We did that. We raised some significant money and we created the Institute of Biomedical Engineering at Imperial College. It was fascinating to see that almost every department in engineering, and almost every department in life sciences, natural sciences and medicine, was doing some form of bio-related research. So why compete against each other? Why not create these large-scale, interdisciplinary institutes?

New Imperial College: Institute of Biomedical Engineering

The Institute was opened by the Queen in July. We have about 100 PhDs so far there, and about 30 post-docs. Of those 100 PhDs, I have 10 general practitioners doing their PhDs in biomedical engineering. We have biochemists, electrical engineers and medics, working around the same laboratory, working on the same bench, and that is where the real interaction will take place.

In electrical engineering, it would be hard for us to have a biochemist working with a mechanical engineer, working with an electrical engineer working with a medic, because that system does not allow it to happen, but this interface does.

Challenges to healthcare

There were three core, disruptive areas that we developed in the Institute. One of them is with Brian, Ara and Guang-Zhong and so on – the whole area of robotics and robotic surgery. Another area is bio-nanotechnology, driven by the life sciences, and the third area is the healthcare monitoring – the bionics, as I call it, with the disruptive, disposable technologies.

Personalised medicine – the new wave

It is all about quality of life. It enables chronic disease patients, in particular, to go home and not worry about taking their blood pressure three times every day, because that is more stressful than anything. You need these technologies to be unobtrusive and wireless. As I mentioned earlier, it is not big deal, as far as technology is concerned, but it is in the area of acceptance that the issues lie.

The silicon transfer

One way of pushing this disruption is leveraging on the economies of scale of silicon technology, which is the underlying technology that we use in the computer, mobile, cellular sector. There have been billions of dollars invested into this space, so let us now start to leverage on that and bulldoze this space into the healthcare arena, for the advantages that you will see in a moment.

The healthcare sector is changing

We heard from Ara earlier that a huge amount of the healthcare budget is now being spent on chronic disease management and there is this whole personalised healthcare push from the hospital into the home.

[Slide]

It is not just demographics, it is not just people getting older – it is a bigger problem than that.

The challenges

There is the problem of eating too much – obesity. Twenty per cent of the UK population have a poor diet and sedentary lifestyle, leading to the onset of Type 2 diabetes, heart disease and so on, and so we need to accommodate that.

State-of-the-art telecare system

I have mentioned new technology but look at how primitive some of the technologies are. We are still pushing out these sorts of technologies. Is it because people understand this technology? People like to understand that this is a blood pressure cuff – so ‘I wrap it around my wrist, and that is how I take my blood pressure.’ We need to have the models that push away from that old-style technology and much more into the disposable, affordable healthcare state.

Technology needs ...

We know that low power is very important and I do not need to explain why. The next point on this slide about 24/7 monitoring is very significant. We need continuous monitoring. If a chronic disease patient takes his or her blood pressure and it is very elevated, you worry and panic. You then take it an hour later, but it is still elevated, and you worry and panic. If you are blind to that, that might just be an anomaly and most of the time your blood pressure is fine.

We are trying to move towards a way of continuously monitoring that vital sign, that parameter and only if there is a problem will the GP be called in, or will the consultant be

telephoned via this wireless technology. You will see in a moment how we are starting to use this at the bedside in the hospital initially, and then in the home.

The last point on this slide is disposability, because these technologies have to be affordable and disposable and they have to be mass produced. All of this relies very much on an end-to-end infrastructure. It is a multidisciplinary infrastructure: you have a sensor; you have the wireless to the PDA; you have from the PDA to the patient information database in the hospital, and you have the database. That is a whole end-to-end play, and not a single play, that is important to leverage this into the system.

For shorter distance standards; [Graph]

Just to show you how things have changed as far as technology is concerned, 10 years ago we were all talking about GSM. Great – we could communicate over a wide distance, and we still do. We use mobile phones. We do not need very high data because all we are sending is voice and SMS signals. However, things have changed over the past few years, so that we have Bluetooth and Zigbee – we have all these short-distance communications standards, because most of the power in this GSM device is the transmit power, because I am communicating over kilometres. However, when you reduce the distance for communication to that last meter – if you like, the body network - then the power consumption in the transmit has gone down enormously. The real power is in all the processing and all the data manipulation that we need to send.

Intelligent local sensor processing

How do we overcome that? Over the past four or five years, you have seen all these conferences now on intelligent local sensor networks, or body sensor networks. You overcome it by developing sensors, but having the intelligence on the sensor and doing as much local manipulation and signal processing on the particular sensor. It might be an ECG monitor, a BlueCoat monitor, a blood pressure monitor, and then you just send in the results of the data. That reduces bandwidth requirements enormously. It is only the results of the data that you want to send and you only need all of the data if there is a problem and the GP or the medic decides to interrogate the sensor and asks for the information to be sent. You then need all that data but, most of the time, you do not need it all.

Transistor Integration Capacity

What is the technology doing today? You have all heard that it has now gone up to 5 billion transistors on a single piece of silicon. The old world was the digital egg and the digital egg was getting bigger and bigger and the animal's shell, the bit that interfaced to the real world, was getting smaller and smaller. Things have changed now and the world has

become digital. All communications have become digital but we are starting to re-think the egg in terms of low power analogue.

The real world is analogue

Think about a human's vital signs – we do not think with 20 bits of precision and we do not see with 20 bits of precision, and we do not hear with 20 bits of precision, so why do we need all the precision that we have in devices like this or like that, when we are looking at local manipulation of biological functions? There is a whole paradigm shift in the way that we are starting to process on these sensors.

For Biosystems

Some would say that we are at the end of the digital road for Moore. Some of you look at Moore's law – the transistors are getting smaller and smaller and smaller, but we are starting not to use the transistors as switches any longer.

In the human space ...

We are starting to use semiconductors as [*inaudible – coughing*] devices and I will show you why in a moment. We do not need the 20 bits that digital electronics gives us, so we can trade power. We can save power, and get effectively low power, but we are trading in precision by going to that low power.

Bio-inspired processing

I have to show you a little physics because, after all, I am a scientist. Effectively, if you go back to some of the early work by one of my heroes, Boltzmann – there is Boltzmann's distribution of energy. Boltzmann, you will have in every single field, from semiconductor physics right through to biochemistry and medicine. Boltzmann looked at kinetic heat energy and showed that the movement of energy followed an exponential behaviour, in exactly the same way as electrons flow in transistors. In semiconductors, you have this exponential movement of electrons when you modulate with the voltage.

In fact, in biosystems, you have exactly the same scenario. If you modulate bionic tissue with a voltage, you get the movement – a bionic current, effectively, following that same Boltzmann distribution. In fact, there are a couple of Nobel Prizes – there were Hodgkin and Huxley who identified these non-linear conductancies, all following these exponential behaviours.

Exploiting new technology paradigms

I am showing you this now because there is great synergy. If you have medics, biologists and physicists working in the same lab, then there is great synergy in

understanding the mechanics of biology, to create and innovate some new ideas. As far as technology goes, we have got down to 90 nanometres and below, in terms of the size of our semiconductor. In fact, a couple of weeks ago, Intel launched a 45 nanometer semiconductor.

If we start using those semiconductors with their natural physics – with their natural physics being these exponentials with which we can model biology – then we can start creating very low power, intelligent functions, not in software but in hardware.

Exploiting new technology paradigms

You might think that this is just a crazy idea, but I will show you how this has been commercialised and is being used to make some very, very low power vital sign monitors.

Simple maths operation

Just something simple like logarithms, I hope many of you will have heard of logarithms – I certainly have and I was taught with log tables. If you want to multiply two numbers, if you add two logs and an anti-log, you get multiplication. Do you remember? That is how you would multiply.

To multiply digitally with software, you need 20,000 transistors being switched on and off, with some C-code, to give you a very precise multiplication. Here, I am showing you multiplication just out of a handful of semiconductors, because I am using the natural physics of the device to do some of that computation.

AMx – a new way of thinking – Advanced Mixed Signal

We have actually labelled this new processing paradigm AMx – advanced mixed signal processing, where analogue works much as the digital used to work. We are using analogue computation to do a lot of the intelligent processing. Digital works like the analogue used to work, because digital is actually the communication medium now. So we have changed the thinking in the human space for biomedical applications.

Anatomy of the human ear

I mentioned that the cochlear prosthetic was one of the first examples, where we replaced the function of the cochlear, which is basically a fluid-filled tube with about 20,000 hair cells connected to the eighth nerve, with a bank of filters. Quite interestingly – and this is the bit I do not quite understand about biology – we replaced a biological function that has, in the biology, 20,000 hair cells, with 16 electrodes instead of 20,000 electrodes. Nevertheless, the brain took over, with all its plasticity and regeneration problems, to give

born deaf hearing – or, as they understand it, hearing. So there is this whole fabulous regeneration process.

Lowest power silicon ear

So that was the chip, but the demonstration was that it used two orders of magnitude less power than the world's best microprocessor to achieve that functionality.

Implantable, micropower retinal prosthesis

What about retinal prosthetics? The retina is a fantastic piece of neuronal wetwear – it is the only part of the brain that sticks out of the head. It has this fabulous photopic range of about 17 bits, which means effectively that it is doing a lot of processing locally. It is taking bandwidth of about 10GB/second. As scientists, we have struggled for many years to try to replicate the behaviour of the retina because the weakness of computers is the ability to access information, store it, number crunch it, and ship it out instantaneously.

Where's the monkey?

Spot the monkey! This is an old slide, but the idea is that you automatically spotted the monkey, and you were able to do that instantaneously. The point is that, by doing that instantaneously, you have actually taken in all that data, manipulated it, and sent out the result. In fact, the brain of a common housefly, which is smaller than a grain of rice, can do it instantaneously – and yet the best super-computer on this planet cannot do that. In fact, we make CCD cameras that bloom and over-expose, because things are done globally and not locally. However, in the retina itself, things are done locally.

Retina structure and operation

We have 100 million photoreceptors, on every single one of which you have some local intelligence, made up of bi-polar and horizontal cells, gain control, local quantization, local filtering. Everything is done on each single pixel, and that is how we can take in all this bandwidth of information, manipulate it and then send out all this data, but with much lower bandwidth. There is a lot of compression taking place. I am showing you this because a lot of the technologies that we are developing are bio-inspired – we are inspiring technologies from biology, and we are understanding how biology works to inspire technologies which will eventually then replace biology. That is a very interesting way for the biologists, the medics and the engineers to work together to understand these problems.

Bio-inspiration – wireless sensor processing

That whole idea of having some local intelligent processing, some automatic algorithm control with a very low power radio, is labelled the Sensium, not the Pentium.

Toumaz

This company is now about seven years old, up in Oxfordshire, called Toumaz Technology. They are making digital plasters, or digital band-aids. I have an example of one here – I could not wear one today because I did not think we would have the audio visuals so that I could show you it working on the screen. This is a piece of ‘power paper’,

The Sensium

You can take something like a Holter monitor and reduce all its functionality onto a single chip. That single chip has all the ECG algorithms for full ECG monitoring. It has a very low power radio on it and it has some intelligence. The power is in nanowatts and so, effectively, we are powering it up with this zinc air environmentally friendly piece of power paper. That is providing the energy requirements, 30MW hours, to provide the power to this chip.

We have called it a digital plaster because, once you make it look like a plaster, you just stick it on the person. People understand disposable plasters. We are getting this manufactured and it should be pushed out into some of the hospitals, initially in the States. The idea is that effectively, now, for this particular chip, we can have full ECG monitoring for five days, 24/7 and, after five days, you can throw away your plaster. That is the concept of the digital plaster.

We have our first prototypes out, and we are on the final let of FDA approval. You can imagine that initially this is at the bedside, for vital sign monitoring in the hospital. You do not want the nurse going to every patient, taking their temperature and blood pressure, so you can have this as a replacement. It is wireless tagged and so, if the patient walks around, you have ID, so you know where they are. We have the complete functionality but this is just the last metre, as I have said. It needs to interface to the patient information database and back to the consultant. Once again, it is powered up with thin battery paper.

The “Sensium” digital plaster

Magdi Yacoub, who works with us now, has used the chip. When the Queen opened the Institute some time in July, I was wearing one of these, which was remotely monitoring my ECG on a big screen. Magdi had his mobile phone, which basically had the full ECG – it was meant to be on his phone. I asked Magdi how I was doing, which might have been a big risk while having the Queen there. We tried it out and he was there for 30 seconds, but he did not switch the phone on! To me, that was a classic example where the endpoint will not be the technology play but it will be the acceptance and the understanding by the medical clinicians and by the community. On the spot, that was a real and fantastic example of how

there was a failure because of the complexity of the technology that we were trying to use. We managed to bluff our way out of that.

Mechanical plasters ...

It is not just for ECGs. We have accelerometers on there, which are these little devices that can measure movement – things like activity.

Well-being lifestyle wireless sensors

When we talk about these digital plasters, it is not just to make sick people healthy but it is to make healthy people healthier. There is this vanity thing about lifestyle and monitoring. Perhaps the lady on this slide was not the best example for healthiness but, effectively, it is a matter of being able to have these remote sensors around your body, and being able to pick these vital signs for wellness.

Body sensors for sports medicine

Then there is also the sports area, with things like training and looking at athletes, being able to measure their ECGs, their blood pressure and so on, in a very unobtrusive way.

End-to-end system for disease management

This whole issue is part of an end-to-end play. You cannot just have the sensors because you need the tie in with the providers of the networks, and with the providers of the databases. This is a whole cyclic, end-to-end system that needs to be in place before you can push these things into the environment.

Continua Health Alliance

Over the last year it is interesting that the Americans, with a few of the European big players, have got together to create the network called the Continua Health Alliance. All the big players such as the Intels, Philips, Siemens and Medtronics of the world, who have spent so much money on medical devices, have got together and they are all now trying to create the standard. Once there is a global IT standard around these technologies, then things like security, approvals and sanitisation and so on will all fall under that wireless healthcare standard. It is great to see that there is a big move with some of these big players and it is these players who will disrupt the NHS in the end. They are the ones who will bulldoze these new technologies right through, to get them sold.

Where next?

Where is the future? Where next? I have shown you the sort of marriage between electrical engineering and medicine.

Chemical FETs

I think there will be a huge marriage between chemistry and sensors and we are already seeing some of these chemical devices now – these old pH electrodes are becoming much more real-time, blood monitoring devices. This, once again, is a mixture between chemistry, between sensors, biosensors and silicon chip design.

Diabetes treatment

These are the sorts of things that diabetics are used to. You take your strip measurement, you take your blood and then you inject your blood and that will inject your insulin. That is great, for compensation of your glucose level at that particular time of day. However, this technology, whilst it is personalised, is still pretty primitive and it has not moved very much over the past few years.

Benefits of continuous monitoring in healthcare

We are getting better strips and better injectors but one of the problems, as was mentioned earlier, is that if you do not have the 24/7 monitoring then you can get all these side effects due to diabetes.

For example, if you take a strip measurement here during this time of day, and then you do not take it for the rest of the day, but you take one there [*on slide 46*], then yes, you can compensate with insulin during those two spot measurements. Most of the time, however, you could be outside of your range. You could have eaten some fatty food and you could have done some over-exertion or exercise and, effectively, you end up with hypo- or hyperglycaemia, which brings about side effects such as renal failure, retinopathy and so on. The idea therefore is that we need to be able to monitor our insulin levels 24/7 and compensate for them 24/7.

The pancreas

There is some really fabulous work taking place, both here in the UK at the Institute, and also some work in Harvard, where the guys are looking at trying to model the behaviour of the beta cell. I will not go into too much of the biology here but the beta-cell is the part of the pancreas which is responsible. It is the intelligent part which determines how much insulin needs to be secreted into the blood as a consequence of your glucose levels.

The beta cell

If you look at the dynamics and the biology of the beta cell, you see this spiking pattern which is very much like neural activity – like neural axons. This spiking activity determines the amount of time that these beta cells are released in insulin. Thus, the longer

these spikes are for the time, the more insulin you have, and the shorter, the less. That is controlled intelligently, so there is local intelligence.

Application: the pancreatic beta cell

It is only now, with the technology that we have – the very low power, the very small dimensions, that we can replicate that behaviour in silicon and make, therefore, very intelligent biochemical pancreas or beta cells. By mixing chemistry with silicon mathematics, we are creating these chips. This chip is now going into trials. We are putting this chip on the front end of an insulin pump because we want that pump to be intelligent. That pump continuously secretes insulin, based upon the dynamics and glucose levels of that individual. Once again, this is personalised because we are closing the loop and giving the right therapy throughout the time.

The silicon pancreas chip

However, this is only possible because we now have a technology which will enable that patient to go about their daily life without worrying about bringing in all of these obtrusive pieces of gear.

Early disease detection

Where is the future going? The future will basically be not therapy, not diagnostics, but early detection. That is where we have to be and this is where some of the genetic technologies and early markers are very important. Hopefully, we have all heard about these SNPs (single nucleotide polymorphisms) which are genetic mutations for particular genetic diseases. You have SNPs for various drugs and so you can imagine that, in the drug testing area, where you want to speed up drug trials, and you want to know whether or not a patient can actually metabolise a particular drug, you can tell that by their particular SNP and the SNP of the particular drug.

Ion sensitive field effect transistor (ISFET)

This whole area is getting a lot of traction. One of the companies, called DNA Electronics, is where we are looking at electrical markers instead of optical markers for DNA. We take that whole surface of a silicon transistor but we immobilise DNA polymerase. Every time a base pair is inserted, an A with T or a C with a G, you get change in pH and change in electrical current. So this is an electrical read-out, and electrical marker, for DNA, and it is disposable because it is a silicon chip, so that we can throw it away after you have done the genetic test. So this is real-time, point of care, genetic tests, either in the GP surgery, 'this drug is better than that one for you', or in a pharmacy, or it could be for a particular disease that you do not want your wife or husband to know about, so you go and get your SNP chip

from the chemist. This whole area is starting – over-the-counter is starting to revolutionise, because of the genome project.

Where next?

We will see that there is a great deal of work going on in stem cells. There is a lot of work developing stem cells and, once we can start putting in some of these silicon chips, we can then start to monitor these stem cells and nerve tissues.

Cell-tissue bionics: how does it work?

In fact, there was a big project that was jointly funded by the BBSRC and EPSRC not long ago, where we were actually looking at these low power diagnostic chips – putting them in bio-reactors to measure online the pH expansion properties, oxygen levels and different blood chemistry levels within stem cells as they are growing, so that we can control what is happening in an unobtrusive way.

Disruptive technology

In conclusion, I mentioned disrupted technology at the start. Disruptive technology will disrupt the business model of the customer. If you take a big distributor, like United Health, which understands distributing disposables – how will they distribute things like digital plasters? There is a whole paradigm shift in the way that they have to change their own business model to make these things possible.

There is then obviously the acceptance within the hospital environment. Much of what I have talked about is translational technology – technology from one sector to another sector. We need the end-to-end play but the key is multidisciplinary, as I mentioned earlier, with the Institute. It is important also to make these affordable technologies.

Doctors look at your medical history ...

The future perhaps lies in the quotation I found in *Nature* a couple of years ago:

“Doctors look at your medical history; imagine if they could look at your medical future”

That is really where we want to push this technology.

Thank you very much. [*Applause*]

Sue Ion: Thank you, Chris, that was absolutely fascinating. If there are questions for Chris, perhaps you would save those for the Q&A session at the end.

We will take a break now, and resume in 15 minutes.

[Resumed after Break]

Sue Ion: Our next speaker this afternoon will be Professor Tony Unsworth, who is also a fellow of this Academy. He will talk to us about 'Joints from Concept to Implantation – good things and bad things.'

Tony is Chair of the UK Focus for Biomedical Engineering, which is the organisation that provides a forum group through which the principal organisations concerned with biomarkers and communicate and interact with one another. He is also doing a great job in looking to influence the Department of Health and central government research funding sources and so on, so it is a pretty important voice that has had a good deal of success over the last year or two. It has an event in a couple of weeks' time, which is the annual lecture on Systems Biology and Medicine, and you will find some more information about that in your packs.

Tony has had various posts, initially with the David Brown Corporation through to 1969. He was at Leeds University and then went on to the University of Durham, where he is a Director of the Centre for Biomedical Engineering.

His main research area is the tribology of human and artificial joints but, additionally, he has published many papers with respect to rehabilitation of the upper limb. He has been awarded the Tribology Silver Medal, which was the inaugural medal in 1972, and the Donald Julius Grand Prize, the James Clayton Price, all from the Institute of Mechanical Engineering. In 2004, he was awarded the James Alfred Ewing Gold Medal of the Institute of Civil Engineers for his research into the tribology of human and artificial human joints.

He has been appointed to a number of special lectureships, including the Brunel Lecturer for the British Association for the Advancement of Science; the Woolmer Lecturer, which was the Institute of Physics and Engineering in Medicine; and the Smith and Nephew Lecturer of the institution of Mechanical Engineers. As you can see, that is quite a diverse portfolio. He is a fellow of our Academy and he is also a fellow of the Institution of Mechanical Engineers and of the Institution of Civil Engineers.

Over to you, Tony, to tell us the good things and the bad things.

JOINTS FROM CONCEPT TO IMPLANTATION – GOOD THINGS AND BAD THINGS

**Professor Tony Unsworth
University of Durham**

I was taken by the talk by the Professor Cuschieri, when he said that scientists and engineers often have a low level of entrepreneurial drive, because that describes me very well. I have often said that, if I was the only owner of a product that everybody in the world wanted, I could manage to sell it at a loss.

I came into engineering because I like making and doing things. Whilst I do not have any great desire to make a massive profit, I would like to see things that we produce being used to help society at large.

Mid-twentieth century

When I first came into this, the person who attracted me to biomedical engineering is sitting in the audience, I am pleased to say, and he is Professor Duncan Dowson. He dragged me away from tractors into looking at human and artificial joints. It sounds good when you say it was in the mid-twentieth century, doesn't it – it sounds a long time ago, and it was. These were the sorts of joints that were being put into people and I have to say that they are not much different if you have one put in now. In fact, the Charnley joint is still used quite extensively. Some of the others on this slide have gone out, but others have come in to replace them, perhaps with different metals. Basically, however, the materials used here are exactly the same now as they were half a century ago.

Friction simulator – natural joints

When I first came in, this was the first project I ever did with Professor Dowson. This was to look at how natural joints are lubricated and how they work. Here, we are looking at a natural joint, part of a hip joint, the actual tabular component. Basically, this showed that this cartilage on cartilage, soft material in the body – this is the bearing material of the human body – is fairly low elastic modulus compared to the materials you saw in that first slide. We have very little asperity contact shown, which showed that the friction is remarkably low in here. This was because we had a film of fluid separating the two surfaces – fluid/film lubrication - for much of the time that these joints were operating. However, when you needed it, there was also a boundary lubricant. So this was the work that we did way back in the beginning.

[Photo]

However, all the artificial joints did not work on this principle. This is the machine in the laboratory in Durham but it is very similar to one that I built at Leeds before I left there to go to Durham. It just swings backwards and forwards and puts a dynamic walking cycle onto the joint and we can measure the friction throughout the cycle using this transducer.

Stribeck plot f. against $\eta uR/L$

The reason for showing all of this is to give you an appreciation when I show you some later slides that, for those who are not familiar with this Stribeck plot, if you have dry rubbing friction, then basically you have a high level of friction and it is independent of sliding velocity. Sliding velocity comes into this thing down here.

If you have full fluid/film lubrication, where the two surfaces are separated, then the friction is low but it rises as you increase the velocity or the viscosity of the fluid. It rises as you go in this direction, so you can identify whether you have this fluid/film lubrication or not. If you have a mixture between the two, where some bits of material are touching and some are not, where they are separated by a fluid film, then you have this falling characteristic. I am showing you that so that later on you will see what we are trying to do with these joints.

The star that has just appeared shows where we tried to design bearings. When I was at David Brown's, one of the things I had to do was look at bearing design and we tried to design it so that it is in the fluid film lubrication area, but you are not too far in because you do not want to waste energy up here.

Stribeck curve for young male hip

From these human joints, we found this sort of thing. This is a 20-year old male hip, lubricated with its own synovial fluid, and you get this rising characteristic in that way, indicative of fluid film lubrication.

Stribeck plot for CoCrMo/UHMWPE lubricated with CMC fluids (28mm)

This is one of those metal on plastic joints. On the same plot here, you can see that this is coming down – it is in the mixed lubrication regime. That is pretty well true of all the joints that were around, although there are a few now that have moved into the fluid film area.

This [on slide] is the point that would apply to most people who need an artificial joint – that is, people with arthritis. The Sommerfeld number would be about 10^{-9} and that gives you the friction across there.

Having said that, we have this mechanism of lubrication of the natural joint, which is fluid film lubricated and, if you are separating the two surfaces with a film of fluid, you then have not just low friction but also low wear, because they are not touching. In this case, wear is taking place all the time, because you have mixed lubrication.

Elasto-hydrodynamic lubrication

The way that makes it easier in the body to generate this film is, if you have a hardish material, like this metal one, or a harder plastic, against the surface, you only have a small contact area when they put a given load on and so you need a bigger pressure if you want to integrate the pressure over the area to carry the same force, then you need a bigger pressure generation than you do if you have a soft material which will give you a bigger contact area. It is thus easier to generate a film of fluid here than there.

[Slide]

If the body can do it, why shouldn't we do? Why do we not make artificial joints in that way? That was the concept initially. We did a little work, but we do not need to look at the detail of that – it was just to show that we did some finite element analysis to show that it could work, and we produced these joints.

Soft compliant bearings to simulate human joints

These were a few early attempts – and I should say that the very first attempts I made were not as good as this, but they were fairly crude estimations or approximations as to what human joints were.

We looked at different materials but all of these have soft compliant layers attached to a harder backing. That is just stainless steel, because it happened to be one of the materials that were used a good deal. This is a porous stainless steel, the tinted one, to help bond these surfaces to the backing. There were a number of others, which I shall talk about later.

Hardness selected to give fluid film lubrication

These are experimental results which basically showed that, if you take a typical plastic on metal joint, there is friction at this point. If you then add different layers of lowering hardness along here, you get down to these exceedingly low values of friction, indicating fluid film lubrication. It thus seemed that we had proved that this could work in these joints and that we could get a film of fluid, just as you do in normal healthy human joints.

Chronology

This is the story so far. I am trying to show you how I did not really have very much of a clue as to how I was going to get this into patients. All of that started in 1979, with those

experiments being funded by what was then the SERC (Science and Engineering Research Council) which has now metamorphosed into the EPSRC, so that was a good thing.

Then in 1981 I published the results at an Edinburgh British Orthopaedic Research Society. That was a bad thing. It was a good thing in the sense that all the surgeons were very enthusiastic and thought this was great and that we should take it further, but it was a bad thing from the point of view of patenting and all the other aspects that I had done wrong. So that was the first mistake.

Between 1981 and 1987, we developed this concept into a working prototype – and those were some of the things that you saw earlier on the slide, and then started to do serious work on it. However, I then compounded the problem by publishing at the IMechE World Tribology Conference in 1987. Again, there was a lot of interest – the manufacturers were then very interested.

I also managed to secure a Wolfson Foundation funded development grant. You saw that Death Valley flag at the beginning of today's proceedings, and it was really designed to try to fill that gap. This was a long time ago, back in 1988/90. So we got that and developed it sufficiently to get quite a few manufacturers interested. However, the one I decided to go with was, at that time, the largest UK manufacturer because I thought that would be a good thing to do within the UK. It turned out to be a bad thing because it took them two years before they told me that they did not want to carry on with the product. I had therefore wasted two years and, in the end, I went with an American company who were interested in taking this forward.

The decision

At this point, we had another minor problem. Secrecy depended on it, because they did not want any more of the work to become public until they were ready. That was not good for my academic career at the time, but it is helping me in my old age because I now have 10 papers on work I did 10 years ago and beyond, which are all in the process of being published. So I should be alright for the research assessment exercise, but it was not good for me at the time. However, I managed to negotiate a deal for the university, worth 2.5 per cent of the sales, which the company has been trying very hard to renegotiate – but 10 per cent of that should have gone back to the Wolfson Foundation, under the grant agreement that we had. That was a good thing, because it helped the re-stock for funds coming forward.

Two grades of PU bonded

I will just tell you a little about some of the problems we faced, and the actual technical problems. We wanted to have a soft, compliant layer. I do not know whether any of you have ever played with cartilage but it is very soft and squashy – if you push it in one place, it comes out somewhere else. This means that you really have to be careful about how you design the thing. However, I also have to join a soft layer on the inside with a harder material on the outside, so that we could fix it into something – either into a metal backing, to fix it to the body, or directly fixing into the body. It seemed, at the time, that polyurethane could be an excellent way of doing this because, of course, you can get different grades by mixing them together in different hard and soft segment combination. You can also get rid of this bond line – you do not want a discrete bond line, but you would like it to be soft at the surface, hard at the back, and moved gradually between the two.

Layer adhesion evaluation

When we first started, we just thought of sticking them together and we tried the materials that were already used in the body, to stick these polyurethanes to. In this case, it was ultra-high molecular weight polyethylene. I do not know whether any of you have ever tried to stick anything to ultra-high molecular weight polyethylene, but it is about as much use as a chocolate fireguard: it does not work. Nothing seems to stick to polyethylene.

Blister test

This is our first attempt: pathetic. This is the adhesive fracture energy, and it was pathetic because everything peeled off at the slightest thing – if you put it in a ?duction machine, and it would be off before you finished the first test, so that was no good.

We modified the surface chemically, working with our chemists, and we achieved a slight improvement.

Fused interface assessment by FTR

We then started sticking it to itself, to different grades, and we got better and better at it, until we discovered a way – called an inverse moulding method – of putting them so that we could have a sort of flow between one and the other. This is one material here, and that is the other material, and we got them to flow together over a region of about 65 microns, which helped. We no longer had a discrete line, and we then started to find that these things just did not tear apart.

FE analysis

We did a lot more finite element analysis, looking at the deflections and the contact areas in particular.

Definitions

This was the reason for doing this work. We were trying to make sure that, first of all, the pressure distribution within a contact – and this was a ball and socket joint – was all contained within the cup. We did not want this coming over to the edge and we certainly did not want large, stressed gradients at the end, which would help separate the surfaces. We want to keep that away from the edge. We did a great deal of work on that and showed that we could do it, but we had to compromise on the elasticity of the material. I would have liked to have made it softer but we could not make it softer and maintain the geometry we wanted to.

So we now had our soft compliant bearings to simulate human joints – polycarbonate urethane

So we then had polycarbonate urethane, but this was another problem. I had a working joint but polycarbonate urethane had not been produced at the time when we had the working joint. I do not know whether any of you are familiar with polyurethanes but the ones that are used in the medical area always used to degrade very quickly in the body – two years was about as much as you would get in the body, and then they would just fall apart. We therefore had to wait and chase various manufacturers until we could find something that would not do that – and this polycarbonate urethane turned out to be one of them. So we then had a material that would work and would survive in the body, and we have lots of tests to show that, so we could now start making it work on this scheme.

Compliant layer

I have just put this up on the slide to remind you – what we would like is to see it rising. These are the results that we got from that particular joint. There are two points here.

Compliant layer against Exeter head

You may have noticed in the previous slide, where I showed you the metal on plastic joint, that the friction factor was about 0.03. Now, these are the experimental points here and this is the theoretical curve that we would like to get to, but we are not quite there. This is where we are operating in the body, at 10^{-9} again. You can see that the friction here is now at about 0.001 or less, which is really low friction. This is because we have fluid film lubrication in there and that is just against an ordinary existing metal head, which is in a different joint, and we just put them both together. We seem to have a product which works

and it seems to give us fluid film lubrication and it certainly gives low wear, so we now just have to get it to the market in some way.

Durham hip wear simulator

This is just to illustrate – we tested all of these and compared them on the same machine, with different kinds of joints. This illustrates roughly where it fits.

[Slide]

I have not shown you these joints – they are other new, fairly modern joints too. If we go back to that Charnley joint, the wear rate of the plastic is about 48 to 60, depending on what it is up against, and the size. This one is slightly bigger than that one. Those are mm² per million cycles, and you probably walk about 1.5 million cycles a year, so that is what the wear rate would be.

If you put the polythene now against alumina, which is harder and smoother, you will get a slightly lower value. Our polycarbonate/urethane special joints were about somewhere in that range. The best ones, once we had got the design right, were down at about three, so it was about one-tenth of this, or less. The earlier ones were not so good, at 20.

If we now go to the knee joint, where you are getting down to these incredibly low values – and I shall say more about that shortly – if you compare that with these new metal on metal resurfacing, it is not as good but it is still pretty good and you do not get metal ions floating around in the body. To be fair to the metal-on-metal, there is no evidence to suggest that those metal ions that float around the body are doing much harm, but they are there and some surgeons worry about it. Also, of course, alumina on alumina being very hard, and producing fluid film – as both of these do – they work very well.

Patents

Turning to patents – I had already published it, so I could not do anything about that when it came to it except that, when I eventually started to look at patents, I found that this had already been patented anyway by a surgeon called Muller, but he had done nothing about it and so that had lapsed. That was okay.

We patented the manufacturing technique, because it is not easy to make those things. That has been patented and the company with which I am working has that patent. However, I have just discovered that in 2004, two British surgeons patented the idea again in the USA, so I am not sure what happened there, or how. At any rate, I believe that the company has contested it.

Hard and soft layers

We then moved this idea into knees.

Uni-condylar knee

This is a uni-condylar knee that we have tested.

Wear rate comparisons

I have just put this on the slide to show you that these are comparable knees made from metal and ultra-high molecular weight polyethylene – these are just two knees. Those are the values that we got from the knee simulator, and that is what we got for our compliant wear, which was very low because it is literally floating on a film of body fluid.

Wear with cement lubricant ...

This is a soft elastomer and so we had to throw in hard particles, in case you have bits of cement or bone getting into the interface. Would it tear them apart?

[Slide]

We did 3.5 million cycles with bone cement in it and after that we measured the friction – this is the polyurethane one – and it is still producing this very low friction.

Sheep study

I had nothing to do with the sheep study. We had pretty well finished all the work that we could do but the company then commissioned the sheep study in Australia. They did a pilot study first and then they looked at these Merino withers for six, 12, 24 and 48 months, and they implanted these joints and then examined the results. The analysis of this work was done at Cambridge and so all I did was to design the joints and test them in the lab to make sure that they worked in a smaller size for the sheep, and then shipped them all off to Australia. They were then shipped to Cambridge and I have never seen them since.

Typical post-op X-ray

That was an X-ray from Australia, when they had done it.

After 24 months

After 24 months, this is one of the slides they sent me, just to see that there was no obvious wear. They could not detect any wear – this was in Cambridge afterwards, to see whether there was any problem.

Long-term performance

There was no de-bonding after about 14.3 million cycles – that was in the simulator in the lab. The friction factor remained very low. We calculate that during walking there is less than one per cent of spherical contact. You can see the other attributes on this slide.

From start to finish

I will just finish off with a little more of the history of this. We had this hypothesis in 1979 and proof of concept in 1981. There was research funding in 1988 and Wolfson funding from 1988 to 1990. We then had an EU grant – one of these Brite-Euram grants – to take it forward as well, so that went up to 1995. Whilst that was on, the company that took it on then started to fund, and they have funded it right up to today.

I have put that clinical trials begin in 2007, and that is what it says – and that was right when I wrote this slide, when I agreed to come and talk to you.

The final chapter????

So now there are the question marks – why are they there? They were supposed to start in February, using the knee, but then all of a sudden they became slightly worried about the fact that the sheep trial was only four years for a brand new concept, when nobody has used this material in the body in the body in this way before. They have now decided to do more controlled animal studies and a clinical trial is starting already – but not on the full knee, just on these focal defects, a tiny part within the knee joint, to see whether or not it behaves okay in people, before they start to go to the full knee.

Reflections

Just to finish off, I am reflecting that several successful hip joints, according to anecdote, have been designed, made and implanted in patients in less than a year. We hear surgeons say that, in the old days, they used to go out in the garage and make a joint and fit it to the patient the next day. I do not know whether that is true, but that is certainly much less than the 28 years that it has taken me so far. I reckon that just the cost of the lab work that we have done is £2.5 million, so heaven knows what the company has spent on it. It has been quite a long road, as you well know.

Reflections contd ...

Regulatory issues increase the need for free market testing. Fear of litigation is another issue and big companies are scared to death of being sued if they have a lot of money and they think that people would like to help themselves to it.

There is perhaps a better chance of getting it through a smaller spin-out company, but here is an idea which a great many surgeons that I talk to think is terrific. They would all like to have it produced but, at the moment, it is taking a while to get it into the market place because it is a completely new concept and the stakes are quite high. [Applause]

Sue Ion: Very many thanks, Tony. Tony will be staying for the Q&A session later.

Sue Ion: Let us move on to our fifth talk this afternoon which is in the field of medical imaging. Professor Chris Taylor from the University of Manchester, where he is Professor of Medical Biophysics, will talk to us.

Chris received his BSc in physics and a PhD in computer image analysis from Manchester and he currently holds joint appointments in the University Medical School and in the School of Computer Science, where he is Head of School. His research group is actually based in the medical school.

His research is in computer vision and medical image analysis and his central interest is in developing generic methods to underpin practical applications in medicine, industry and commerce. He has a long history of involvement in technology transfer and he has established long-term partnerships with industry and spun out five new companies.

He was awarded an OBE in 2000 for contributions to Foresight and Health Informatics and was elected a Distinguished Fellow of the British Machine Vision Association in 2003, and the International Association of Pattern Recognition in 2004. He has been a Fellow of the Royal Academy of Engineering since 2006. Over to you, Chris, to tell us about Medical Imaging.

MEDICAL IMAGING

**Professor Chris Taylor
University of Manchester**

It is interesting that we have all taken a slightly different tack here – and I have done something different again. I was given the hopelessly broad title of Medical Imaging and did not take the trouble to narrow it down, but I have done so now.

Clinical information from images

What I am interested in – and it is summarised here – is getting clinical information from images. There are clearly huge areas of medical imaging that I will not touch on at all. I

shall not talk about acquisition, which is a massive area in itself, and I will not talk about things like image-guided surgery. I shall talk about the bread and butter of imaging and how you get information out of medical images.

The motivation for this is the commonly repeated observation that our ability to acquire images is outstripping our ability to interpret them. This is partly to do with the volume and complexity of the data that we are now able to generate. It is also due to the fact that we still persist in making qualitative rather than quantitative interpretations of images, which is labour intensive. It is increasingly to do with the fact that we still concentrate on individuals but, to understand what images mean, you really need to deal with populations. These are all reasons why we are struggling.

I shall talk about an area that is now commonly referred to as imaging informatics, which has applications in screening, in diagnosis and prognosis, and in planning and monitoring treatment.

My journey here

I thought it might be worth saying a little about my background. I studied physics, as Sue said, and the training in intellectual arrogance has stood me in good stead ever since. For my PhD, I went into computer vision and medical image analysis and my interest has been in practical applications – particularly in producing complete engineered systems – but my interest in that is both because of the direct value but also because of the way that that drives basic research. The practical applications have been just as important to me in terms of generating new ideas for producing the challenges that make you bring on the basic technology.

I have been involved in commercialisation in a number of areas, with several spin-outs and strategic alliances – I will not read out the list on this slide, but you can see that it is not all medical and it is quite varied. Those are all things that have had commercial impact at some level or other. I will pick out a couple of those.

Overview

I shall talk about two things that I have done – the first and the last – where I have been directly involved in commercialisation, and one in the middle where I have been involved in a good deal of research but where I have not been directly involved in the commercialisation, although I have been peripherally involved in evaluating commercial systems. I will then try to draw some observations and conclusions along the lines of what makes something work or not work, and finish by talking about some current challenges.

So, I will give three examples. I shall discuss the first two relatively briefly but the third one, just to give you something to get your teeth into, will be covered in a little greater depth.

Chromosome analysis

A long time ago – and I have been shyer than Tony about giving dates – I was involved in chromosome analysis. These are microscope images, but I am not really bothered about where the images come from but rather what you do with them. The characteristics of chromosome analysis are that it is a high-volume screening service which tends to take place in dedicated labs. It is relatively labour-intensive – or it was at the time – and it relied on scarce expertise.

There was a relatively large market because the requirement was fairly homogeneous and there was already a perceived need for something to help people in this area. Another key factor was that the analysis was routine and you always did the same thing. This involved two steps – finding cells that were replicating and then going in and looking at those in greater detail, looking at the complement of chromosomes and trying to detect abnormalities.

Metaphase finding

This is a metaphase finding system – a more modern one, because my old photos are awful. On the right hand side of this slide there is a microscope on which you can mount lots of slides, that can be moved around automatically. The system searches for cells and, having found cells – and these are fields of medium magnification – it selects the ones where the chromosomes in the cell have been captured in this state where they are mid-division and you can see the chromosomes clearly.

Metaphase analysis

The second stage involves taking these metaphase spreads. Here, we are looking at high magnification and you can see that they are stained so that each of the chromosomes has a banding pattern which is characteristic of that chromosome. That allows you to arrange them in this kind of standardised pattern where the chromosomes are paired up and can be assigned to chromosome groups.

The characteristics of the solution that we produced here was that it was actually a computer-aided approach. It was not completely automatic but it reduced the amount of manual work to about 10 per cent of the fully manual approach. This was the first system that was deployed clinically and we were responsible for producing both the hardware and the software. We did that in partnership with an electro-optical instruments company.

That was an interesting early experience. I guess the image analysis involved was probably considered hard at the time, although you would now look at it and call it relatively straightforward. Systems like this have now gone on to be routinely used – they are a commodity in the cytogenetic lab. More sophisticated versions of this approach have come to replace the simple staining that was used in these original systems.

I will come back to these and draw some common lessons from them.

Mammographic screening

Next, mammographic screening. This is an area in which we have been involved a good deal in research but not directly in commercialisation. The list of attributes of the problem are rather similar. Once again, it is a high-volume screening service that is often separate from the other NHS services. Again, it is labour-intensive and makes use of a scarce resource. There is a reasonably large market, which is reasonably homogeneous, although there are real differences between the US and Europe in the way that mammographic screening is used. Again, there is a perceived need and there are similar characteristics in that one uses standard views – the images are always taken in the same way, with quality control, and you know what you are looking for. There are known signs of cancer in mammograms.

Computer-aided detection

The kind of systems that have been developed, interestingly, are computer-aided systems rather than automated systems. They are designed to allow the radiologist to look at the original films or, if they are using digital imaging, to look at high-resolution displays of the digital images. However, there is also this display provided, which is blown up here, where the system has automatically identified possible abnormalities, to draw them to the attention of the radiologist. The idea is that the radiologist first looks at the original images, then looks at these prompts, and then looks again more carefully at the areas that have been prompted. That has been shown to be more or less as effective as having two radiologists look at the films.

This has developed quite a large market – I have the figure somewhere, but I could not find it last night. That is predominantly in the US, where the benefit has been shown to be more significant in terms of improved performance than it is in the screening service in the UK. This is basically because the screening means that you are always tending to look at women in the very early stages of cancer, if they have cancer at all – so it is a harder task than is faced with the rather more anecdotal screening approach that is used in the US.

Biomarkers – an expanding niche

Let me talk a little more about something that is rapidly becoming an expanding niche. I have talked about two things there that are used in clinical practice, and at the end of this presentation I will explain how there are really rather few things that have found their way into clinical practice, despite the huge amounts of research that have been conducted in this area. However, there is a halfway house that is increasingly becoming important, and that is in finding quantitative measures of progression and response for use in developing drugs.

One of the major barriers to developing new treatments now is the ability to tell whether they work or not. The pattern that is beginning to emerge is one of partnership with pharmaceutical companies rather than directly with healthcare providers, in order to be able to provide early go/no-go decisions on potential drugs. Given that it takes of the order of \$500 million to bring a drug to market, knowing even a few days earlier that you ought to stop the develop of a drug is worth a lot of money. This is an area into which pharmaceutical companies are prepared to put a lot of money, and it is certainly one that has been identified by the Food and Drug Administration as one of the major challenges for the pharmaceutical industry over the next few decades. Long-winded testing and having to wait to find the answer is one of the main things that eats up investment in drug development.

There is potentially a significant market here, both for products and for technology-supported services. The drug industry is used to buying services. This is an interesting halfway house to clinical applications because it provides a rather more controlled environment than the normal clinical environment and one in which there is a need for quantitation. You cannot get drugs through the regulation process without having quantitative data to demonstrate that they work.

It is also interesting in that it provides a new way of funding the basic methodology that might ultimately find its way into clinical practice.

Case study: osteoarthritis

Next, I shall describe a collaboration with AstraZeneca and a spin-out company from the university, iMorphics. The example I shall use – and I could have chosen one of several – is in osteoarthritis.

The interest is in measuring progression and response to treatment. Ideally, one would like to be able to do that with a small cohort of patients over a short timescale. You want to know as quickly and cheaply as possible whether something is working or not.

Imaging is of interest because the clinical endpoints – the things you are ultimately interested in – are pain and mobility, but they are subjective and are confounded by all sorts

of other things. Doing trials that measure directly those kinds of clinical endpoints involves large cohorts and long timescales. On the other hand, an image-based biomarker can, in principle, allow you to observe the disease process directly. One of the main elements of that – and it is not the only one – is loss of articular cartilage. It can also help you understand the requirement for joint replacement by providing population information about bone shapes, incidentally.

We are working with 3D MR images of the knee. This is someone lying down, so the leg is horizontal on this slide. As the slice moves through, you can see the two articulating joints here. *[Plays 3D image clip]* We will try to produce maps of cartilage thickness and you will see in a moment that we need to talk about not just individual maps, but maps over populations.

MR imaging

To do that, we use a couple of types of image for each study. There is one that is optimised for detecting the bone and one that uses a different MR sequence for detecting the cartilage. I shall skim over details here but I hope I will give you some of the interesting ideas.

Cartilage thickness maps

We start out by segmenting the bone and the cartilage, delineating the boundaries, but we are doing that in 3D, so that we end up with a bone surface and the 3D bit of cartilage, which we can fit together. This means that, at every point on the bone, we can then measure the thickness of the cartilage, which is what is being shown here – so redder and darker denotes thicker.

This allows us to produce individual thickness maps – a thickness map for each patient visit. If we do that for a couple of time points for the same patient, we can take the difference between them. This is red *[on slide]* getting thicker, while blue is getting thinner. This gives us a map of the cartilage thickness change in this individual over a fairly short period – this is six months, because it is one from a study which I shall describe shortly. The measurement accuracy for an individual is not all that high but, in any case, the biological variability between individuals is high and so we would not really expect to get anything all that interesting out of an individual patient, so we need to deal with a population.

Dealing with a population

This slide illustrates an interesting idea. We need a common frame of reference and we use the bone as an anatomical reference. We want to measure thickness at the anatomically equivalent points on the bone between different individuals. This is related to

the idea of building statistical shape models. I have used the image of a hand, because you know what the answer should look like.

If you establish some commonsense correspondences between this set of shapes – so you can see that I have put the same coloured dots on the end of all the fingers – and do some statistical analysis, you end up with a parameterised model in fairly low dimensions, which describes the variability over the set. I am showing you what happens in one of those dimensions, and about 16 dimensions is sufficient to describe the variability over a population of hands. You end up with a model that looks fairly convincingly like hands.

Suppose I did not do that very well. Suppose I established the correspondences in a way that was not anatomically plausible. It turns out that what you get is a not very good model. That model is still capable of representing all of the hands that were in the training set, but it can represent all sorts of other things that are of no interest at all. That gives rise to the idea that, if you get correspondences right, you end up with a simple and efficient model. You can measure the efficiency of your model using information theory. You can ask how many bits are required to describe that training set, using the model.

The idea that we adopt is saying that if we want to get these anatomically corresponded, all we need to do is to do the correspondents, build a model from them, and then measure the description length of the model.

[Slide]

That is what we see here, applied to some real bone surfaces – these are femoral surfaces. You can see from the coloured dots that we do not have the same coloured dot in the same place, anatomically, at all. We are starting out from a really bad solution here. Shown on the right is the value of the description length, so what is going on is an optimisation where those dots are being moved around in such a way as to minimise the description length. It will stop for a second there and hopefully, you can see that now, similar dots are clearly in similar anatomical positions.

Corresponding thickness maps

That allows us to build a model, and that tells us about the kind of variability in bone shape. What is more important here, however, is that we know an exact correspondence between each of the points on each of these examples. That allows us to get a set of different maps from different individuals, into the same frame of reference. The frame of reference we choose is actually the mean of the model, but you could choose any reference frame – but, because they are all corresponded, you can get them into the same reference

frame. This means that we can now easily do statistics in an anatomically sensible way – so we are averaging the change in thickness in an anatomically consistent way.

Functional regions

There is an international convention about defining areas on the cartilage and that is shown here. You can do it either by using the whole of the cartilage, or just the essential regions that are marked.

Clinical result

This shows what happens when you aggregate the thickness change over those regions. The bottom line is that, with a very small cohort of not very seriously ill women, over a six-month period you can detect a significant loss in some compartments. This is the most sensitive approach that has been devised yet for detecting strictly cartilage loss in osteoarthritis. That is currently being used in clinical trials by AstraZeneca, so that is in real use.

Observations, conclusions and challenges

Finally, let me make some observations and conclusions. As I have said, a number of these things have gone on to be both commercially and practically successful.

Factors leading to success

I have looked back and asked myself, what were the characteristics that made that possible. Clearly, the first and most important point is just to have someone who wants it – to have a clinical or, in the case of a pharmaceutical application, a pharma champion – someone who is prepared to stick with it over the years and really wants it to work.

Another characteristic is that we employ someone in the lab whose job is to do technology transfer. He works with the scientists on the bench.

The corollary of having the champion is that you seriously have to commit on both sides to working together and have total immersion, and this requires a long-term strategic commitment. Part of that involves bothering to engineer the solution, and what does not work is just throwing the idea over the wall and hoping that someone will pick it up and make it work.

A characteristic of a number of the things that have worked, although not the last one that I have just described is that, in our experience and that of other people, computer-aided is easier to insinuate than a completely automated approach. Interestingly, probably the most significant factor is managing to find a workable business model which means that you

can actually make money out of it because, if you cannot make money out of it, no one will bother to do it and it will not be used.

Current landscape

The current landscape is a curate's egg. There are a few well-developed applications, with things like co-registration of different modalities, detection and quantitation methods – but these are few. We have in principle the infrastructure to do much better. We now have pretty ubiquitous picture archiving and communications systems, so that we have digital imaging everywhere, but these do not actually exploit that potential very effectively. They give a few fancy displays but few effective analysis tools.

We have a national programme for IT, which means that we ought to be able to use images as first class information. The reality, however, is that where quantitation is used, it is often done with a ruler – it is measuring the longest axis of a tumour. Nevertheless, there is significant growth in the development and deployment of biomarkers in this drug development arena rather than the full clinical arena.

Barriers to technology transfer

Why is the situation not better than one might have hoped? First, there is the fact that we still often talk about hand-crafted solutions to problems. The development costs of individual applications are high and often not justified by the individual application. Some of the examples I gave included things where there really was a mass market, and that made the business model work.

Many of the solutions are still ones that require a great deal of expertise to use them so that, in the wrong hands, you can easily get the wrong answer – and you can easily do something stupid. The market dominance of major imaging companies, however, has not been particularly benign, which means that finding a workable business model is more difficult because most of the imaging equipment provided to clinicians comes from three or four manufacturers who, by and large, do not seem to be very interested in providing analysis tools, which would cost money to develop.

As has been said earlier today, the conservatism of the profession is clearly a problem. It is probably appropriate but it means that there is a high barrier to entry and you have to be able to stick it out for a long time.

A key issue is that images are still second-class information. Although we have a national programme for IT, images are integrated in a very poor way with other clinical information systems. The leverage that you should be able to obtain from different kinds of evidence just is not realised.

Challenges for the future

What are the challenges for the future? The first and most obvious one is that we still have quite a long way to go. We still need more re-usable technology because, at the moment, too much hand-crafting goes on in solutions. I have shown you there an example of something where exactly the same method can be used on different problems – you just train it on a different problem – but there were still elements of it that had to be hand-crafted for the particular solution.

One of the key things will be integrating with clinical information systems – there will be a major effort involved in making images first class information objects rather than bits of data that are referred to by other bits of information.

Increasingly, we need to work with populations and not just individuals. There is a two-way play there. Working with populations is necessary to understand patterns of disease and responses to intervention, but equally an understanding of natural variation within a population provides the framework that helps you to treat the individuals more effectively. Given the difficulty, we probably need to think of new business models. That is rather difficult but what is happening in the pharmaceutical industry is a model that you might imagine working in the health service, where people provide services rather than products.

Another obvious the development is that pharma are increasingly interested in diagnostics. We have already seen how funding from pharma can help to develop the methodology, because it is really worth a lot of money to them. *[Applause]*

Sue Ion: Thank you, Chris.

Sue Ion: Once again, there will be a full Q&A session after our final talk, which will be given by Glenn Wells from the Wellcome Trust. He is the man with the money, and we hope he will share some of that with us. He has been key to the development of technology transfer through his role in leading a portfolio of healthcare projects with the Wellcome Trust, looking at IP issues and commercial transactions and also the identification of new technologies.

He is responsible for the day-to-day management of the Trust's Translation Award Fund and he previously worked in the biotech sector after gaining a PhD in cell biology. Over to you, Glenn, to tell us more about what the Wellcome Trust does in tech transfer.

TECHNOLOGY TRANSFER AT THE WELLCOME TRUST

Dr Glenn Wells

Wellcome Trust

Allegedly, I am the man with the money, but I have no cheque book with me today! I will try to give you an idea about how you go about getting the cash from us and what we are looking for in this space.

From going around the country and talking to different groups, we are acutely aware that the Wellcome Trust does not really have a profile in the engineering sector, so I will talk through a couple of slides just explaining who we are.

A few misconceptions

To start with, there are a few misconceptions, one of which is that we do not fund companies. When we first talked to the Academy about this event, they wanted to know what some of the key points were and some of these came up.

[Referring to slide] This is not true. We have funded about £60 million since 2003 and about 50 per cent of our projects are in a company. That is not by design but purely by luck, depending on how you look at it. They are small companies, large companies, public or private – it does not really matter to us because we will look at wherever the technology is, so that we can progress it through the healthcare impact.

Are we any good at it? The companies in which we have invested have attracted just shy of £100 million VC funding in recent years and I am sure that those of you in that sector would understand that it is not too easy to do that. It is very tough to secure early stage investment right now.

Do we want to own your IP? No, we do not want to own your IP. The IP ownership stays with the university and it stays with the company. It is true to say that, in certain circumstances, we will look to have a role in the management of that IP, but that is on a project-by-project basis and we are not in any way predatory. We just want to make sure that the assets developed by a project are successfully pushed out there for their healthcare impact.

We do not just go for Trust-funded research but we go from any background. We will look anywhere – at the Research Council and other charities. It does not matter, as long as there is an opportunity there, where we can push a technology to create benefit for patients, then we will look at it.

Are we only interested in biology? The very fact that we are here today means that the answer to that question is no. We fund across a wide variety of sectors, including engineering. I should say that we are really talking about physical sciences and engineering,

so we will include computation and engineering, as you have heard today, mathematics, and chemoinformatics – there is a wide range of things and I will come onto those later.

The Wellcome Trust

Who are we? We are a fairly well established charity, and fairly large at that. We are the largest UK charity – actually, we are a global charity with reaches into developing countries and developed countries, and also UK-based funding as well. We fund very many things, from pure basic science, through to the history of medicine – so there is a humanities side to the Trust as well.

Private Foundations – 2006

To give you an idea of where that sits, we fund more than anybody else in the world – just. Whilst the Gates Foundation probably has more money than us, depending on the exchange rate, we do not do too badly. This is just to give you an idea that, as a global player, we have a presence and we will use that where we can to get healthcare innovation out there.

Mind the market

I will just take a moment here to point out that what I shall talk about today is funding in this ‘valley of death’, as it was called earlier on. That is rather a doom and gloom way of looking at it. It is an opportunity, really, but we are not the only people doing this. You have heard today about the EPSRC and the MRC. Other research councils and charities have very active programmes in this space, where they are taking their basic research and pushing things along this way, through to where they are attractive to market. However, I will obviously just focus on what the Trust does from now on. I am talking about translating basic research findings, so that as a division we do not fund hypothesis-driven research. We want to do things that are validated and push them through to where the market would be interested.

Something to bear in mind here is that, because we are not necessarily driven by the financial return – because that is not our primary driver, but healthcare is – an exit to us is not the same as an exit to a VC or other institutional investor. If we find that somebody here [*on slide*] wants to pick up the technology and run with it with their own money, that is a valid exit for us because we will have de-risked something sufficiently so that another partner can come on board, put some money in and take on the risk themselves. We really do not mind where it goes, with the exception of the usual Trust proviso - no tobacco company. How it goes out there – it can go through more development and come back to us for money if necessary: we have done this and probably will continue to do so. We are aware that this

gap, this valley, is big or small, depending on the climate, and it is not a static thing. We have to adapt to that and be flexible. However, we have been successful in putting things on the market and we have had IPOs in the portfolio of companies that we have.

Perspective on European market

Why do we think we should invest in this space? This is a depressing slide, really: US investment/European investment. It is low and it is actually getting worse, so people are not investing in this space. They are looking to take things that look far less risky, at a far later stage, and push the money in there for a quick return. Because we are not in it for the return, we do not have this three to five year horizon – we can have eight to 10 years. I know that one of the earlier speakers said that the horizon needs to be long and we are in the fortunate position where we can take that very long-term view.

France surpasses UK investment level

As I said, it is getting worse. France is the only country changing that trend. We are investing less and less in early stage venture.

Biopharm attracts majority of HC investment

In the healthcare sector, this maps onto a very large interest in the pharmaceutical sector for obvious reasons, because the upside there is enormous. It is where you should put your money if you want a massive return. However, there are medical devices, medical information systems and healthcare services – although small pieces of investment are still an area where you can make big healthcare impacts. That is really what we are here to discuss today – those sectors of healthcare.

Top European investors '06

This slide shows a quick snapshot of who is in this space, with single figure investments '04 to '06. Again, there needs to be money in this space, and that is where the Trust can play a role.

Charity funding

The Trust is involved here because we want essentially to stimulate early stage projects to the point where they are de-risked sufficiently, and have the right components – and that is interdisciplinary or interface research, although I am no longer quite sure what I mean by that. It is integrated research, however, which covers all of those things. We are looking to see where they can assimilate into research projects good R&D but, if necessary, bring into play all of these components to get the job done.

Funding types

Let me just look quickly at the general translation funds. These are our standard translation awards and they are open to any area of healthcare, through engineering, computation, mathematics, biologics. We will look at anything you can think of in healthcare, and we have even done policy research. We really have a broad spectrum of projects to look at.

This average here is as of the middle of this year, and the projects usually take two to three years. I will give some examples later on of where we do not have this 20-year problem to get to a product but we have been fortunate to do it in two to three years to get product out there. However, that is cheating slightly, because we are coming in at the applied stage. Sometimes, we can leverage the right resource and we can speed things up. We used to set this at £300K, and that was only two or three years ago, but you cannot do much with £300K these days and, as you can see, the average has gone up.

The translation awards themselves have gone up to about £2.5 million to £3 million, so we try to put a good deal of resource in there.

Let me give you an idea of what we do – and you will be very used to this. It is preliminary application, triage and committee presentation. We give the applicants the opportunity to be iterative with us: we shortlist, and then you have the chance to have your day in court. So it is not just the ‘application in/answer out’ approach that we used to use.

I was asked earlier how we manage the projects. We actually have the standard translation awards with an open-door management style. We will not be there on a day-to-day basis as project managers, managing a project and making sure that it is going on. They are milestone projects with milestone-dependent funding. However, we are on the end of the phone and we will come up and visit projects and go out. If you need help, then we will do what we can to provide it, but we will not be really hands-on: we will let the project control itself but be there when needed.

We have another brand of the translation awards and these are ‘Strategic Translation Awards’. These have to be core to the Trust’s initiatives and objectives and they are typically much larger investments. They are not only larger in terms of cash but they are larger in terms of our time and commitment and the leverage of our own resource – be that in the office with the analysts or legal support, or it could also involve using Trust centres overseas. It could be using things that we have already done and building on Trust research.

These are by invitation only and you cannot just apply for one of those – they are working in partnership. This is an example of where the Trust will take a role in the day-to-day management of a project, and this is *really* day-to-day. They can be involved in the

project itself, in the IP and in the commercialisation – all of those things where we think we can add benefit, we will do, for the Strategic Awards.

Interdisciplinary research programmes

This [*on slide*] is what I mean by interdisciplinary research. This is a real example, although I will keep it anonymised. It is an example of how we went about building a Strategic Award. The idea was, 'Wouldn't it be great if we had a novel diagnostic using this technology. Much in the way that Professor Toumazou said, it is an established technology but in a different field – we are going to apply it to life sciences and to healthcare but how do we go about doing that?

In this case, we had detection technology. We were working with a team that are world class – an established team who can essentially do this in their sleep. There was no real risk for us in that space in saying, 'Yes, these guys can do this.' However, one of the other messages that you have heard today is about how you go about getting this accepted. The way we look at things is that disease expertise does two things. Firstly, it gives a concept of the perspective and what you are doing and why you should be doing it. Secondly, it starts to open the door to breaking down the barriers to entry that clinicians will put there because this is not the way they do things now. If you involve them at a very early stage in the validation and evaluation, as I have said before, then you have better chance of getting it accepted by that community.

As regards infrastructure, I do not just mean buildings here, but the support of the institutions that are involved. This is a multi-institution project, each institution having a key expertise in one area of the ingredients needed to pull this project off. The structure does include buildings, because we have the staff and expertise there on hand to carry out the project, but we like a broader definition of structure really.

Commitment and drive refer to the internal champion requirements – and you really need that champion. You need the buy-in of your partners and you need to involve the clinicians here to speed up this commitment and drive. Without that, you will get nowhere. It might be a fantastic idea but, without all of these things, it will not get to your product – it will stay at the other end of the scale because it will not be developed correctly.

What we look for

What do we look for? This is a variation on the theme of the earlier slide. We have an application form, as do all funders. It is a 59-page document, so it is not the smallest of hurdles to overcome. What we look for here is really what you would expect a VC to look for – although I have to say that we are not a VC in any way. We are trying to de-risk things in

the same fashion although not with the same strings and pint of blood that you may get with VCs.

We would look at all of these issues – technical, regulatory, clinical, business, commercial, IP, milestones and risk. I have included milestones in this list because we ask you to set the milestones – we do not dictate the structure of the project. It is something we need to think about, as in whether the project is a 4-year or a 2-year project. For £2 million, can you do it in one year? We would also want to know that projects are appropriately structured for the technology that they are trying to develop.

I will take a few seconds to talk about the items on this slide. Technical credibility and validation – we are not basic research funders in this division and we only want to do applied research and applied projects to get things developed and make them commercially attractive. As you would expect us to do, we conduct quite rigorous peer review on technical feasibility. I should say that, to avoid the patent problem, all the peer reviews are done under confidentiality. We are very conscious of where we operate and the need to be very protective over the sort of knowledge that comes to us.

Regulatory requirement is very similar to the requirement for having a clinician on board. From day one, we want people to realise that, without this correct framework having at least been thought about – although perhaps not in place because having the approvals granted at the time you apply is rather too much to ask. However, you need to be aware of what you need to do, to get this approved at the end of the project – or at least to allow somebody else to run with this, with minimal stress. We therefore look for some awareness of the regulatory requirements for your technology.

Informing clinical practice is something that Lord Darzi touched upon. We need to know, preferably by the involvement of clinicians at an early stage, that this will make a difference in clinical practice. We could make the best imaging technology in the world, or the best diagnostic tool in the world, but if that is not being picked up by the clinical community then we have wasted our money and there was no point in getting involved in the first place. We therefore need to have at least an idea of how to get this rolled out and implemented into the NHS for example, although it does not have to be in the NHS and it could be anywhere. Nevertheless, we need to know how you are going to do it.

This is not a business model in the classical sense because the business model here might say, 'We're going to come back to the Trust for more money.', or 'We're going to go to another funding body for more money.' Again, those could be valid for the technology. We are really quite flexible in our diligence here and we will look at the right way to do your technology, rather than having a one-size-fits-all approach to technology development.

These elements go pretty much hand-in-hand – the commercial, IP, milestones and risk. We want to know what the difference is. Do you have any intellectual property assets? You do not necessarily need them but what we look for is value creation for the project and so arguably you will have to have them at the end of the two to three year term, so that somebody else will buy into that concept and run with it. However, that is not a requirement at the outset. As I said before, there are milestones and risk, and we mitigate our risk by milestones and we evaluate the risk in terms of feasibility and the team coming to us. It is important for us that the team that applies to us will be there for the duration, and they will have the support and infrastructure in place for the duration of the project, so that we can hopefully be successful.

Engineering in healthcare

You know about these [*on slide*]. I will not go through this – this is not a prescriptive set of four pictures, but they indicate places into which we have funded as a division. This one is still a live project, the novel material science of phosphate binders.

Again, they would have joints – and I have talked to you about joints, and the application of imaging technologies for medical use. This is an example of where we have funded in this space and we are coming into the interdisciplinary – as Alfred Cuschieri said – and we are actually poaching our way into a technology developed by somebody else. We see an opportunity and we fund in there.

Molecular understanding of disease

To try to rescue our pride, what have we done ourselves, along with other funders? The UK is a world leader in the understanding of the molecular basis of disease and I do not think there is any dispute in that. There are the programmes shown on this slide – Biobank, the Cancer Genome Project sequencing the human genome, and the Case Control Consortium. At the basic science end of things, we have a lot to build on. The human genome was supposed to give us thousands of new drug targets, although it has not done that yet. What it has done is to create an awful amount of information that we need to process and make sense of, to see whether we can translate technologies out of that space.

Genomic tools

Are we doing any of that? Genomic tools – these slide should give you a feel for where we are funding. These are real projects and each has an inter-disciplinary flavour.

This BlueFuse product is by a company in Cambridge, with three graduates in computation in chemistry brought together to look at using imaging to interrogate micro-array data. They then combine that with other genomic data to give a meaningful output for the pharma company, so a number of disciplines come into play. That company is doing very well, the product sell moved into array manufacture and is growing quite nicely.

This down here [*on slide*] is probably one of the highest risk things we have done. This was Nobel Laureate Sydney Brenner's company. This is disruptive in that it is technology which allows you to do population-based studies in one arena essentially. It is chemistry, it is imaging again, and it is using tools that are already available – it is inventing some pretty good stuff but using established technologies to make a difference. It is truly disruptive, because it will commoditise the expertise that is out there now and make population studies available to any researcher, at any bench, in any lab.

Diagnostics

Diagnostics: we have built on Trust-funded research here, so we will follow our money and follow our nose, where there is a really good project. This company is not-for-profit and it is a good model for the Trust. It is the detection of – and developing countries need it also - a Chlamydia dipstick test. It has not only this test kit here but also a device manufacture for getting the first burst of urine, so that you are getting the right bit for your test. It is highly integrated and a very long-term project, with a very long investment horizon. There will be an exit but it is not-for-profit and so, in terms of a venture fund, it would not be an exit.

CardioDigital – this is signal analysis, built on MRC funding. This is an MRC career-hopping fellow who started the company to analyse stress data to give you things such as respiration rate, heart rate and all sorts of extra information that is already there, but just applying mathematics and engineering disciplines to extract biological information. Again, this is doing very well, with products in the pipeline and soon to be launched.

At the University of Bristol, we have a mass-spect-based technology for examining the headspace of warmed up diarrhoea samples, basically, to detect organic compounds that would give an indication of the agent responsible for that disease. This will eventually become hand-held and be rolled out to both developed and developing countries, where there is an equal need.

Clinical tools

Clinical tools includes Aircraft Medical, an example of a product that was launched 18 months from funding. This was a graduate from Edinburgh who was in fact a design student, who came to us. I will give you the timeline: he came on Tuesday, with three boxes, some straw, a screen and a bit of wire. He applied by Monday, was funded three months later and launched the product 18 months after that. That one is not cheating – he did not have anything until that day. This is an exciting area – a *very* exciting area of devices – where you can see a tangible healthcare impact in a very short timeframe. This is also the beginning of the examples of where the clinicians are involved.

The entire design process for this was done in collaboration with an anaesthetist. In fact, for his research project in his final year, he just camped outside operating theatres, to grab anybody he could to ask them what was the problem with the current laryngoscope. They were then on board from that point on, telling him, 'We'd love this, and we'd love that.', and that is what you see there. This probably has about \$80 million worth of distribution deals around the world at the moment.

Another example of a clinical and engineering parallel track project is this one from Hugh McCann in Manchester. This is brain imaging using function impedance tomography. I am not a physicist but, as I understand it, this group has used this in the automotive industry for quite some time and decided that they could probably use it on the brain to try to look at the functionality of the brain, and try to map areas of functionality. Originally, it was for pain but then it went to depth of anaesthesia, basically.

This one is just about to enter the clinic. Along the way, they have created not just their product but they have created some of the best electronics in this field in the world, and the data are incredible. You can get academic excellence alongside developing a product because they are not mutually exclusive.

Tissue repair

We have heard a little about tissue repair. We have quite a history in this space. This is stem cell work, growing new teeth at King's in London.

Up in Sheffield, CellTran is a company and we actually funded Technological Tran Cell, which then became MySkin, for treating diabetic foot ulcers. This is a polymer technology from material scientists, not biologists – but they brought the biologists on board very early. This was actually launched 27 months after funding, but built on a few years of basic research, so this was still within probably about the seven to eight year window.

RegenTec is a company in Nottingham, dealing with novel polymers for cranio-facial work. We are moving on from here to smarter polymers and there is another project which is to do with repair of the knee, having materials that stimulate growth and migration of the right cells to the right place.

Enabling technologies

'Enabling technologies' is our catch-all category, to give you an idea of what kind of risk we will take.

Daniolabs was a zebrafish-based screening company. They came to the Trust and said that they were going to use zebrafish embryos to screen drugs, and that they would feed them to the fish. It sounded like an interesting idea and so we funded that. The company has been acquired by what was VASTox and it is going quite well. They have world class drug screening and drug models there, for use by the pharma industry.

Cresset Biomolecular Discovery Ltd – this is a chemo-informatic tool for a novel way of looking at compounds to see what the protein sees in a chemical molecule, and not necessarily what we think it sees. It is scaffold, and is based on charge. Again, this was a concept that was quite old and which needed to be pump-primed at a very early stage to get to where they are now. The company still trades and they have pharma and biotech partners.

Sarissa Biomedicals – I always leave this programme in as an example of our non-profit driven activity. This is a research tool and always was envisaged that way when it came to us, and it still is a research tool. However, there was no tool for looking at the purine in the context that these guys wanted to do, anywhere – so this was needed, to stimulate the healthcare research in that field. We can take the view that it will not make us \$1 billion, but it will make a huge difference to that particular research discipline. We have therefore backed this and the sensor is still in use today.

Key Points

I apologise for the slightly corny nature of this slide. The good idea is only the beginning because, as I said earlier, you need to have the right team on board, with the right structures and drive, to make sure that you can take not only the technical stages of the development but the commercial, regulatory, implementation and roll-out. These things are never contained within one brain and you always need to have people around you. There really is a team effort around an idea, to get it to the point where the market wants to pick it up and run with it.

Funding the best ideas

This is a shameless plug for what we do. This slide lists all of our awards and contact details, and the areas in which we fund. *[Applause]*

Sue Ion: Thank you very much indeed, Glenn, for running through some of the examples of the work you have funded and also the philosophy behind Wellcome's work. If the speakers would like to join me at the table, we will have some questions and answers.

PANEL DISCUSSION

Professor Ross Coppel (The Wellcome Trust): I wanted to ask Professor Toumazou about some areas about which I am sure he has thought a good deal – namely, how to make use of the types of monitoring that he sketched out for us.

I want to talk about the area of blood pressure monitoring, because that is something for which there is a fair amount of clinical information. I put it to you that a blood pressure monitoring device that monitors 24 hours a day, seven days a week, is not really of any use clinically to someone who has very high blood pressure. If you have a pressure of 180/150mmHg, there is no clinical issue there: it is a medical emergency and it must be treated. However, if you have a low level of blood pressure – let us say 140/105mmHg – what we know about treating blood pressure comes from very large clinical studies of 25,000 people for 20 years. These suggest that if you intervene in people who are defined as hypertensive on the basis of a static blood pressure measurement in a doctor's office at three visits over the course of three months, and your blood pressure is over 105/mmHg diastolic on all three occasions, and you are recruited into a trial, in a population there will be a benefit of about a 30 to 50 per cent reduction in stroke over the course of 20 years.

If we monitor someone for 24 hours a day, seven days a week and we watch their blood pressures go up and down and enter the range of 105mmHg and drop below it and go higher – how will we obtain the information to know how to intervene, who to recruit and who to treat, unless we do trials of that sort? How do you see this being brought into clinical practice without enormous amounts of further funding in terms of these sorts of back-up? I am sure you have had these sorts of thoughts.

Christofer Toumazou: The first application space of the technology that we are developing is not for hypertension but it is actually for acute conditions. It is for post-transplantation and the interest is really from surgeons, such as Sir Magdi Yacoub, who post-transplant want a 24/7 monitor of the critical blood pressure, after they have sewn the patient up. This is in the intensive care type of environment. Implanting something like this in the

left ventricle, and measuring the blood pressure continuously, is very important for him in that environment.

As it moves to hypertension, my son recently had a kidney transplant and so, whilst he was having dialysis, I was measuring his blood pressure four times a day. The inconvenience of that, psychologically and physically, for both him and his parents, was very difficult, because most of the time his blood pressure was high – within the range of that particular chronic disease. However, just the thought that he could go about his daily life – because blood pressure is quite qualitative, particularly with the cuff measurement, and the variations we were getting with the cuffs were enormous. Having ordinary mercury levels, by having some sort of wireless device, our consultant would only get an SMS if the vital sign of blood pressure was outside of its particular range or a particular instance. The way the technology is working, he would then send a signal back and download the last day's worth of stored data and see what the trend was with the blood pressure. So it is really the trend that we are looking at, rather than exact measurement.

As you say, the range is very sceptical, especially when you are measuring it at home in that sort of environment. It is not competing with the real chronic, acute situation – that has to take place in a hospital environment. It is really competing with the new convenience of something that is not that precise, that we do in the home. Have you ever tried these digital blood pressure monitors? If you compare the accuracy of a digital blood pressure monitor to a cuff, it is way out. It is really more of a qualitative measurement and a trend that we are looking for, rather than the exact detailed result, particularly with hypertension.

Professor Ian Young (Imperial College): I have a little book which ought to be compulsory reading for all of us in this particular field. It is called *Inside an Industry*, and the subtitle is *On the Dynamics of Technological Change in Medicine*. This happens to take imaging as an example and it is a litany of explanation as to how Britain managed to snatch defeat from the jaws of victory four times. It identifies basically that the problem is actually cultural: we are cautious, whereas the Americans are aggressive. Ara was not particularly accurate on his MRI stuff, but that is beside the point. The original mention was American, but the whole development of MRI was in this country – pretty well entirely – but the actual exploitation was all in America, and it was all clinical.

Chris, first of all for you, the interesting point about imaging is that multidisciplinary has singularly failed. There is evidence from other things. Pure physics and pure engineering tend to be the source, while pure medicine is the uptake and the demand. Multidisciplinary, in practice, has not really worked. For you, Chris, you ought to watch

things like magic angle effects in the sort of measurements you make. That T1 fat sequence is vulnerable to all sorts of artefacts and I would beseech you to be careful about it.

Christofer Toumazou: We have been. We will never agree on those trials.

Ian Young: I have a quick question for Dr Wells. Do you actually handle cancer? You never used to. If somebody comes to you with an application which is basically intrinsically in cancer, or cancer relevant, in the past you never touched it.

Glenn Wells: As a Translation Award, or as a basic science project?

Ian Young: Certainly basic science – I never tried translation.

Glenn Wells: Yes, I guess we do have a presence with the cancer genome project, in a £60 million venture by the Trust, to get a molecular understanding of oncology. We will look at cancer from certain angles, although we will not be involved in any direct cancer research, which you would see at CRUK.

Ian Young: So you would look at devices –

Glenn Wells: For Translation Awards, we actually have cancer drug discovery, diagnostics and biomarkers.

Ian Young: Thank you very much.

Professor Iain Cameron (University of Southampton): I have a question for Tony about that good example of taking 30 years to get a good idea almost to clinical trials. How long should that have taken and, if you were setting about that kind of study now, what would be the key steps to get right, to make that time as short as possible? You must have given this some thought before.

Tony Unsworth: Part of the problem is that, with any new material – I think I started off my talk by saying that the materials used in joints now, because they are implanted in the body, are pretty well the same materials as we used 50 years ago. It is rather like if you tried to get dental amalgam past any regulatory authority now – you would never do it. Who is going to approve the use of mercury and other stuff in your mouth nowadays? It is not going to happen. However, if had been used for many years and nobody has been found to have any problem, then it is fine and you can do it. That is the point – all these materials pre-date any sort of regulatory activity.

We are now in a different era, and we are also in a very litigious time. If I were a company intending to put this into lots of people, I would ultimately be worried. I do not know what the norm would be, for bringing a brand new material along that is actually to be

implanted into the body. It would be different if it was going to be stuck on the outside, or tentatively used in the body. I really would not know what to expect but perhaps someone else can tell me.

Sue Ion: Perhaps I might make a comment before we go on to the next question, related to something that Lord Darzi said at the beginning about putting the patient at the centre of the issue, rather than the clinician, the management or the system, in the ability to offer people choice long-term. Anybody looking at the data you have presented, Tony, would say, 'If I need a knee replacement, I want one of yours and I will take the risk.', versus the worry of the companies about litigation, should it prove not to be as perfect as they originally thought. It is just an open question about whether choice comes into it any more from the patient's perspective, and whether the patient might actually volunteer to try something that is new and innovative, even if it was not carried with the assurity of the corporations.

Professor Colin Besant (Imperial College): I would be interested to hear what the team thought of EU funding. An Italian said to me only a few days ago that we should forget EU funding for R&D and save the taxpayers' money. The bureaucracy and the conditions involved are becoming so onerous now that, certainly for small companies and even universities, it is becoming a very difficult situation.

Chris Taylor: I will make a start. I agree, but it is not quite that simple because the problem is that you cut yourself out of research communities if you do not go for that kind of funding. Everyone I know does it, vows they will never do it again, spend a few years forgetting about it, and then try it again. It is not a good way to spend money, I would agree.

Tony Unsworth: It was probably obvious from that list of funders with whom I work that there was one EU project. QED.

Christofer Toumazou: With all this money in Wellcome, who needs the EU?
[Laughter]

Glenn Wells: From my understanding of EU funding and our interactions with it from the translational perspective, its mission is to bring companies under a certain framework, to bring industry partners in, with sometimes massively inflated groups of other research groups and that is a problem. The bureaucracy does not help – you are absolutely right. It is difficult to get and, even when you have it, you have several contracts to wade through to get the money released, although its intent is probably right.

Professor David Williams (Loughborough University): I just have a comment. As one or two people will know, I am involved in manufacturing programmes in Europe. We have to recognise that our European colleagues – particularly the *Fraunhofer-Gesellschaft* and some of the larger commercial laboratories feed off the framework programme but it is a trick that we do not very well in the UK. There are mechanisms for milking it, but it is just that we are not that good at it.

John Erbetta (AIME): If we have a dynamic, innovative culture, it assumes that we have a large number of ideas emerging, of which only a few will get to market. If we are then taking the idea that the patient should be king, who actually filters those ideas and how, so that we actually have patient-oriented concepts coming to market, from the many ideas that would be starting off?

Tony Unsworth: I do not know how you do that. The whole medical scene has changed. You will now rarely find a surgeon telling a patient, ‘You’re going to have one of these.’ The patient will be told the pros and cons and perhaps some alternatives will be given.

I will use the example of the hip joint. At the moment, you have probably seen that there is a great desire to have these metal-on-metal resurfacings done – the ones that were second to bottom on my slide. These are large diameter resurfacings of the joint and everyone wants one of those. Apparently, for the orthopaedic surgeon, when a patient walks through the door now, most of them have already been on the internet and they have seen the clinical results. They have seen everything else and they say, ‘I want one of those’. They may not be suitable for one of those, but the job of the surgeon is now to convince them that, really, they are not the right person for one of those because they actually have osteoporosis and the neck of the femur is going to break within a few months of having one of these things. They will then be offered one of the alternatives, whatever that happens to be.

We have to be a little careful about being patient-centred. We need to do what is right for the patient but we are not always in the best position to judge for ourselves what is the best device, or anything else. It is a matter of striking that balance between what we think we want and what is best for us. We do not want to be told all the time what treatment we want – none of us wants that, because we have progressed some way beyond that. However, we need to find the balance between taking notice of the profession and all the

evidence that is presented to us, as well as our own particular choice. People will still choose to have these joints.

I have just come back from a meeting in the States and these joints that are metal-on-metal clearly have implications for women of childbearing age, because we do not know quite what effect all these metal particles will have on the children. There are some surgeons in the States who say they will not put these in patients unless they sign a document to say that they will not have any children, which sounds ethically somewhat difficult to me. There are all kinds of problems that arise. If people want a joint, they will go to great lengths to get it, even though it may not be the right one for them.

Dr John Egan (BITECIC Ltd): I would like to follow up on the point raised by Professor Unsworth about the metal-on-metal. The issue about the selection of the technologies that make it through is that of matching the prevailing market drivers at the time. The presentation on imaging more or less said the same thing. Those market drivers are almost out of control. That metal-on-metal market driver came partly from a NICE report which said that these prostheses were suitable for the younger patient. Even older patients then think, 'Well, I'm active and I'd like to be young, therefore I want one of these', even though it might not be suitable. Within orthopaedics, there is this growing demand for gender-specific needs.

From a scientist's perspective, I find it hard to argue that there is any benefit in having male and female knees with a tweak in various dimensions, but it appeals in a kind of human way. The market drivers are set almost on that psychological level. Smart people need to align the developments with the forthcoming market drivers in that way.

Keith Davis (Royal Academy of Engineering): I have a question for Glenn about the Trust. We know what you are not – you are not a conventional VC enterprise, and various other things. How do you measure success and how successful are you?

Glenn Wells: The fund itself – over the 70 or so projects that we have, there have been two technical failures in a four-year period. So are we technically successful? Yes.

In commercialisation, we have 10 products launched, with six in the clinic and others on their way there – that is both therapeutic and medical devices. So, in terms of the fund itself, can we match up to an early stage VC? Definitely, yes.

How do we measure success? We measure success by impact and, if we did that, then we would be looking at five or 10 years down the line, when clinical trials are completed and the products are on the market.

Are our projects and technology attractive to somebody else? Yes, they get follow-on funding.

We can look at any of those metrics to see whether we are successful or not. It is easy to say where we were not successful, if a project has failed and – as I have said – there have only been a couple of examples of that. I would like to say that we are reasonably successful.

Sue Ion: I have a rhetorical question, which may be better answered by any clinicians in the audience, rather than the panel – although if the panel members choose to comment, that would be fine. It is about the power of the NHS with respect to procurement. When you look at the potential that ought to exist in the NHS as a body collective, to deploy and push things like Chris's data plasters, what could be done differently in terms of procurement, to encourage that mass uptake versus very small, targeted, single trust uptake that takes many years to translate itself through on a national basis?

Speaker (from floor): I am not a clinician but I am rather a meddler, as one or two people know. It is very important to pick up the signals we had from Lord Darzi on commissioning. The NHS is transitioning very much into the commissioning of services, where those services deliver patient benefit and begin to contain cost. We have to recognise that that cost containment, getting people into their homes and using commissioning as a tool to change behaviour, is a very significant mechanism for changing healthcare delivery.

My perception is that the commissioning process itself is not well-understood yet and we are only just beginning to talk about the nuances of what it actually means. A little vigorous debate at this time, in terms of guiding people on what commissioning is, to deliver patient value and value to taxpayers, would be incredibly useful.

Dr Robert J Dickinson (Imperial College): To answer your question, I just wanted to mention that the NHS has a body through its Purchasing and Supply Agency, called the Centre for Evidence-Based Procurement. We have done some projects for them on evaluating MR scanners and some other technologies. As it says in the title, it is moving much more towards evidence-based procurement and so one way of getting your technology

into the NHS is to provide evidence of clinical benefit, extended quality of life using QALYs and so on.

The NHS recognises that it is very slow in the uptake of new technologies. Perhaps, as it is a very centralised institution, it is hard to encourage that diversity which would really move that on. However, there is a willingness there to take on new technologies.

The answer is that you should contact the Centre for Evidence-Based Procurement, which I think you will find through Google, and produce your evidence for your device.

Ian Young: The main problem is, how do you get your evidence? The NHS, in the case of MRI, decided with the MRC to evaluate it in 1984/5 when, of course, the whole technology was completely at variance with what finally emerged. The analysis was nonsense.

One of the points, Chris, about numerical stuff, is that it has not worked, and that is why people do not use numbers. They use dimensional numbers, yes, but not other numbers. The core problem is how you obtain the evidence for things like NICE, or how you obtain evidence for things like MAGNET to evaluate this sort of thing.

Christofer Toumazou: I have had a number of discussions with procurement officers within the NHS and they are very clearcut, black-and-white, is it cheaper or not? However, the mentality is changing. It might cost more now but, in three years, the overall benefit will be much cheaper. So where does the evidence base come from? I agree with you that, in this country, we are not pushing hard enough. My particular devices are all being trialled out in the States, where we have nurses within the hospital – and nurses are the bridge between the patient and the consultants – who are trialling these devices, replacing current technology and seeing how much of their time is saved if they use a certain technology. That is the sort of evidence, and those are the sorts of trials we need to start to engender in the NHS. The nurses are extremely important in this and they have not been mentioned much today.

Tony Unsworth: I would like to correct something that I said in response to you. When I was saying about how keen patients are to have these devices, I think I said that the surgeons tried to persuade some of them to sign a bit of paper, but it is the other way around. Because the surgeon is trying to say that these are the sorts of problems, in terms of childbirth, for example, because we do not know what happens to the metal ions, the patient says, 'I still want the joint and I will sign the piece of paper that says I take that decision.' I do not think I said that correctly and I wanted to make sure that I said it the right way round this time. That is the way it was: the patient is quite prepared to take that issue, to sign the piece of paper.

Sue Ion: Let me thank our eminent speakers for being with us this afternoon, and thank you for being such an engaging and challenging audience. I am sure you would now like to go to the reception to interact further with the speakers and one another.

This is a tremendously exciting area. We have seen some fantastic innovations today, some of which were initiated over 20 years ago, and others that have been initiated only in the last 12 months or less, because of the enhancements possible with modelling computational capacity and true translational research. I guess, Tony, that from a UK biomedical focus perspective, it is a question of 'watch this space'. Equally, we have to continue pushing the policy makers for better uptake of some of these marvellous innovations.

Thank you, everybody. We look forward to engaging with you in the reception.
[Applause]
