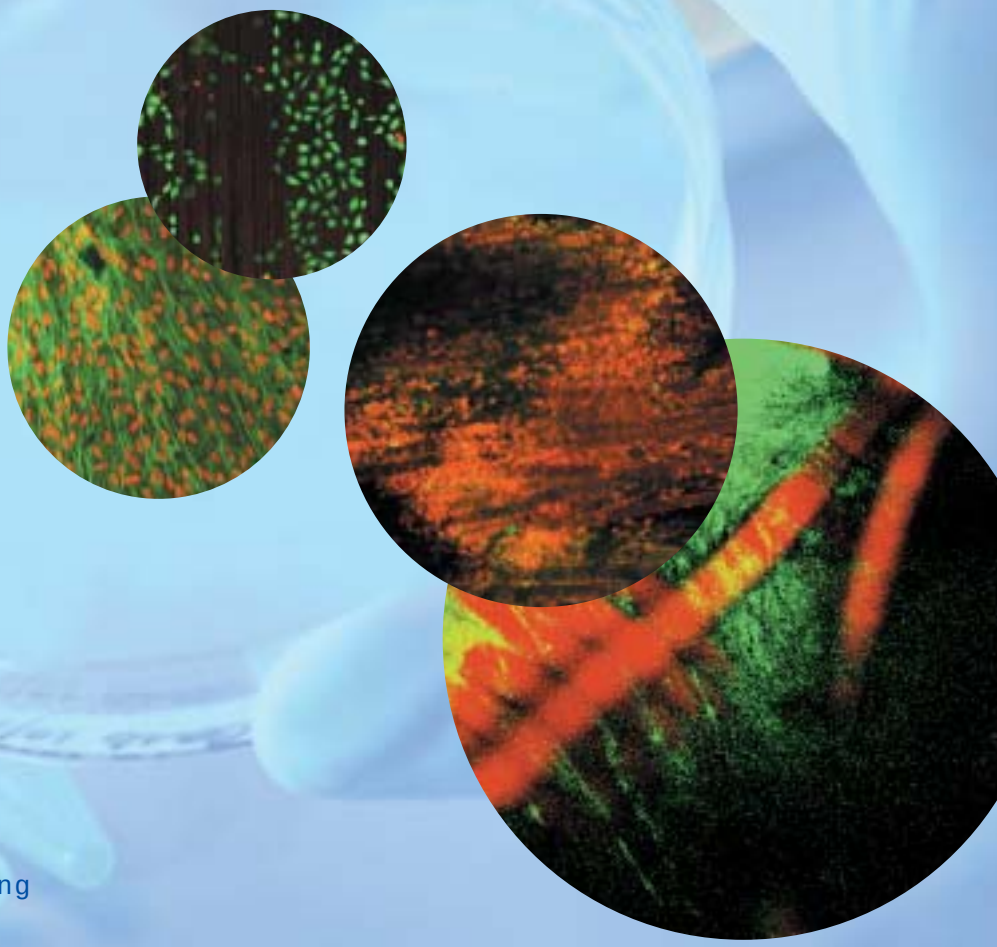
ROYAL ACADEMY of ENGINEERING

The Japanese Approach to Tissue Engineering

The Report of
The Royal Academy of Engineering Mission to Japan

April 2003



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Executive Summary

The Royal Academy of Engineering organised a Mission to Japan in April 2003 which had the objectives of studying the complex issues surrounding the commercialisation of tissue engineering products and processes. This report summarises the findings of the Mission.

Overall the members of the Mission were impressed by the quality of the basic science that is underpinning Japan's tissue engineering programmes and the extent of government and institutional support for the emerging tissue engineering industry. There is no doubt that Japan faces very similar barriers to the successful commercial introduction of tissue engineering products and processes to those experienced in the UK and elsewhere. The solutions to the problems associated with these barriers are not obvious and it would appear that the tissue engineering community in Japan is not necessarily in any better position to resolve these issues. Nevertheless there are several signs of significant changes in recent years with respect to their traditions and it is possible that Japan will emerge as a leading force in the globalisation of tissue engineering.

It is evident that the Japanese government at both national and prefecture levels, decided that regenerative medicine in general, and tissue engineering in particular, constitute one of the major technology platforms for the medium and long-term, which should form the basis of the re-emergence of a strong Japanese economy. Members of the Mission were duly impressed by the scale of this investment but it has to be said that this policy is not without risk. In the context of this investment, government institutions have set very high targets for the emergence of new companies and new commercial initiatives. Although there has been an interesting start to this process, these targets appear to be unreasonably high. Local governments appear to be very keen to play a significant role in this new industry, especially by the provision of very favourable investment and manufacturing opportunities.

It was evident that the Kansai area, and especially Kobe, are amongst the frontrunners in this field with considerable investment in new world-class facilities. The facilities that were evident in Kobe included very impressive cell biology research laboratories, the manufacturing infrastructure for start-up companies and a major clinical facility for the purpose of clinical trials of pharmaceuticals and the products of regenerative medicine. There was a feeling that as impressive as these facilities were, they may have difficulties in attracting the appropriate number of world-class scientists and clinicians that would be necessary for economic success.

It became clear that there was much interest in funding tissue engineering research from private equity and venture capital. The amounts involved are still fairly small in view of the uncertainties in this market but it is possible that this will increase in the medium term if the market is able to mature. Corporate venturing is also evident and may well become the more important route for resourcing these developments.

The Mission visited two universities, in Nagoya and Kyoto. It was clear that some very interesting quality science was being carried out in these institutions, notwithstanding an apparent lack of investment in comparison to some of the government funded research institutes. It is also noticeable from many conversations that the universities are undergoing significant change, first in respect to the status of national universities as they become somewhat independent agencies and secondly in the light of a changing view on the ability of professors to undertake entrepreneurial activity and become engaged in spinout companies. In general the quality of the science being performed in university laboratories is very high and probably comparable to the general level in the UK. Much of this science of extremely high quality. We were surprised to see so much work on embryonic stem cells which, although interesting and rewarding from a scientific point of view, cannot lead to any commercial or

clinical advance in the foreseeable future since Japanese regulations do not allow the therapeutic use of these cells.

The regulatory environment in Japan appears to be as confused as it is elsewhere in the world. Japan, in principle, is no different to any other country and although work on new guidelines and legal frameworks is in progress, these are not yet in place and considerable uncertainty faces Japanese and overseas companies alike. These regulatory issues also have an impact on reimbursement. This report demonstrates the difficulties that healthcare reimbursement agencies have in Japan concerning the ability or willingness to pay for new treatment regimes that are as yet unproven and not well established. We did not see any evidence that Japan had fully grasped the importance of this situation.

Although in general the approaches to tissue engineering in Japan are directed to major diseases that require innovative treatments, it was also obvious that very significant investment was being made in some less glamorous areas such as periodontal surgery. Indeed it was evident that many research groups and start-up companies were directing their efforts toward the regeneration of periodontal tissues and teeth. It was also interesting to note that, in spite of a lack of a regulatory approval pathway for the commercialisation of tissue engineering products, a number of procedures had found their way into clinical practice. We were provided with evidence of the clinical use of tissue engineering processes in the treatment of nerve injuries and in periodontology. These procedures appear to be carried out under the medical license of the clinicians themselves rather than through any regulatory process associated with the product. The ability to carry out such clinical investigations on patients is obviously dependent on cultural and legal conditions.

In summary therefore we found more commonality than differences between the tissue engineering industry in Japan and the UK. The general economic situation prevailing in Japan is clearly a major factor in the establishment of a tissue engineering industry but the confidence placed in the potential for tissue engineering and associated technologies to underpin the future financial health of the country by government is acting as a major stimulus. On the basis of this investment, a number of world-class research facilities have been established although these are as yet not fully populated by groups of world-class scientists. For the moment Japan is leading the tissue engineering field within Asia but they will have to capitalise on the opportunities provided by these investments if they are to maintain this position. We saw many potential opportunities for the involvement of UK companies and academics in joint ventures and collaborations with these laboratories and institutions.

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1. Introduction

Tissue engineering is a relatively new subject that is expected to have a marked impact in the high added value healthcare industrial sector. It is, however, a subject that is undergoing some serious problems in technology transfer just as it is becoming accepted in both medical and manufacturing sectors, and there are several issues that have to be addressed urgently.

The technology of reconstructive medicine during recent decades has largely involved the production of synthetic implantable devices which are placed in patients in order to replace or augment diseased or damaged tissues. Examples include total hip and knee replacements, artificial arteries and heart valves, intraocular lenses, intravascular stents and dental implants. Although these give good performance in some circumstances, there are severe limitations to this classical engineering approach, originating from the un-natural nature of conventional engineering materials. Tissue engineering represents a radically different approach, which is based on the creation or regeneration of new tissue to replace that which is diseased. This may involve the design and production of scaffolds or matrices, the harvesting of cells from a suitable source, the culture of these cells within the scaffolds under the conditions imposed by a bioreactor with both molecular and mechanical signalling, and the subsequent regeneration of tissue, and the transposition of the resulting tissue into the host. This clearly represents a new style of manufacturing since it has to incorporate aspects of the advanced manufacturing of complex structures and the handling and manipulation of cells under sterile conditions. Quality systems associated with the production process, which have to involve both commercial and hospital facilities, have become immensely important factors.

Not only are there significant manufacturing and process innovations involved in tissue engineering, but also wide ranging ethical, regulatory, health economics and socio-economic issues. On a world wide basis, the emerging tissue engineering industrial base has been experiencing significant problems during the last year or so, as appropriate reimbursement and business models have yet to be identified or put into practice.

The UK has a number of highly advanced academic institutions involved in basic and applied tissue engineering research, including the many and varied contributing disciplines (ranging from mechanical engineering to gene therapy and molecular biology) and there is an active industrial base that has enormous potential. There are many opportunities for technology transfer and spin-out of tissue engineering activities within the UK and there are several initiatives which are engaged in underpinning the tissue engineering infrastructure. It is one of the most exciting, but yet risky, opportunities for UK technology to have emerged in recent years. It should also be remembered that tissue engineering impinges on a variety of other advanced technologies, including nanotechnology (and nanobiotechnology), genomic and post-genomic technologies, materials science, advanced manufacturing systems and sensor technologies.

The USA is by far the most advanced country in terms of the commercialisation of tissue engineering, but most of the US based issues are well known to the UK. Within Europe, Germany, Italy and the Netherlands have most of the academic and commercial activity, but again most of the players and issues are reasonably well known. Tissue engineering is also emerging as a priority theme in many Asian countries and activities are quite well advanced in South Korea, China, Singapore and Taiwan. Japan is at the appropriate level of development and sophistication that outwardly has similar challenges as the UK. Furthermore the academic base in quite well developed. However, the details of their technology transfer and the current scientific, clinical, regulatory, cultural and ethical issues have not been extensively investigated from a UK perspective. It was considered important that the approach to tissue engineering and related technologies in Japan should be explored. It was decided, therefore, that a Mission

to Japan should be organised by The Royal Academy of Engineering, which has a strong interest in this subject, under the sponsorship of the DTI through the International Technology Service.

The objectives of the Mission were as follows:

- To examine the state of the scientific base of tissue engineering and related technologies (e.g. cell therapy, implantable devices) in Japan,
- To examine the structure of the industrial / commercial base of tissue engineering in Japan,
- To examine the regulatory, ethical and reimbursement issues in Japan that affect tissue engineering,
- To examine the systems of technology transfer, including protection of IP and R & D funding that influence tissue engineering developments,
- To examine government funding and support of the development of the emerging tissue engineering and related industries.

1.1. Mission Logistics

At the outset, the optimal structure of the Mission team was considered to be of either six or seven members, with the following composition, bearing in mind the multi-disciplinary nature of the objectives;

The Mission Leader should be a Fellow of the Royal Academy of Engineering, with personal experience in both the science base and the commercial infrastructure of tissue engineering,

One member should be from a large UK company involved in the tissue engineering industrial sector,

One or more members should be from SMEs involved in tissue engineering, either directly or in one of the related technologies, recognising that many of the tissue engineering developments world wide are derived from SMEs,

One member could be from a relevant trade association,

One member could be from a regional development agency with responsibility fro inward investment and policy on technology clusters,

One member who could represent the areas associated with the economics of tissue engineering, either a health economist or an investment analyst,

The Mission Leader was Professor David Williams F.R.Eng., Professor of Tissue Engineering and Head of the Department of Clinical Engineering at the University of Liverpool.

The other members of the Mission were as follows:

Professor Gareth Lloyd-Jones, Director, Group Research Centre. Smith & Nephew plc.

Dr Paul Kemp, Chief Executive and Chief Scientifics Officer, Intercytex Ltd.

Dr Mike Hudson, Managing Director, Health Ventures Ltd.

Mr Adam Getliff, Yorkshire Forward.

Mr Meredith Lloyd Evans, Managing Partner, BioBridge Associates.

1.2. Mission Itinerary

The Mission team assembled in Tokyo on Sunday April 6th 2003 and the itinerary for the week was as follows

Monday 7th April
Ministry of Education and Science, (MEXT) Life Science Division, Tokyo
Ministry of Health, Labour and Welfare (MHLW) International Division, Tokyo
A group of Private Equity and Venture Capital providers, hosted by NIF Ventures, Tokyo
Travel to Nagoya

Tuesday 8th April
Nagoya University School of Medicine, Nagoya
Travel to Osaka
Seminar and Reception, Osaka

Wednesday 9th
Tanabe Seiyaku Co Ltd, Osaka
Tissue Engineering Research Centre, National Institute of Advanced Industrial Science & Technology, Osaka
Travel to Kobe

Thursday 10th
Institute of Biomedical Research and Innovation, Kobe
RIKEN Centre for Development Biology, Kobe
Stem Cell sciences, Kobe
OsteoGenesis, Kobe
Travel to Kyoto

Friday 11th April
Kyocera Corporation, Kyoto
University of Kyoto Institute for Frontier Medical Sciences

2. The Infrastructure of Tissue Engineering

Tissue engineering is a subject that is still in its infancy and, as alluded to in the introduction, is associated with many uncertainties. Even the scope of the subject is as yet poorly defined. To some, tissue engineering is seen as an extension to medical device engineering. To others it appears as an extension to pharmaceutical technology, or as a variant of organ transplantation, tissue banking or cell therapy. In reality, tissue engineering is evolving without any clearly identifiable pathway so we have to assume that it will incorporate some of the features of each of these sectors. This is important since they are quite different from commercial and regulatory perspectives and the manufacturing and service traditions in each have evolved quite separately. For this reason it should not necessarily be expected that the development of the tissue engineering infrastructure in Japan would have followed the same pathway as seen in Europe of the USA.

In assessing the status of the tissue engineering 'industry' in Japan, we can assume that there is a reasonably common global position with respect to the objectives of tissue engineering (and indeed regenerative medicine in general) and to the broad scientific and clinical directions. Regenerative medicine aims to treat disease or injury by facilitating the regeneration of functional tissue in the patient. It is different from medical device engineering which aims to replace diseased or damaged tissues by synthetic devices. It is different from transplantation which aims to restore a function by transposing viable tissues and organs derived from some other source, and it is different to pharmaceutical technology which utilises chemical signals to alter some physiological process. Regenerative medicine subsumes certain gene therapy approaches, wherein cellular function is altered by the introduction of specific genes into those cells. It also includes certain area of cell therapy which involves the introduction of groups of cells into the body in order to enhance a specific, deficient function. Tissue engineering goes one step further by introducing into the body either regenerated tissue itself, 'manufactured' for the patient in vitro, or the means for the body to regenerate new tissue internally, through the delivery of signalling mechanisms, which may also be manufactured for the patient.

The complexity of the subject can be seen from this brief introduction. The most common paradigm related to a tissue engineering product or process involves the following steps. Central to the whole process is the acquisition of the cells that will express the new tissue. These cells could be derived from the patient, either as fully differentiated cells of the phenotype appropriate to the tissue that has to be formed, or stem cells, perhaps derived from bone marrow or from circulating peripheral whole blood. Because of the logistics difficulties associated with sourcing cells from the patients to be treated (referred to as autologous cells), and the time taken in growing new tissue from these cells, it may not always be possible to use these cells. The major alternative source is another human donor, such cells being referred to as allogeneic cells. In practice these are likely to be differentiated cells derived from an immortal cell line or stem cells derived from an appropriate donor which then have to be persuaded to differentiate into the cells necessary for expression of the desired tissue. From a scientific point of view, the best source of allogeneic stem cells are embryos, although, as discussed later, the use of embryonic stem cells for such therapeutic use is controversial from an ethical point of view and prohibited in many parts of the world.

Having derived the cells, they have to go through several phases of manipulation before they are able to start the process of expressing new tissue. This may involve amplification of the cell population in order to produce a sufficiently large number, their transfection by genes in order to optimise their performance and the provision of signals that cause undifferentiated cells to differentiate into the appropriate phenotype. These processes have to be carried out under sterile conditions. With complex tissues, there may be more than one cell type involved. In order for these cells to express the right type of tissue with the right type of structure and

properties, they have to be seeded onto a substrate and provided with nutrients, and have to be given signals, either molecular or mechanical, or both. This may involve certain types of materials as scaffolds or matrices that act as guides to the tissue form. Growth factors and other molecules may be provided to stimulate the cellular function and mechanical forces may be applied, either through fluid stresses or structural stresses, in order to provide further stimuli to cell function. Typically, these procedures will take place in a bioreactor, which may be one of several generic versions that are available off-the-shelf, or custom made, and the process may take days or weeks. With simple tissues only one cell type may be involved, for example chondrocytes themselves may generate cartilage tissue. In other situations, more than one cell type is required since the tissue to be regenerated consists of multiple structures. With a blood vessel for example, there will need to be an inner layer of endothelium, a layer of smooth muscle cells and an outer layer of connective tissue, produced by fibroblasts. This will require considerable sophistication with respect to the bioreactor and the simultaneous and/or sequential delivery of signals to three or more cell systems.

At some point, newly regenerated tissue is re-implanted into the patient. This could be done after the regeneration is complete, or at an earlier stage such that the regenerative process that has been initiated in the bioreactor is continued in vivo. The manner of the incorporation of the new tissue into the host will depend on the source of the cells. Autologous tissue should be straightforward, but allogeneic tissue, derived from sources other than the patients own cells, may yield immunological responses which have to be controlled or modulated. The new tissue has to have the appropriate level of vascularity and innervation, the achievement of which are not trivial processes. This functional incorporation of regenerated tissue into the patient still represents a significant challenge.

It can be seen from the brief description above that there are many steps associated with tissue engineering, and a wide variety of delicate procedures. One of the major difficulties with processes such as these is the identification of the ‘product’, and the delineation of the ‘manufacturing system’ There are some individual parts of the whole process that could be separated out and considered from the perspective of identifiable commercial or industrial activities. The production of scaffolds, for example, may be undertaken by a materials company quite separately from the tissue engineering itself. There are already a number of companies that do this, manufacturing scaffolds from synthetic biodegradable polymers such as polylactic acid, natural biopolymers such as collagen or hyaluronic acid, calcium phosphate bioceramics and so on. Equally, companies may be involved with the design and manufacturing of the bioreactors, and pharmaceutical companies may supply the growth factors and other substances. All of these components have to be integrated into the tissue engineering process, however, and the mechanisms for doing so are not always obvious. The scaffold is clearly a very important component, but volumes will generally be small and revenues for a scaffold company may not be high. Many suppliers of scaffolds would like to be more closely involved in the tissue engineering process in order to achieve higher added value, but the company then becomes more aligned to a service provider than to a component manufacturer. In some situations, the bioreactors operate in the laboratories of the hospitals where the cells are sourced and the patients are treated, which has implications for the hospital becoming a manufacturer.

In view of the complexity of the science and technology and the varied issues surrounding the manufacturing process, it is not surprising that tissue engineering, and regenerative medicine in general, has generated a series of regulatory, ethical and socio-economic complications. These do vary from country to country in the light of varying cultures and practices, but there are some common themes. These mostly focus on the uncertainties and risks associated with tissue engineering that have caused regulators to delay the introduction of clear pathways to regulatory approval, since they have been used to dealing with drugs or devices, and tissue

engineering products are neither, but do involve both. Similarly health insurance schemes have struggled to understand the nature of regenerative medicine such that reimbursement procedures for this type of treatment are confused or even disallowed.

Tissue engineering is a new phenomenon. the complexities of which are common throughout the world. The manner in which different cultural and political systems are tackling these problems are clearly varied. One might expect that there would be differences between the UK and Japan in this respect and hopefully this report provides some insight into the similarities and differences between these two countries as far as the introduction of tissue engineering is concerned.

3. The Scientific Base of Tissue Engineering in Japan

3.1. Introduction

The major objectives of the Mission were not directly related to the study of the academic institutions engaged in tissue engineering research and indeed the group only visited two universities, in Nagoya and Kyoto. Nevertheless it is important to provide some background to this academic base since this should underpin to some extent the industrial and commercial infrastructure. The universities should carry out basic research in the contributing sciences, possibly provide the stimulus of new developments through spin-out companies and provide appropriately trained scientists and technologist for the industrial sector. It is also very noticeable that government sponsored research institutes play a very significant role in both fundamental and applied research, and much of the high quality research performed in Japan in tissue engineering is undertaken in these institutes. This is in contrast to the situation that prevails in the UK, and indeed across Europe and in the USA.

The multidisciplinarity of tissue engineering inevitably leads to the involvement of a wide range of parent disciplines and academic departments in this research base. Some of the major tissue engineering activities have emerged from those departments or institutes that were previously engaged in biomaterials or medical engineering research, whilst others have developed within biological sciences.

3.2. Universities

aThe university system in Japan is in a period of uncertainty in general and the national universities will be given quite different status and powers in the near future. There is also a considerable change in the way in which universities have engaged with commercial activities in recent years, with a strong and positive encouragement of entrepreneurial activities by professors and an emergence of university led spin-out companies. The traditional view of university departments and professors in Japan being quite isolated from the commercial world is no longer valid, with much more engagement of the former in the latter. It is noticeable, however, that universities appear far less well funded and equipped than government supported research institutes and this does have some influence on productivity and the quality of the science, especially in the new biological sciences that are associated with tissue engineering. Very considerable investment in state-of-the-art facilities and equipment was noticed in several of the research institutes mentioned above, at a scale not remotely evident in the few university laboratories visited. This may be one reason why collaboration between university professors and these research institutes seems to be very strong.

3.2.1. Nagoya University

The Mission visited two academic institutions, in Nagoya and Kyoto. The former visit was made at short notice following the withdrawal of one company from the programme for reasons mentioned elsewhere in the report. Professor Ueda undertakes extensive research in tissue engineering related to maxillofacial surgery and dentistry. Much of the work is directed towards the treatment of periodontal disease in view of the its prevalence in Japan. His approach has involved the use of bone marrow derived mesenchymal stem cells, with biodegradable bioceramic scaffolds, especially tricalcium phosphate, and molecular signals derived from bone morphogenetic proteins or TGFβ. The work on stem cell based products has been undertaken alongside a more direct approach using porous tricalcium phosphate infiltrated with platelet rich plasma. The significance here is that such an approach would be treated as a medical device, with implications as far as manufacturing and regulation are concerned. Professor Ueda has already been involved with a few start-up companies that seek to commercialise such products. It was clear that the climate within universities now allowed such activity, but that the number of professors who chose to operate commercially was still very low.

3.2.2. Kyoto University

Kyoto University has had a strong tradition in biomaterials science for many years and this activity has now been extended into tissue engineering and regenerative medicine through the formation of the Institute for Frontier Medical Sciences. The research programmes here give some indication of the general directions of Japanese tissue engineering research. There are 41 faculty members at the Institute, currently under the direction of Professor Nakatsuji. The Mission were given presentations by Professors Nakatsuji (cell development and differentiation), Nagata (cellular and molecular biology), Toguchida (biological repair), Tabata (biomaterials), Inoue (organ regeneration), Tsutumi (stimulation engineering), Hiraki (molecular interactions and tissue engineering), Shimitzu (organ reconstruction) and Iwata (reparative materials).. The Institute has a very strong programme in embryonic stem cell research and are an approved laboratory for the derivation of human embryonic stem cells. Their plans are for the production of human embryonic stem cells without feeder cells; identifying the specific cell malfunctions to which stem cell science can be applied, eliminating the risks of uncontrolled division in stem cells; identifying and eliminating extra chromosomes and identifying and then making use of the genes involved in adult cell de-differentiation.

One group works on biomaterials, cell-biomaterials combinations, scaffolds, drug delivery systems, biodegradable polymers, biomaterials that support stem cell growth and differentiation in a 'smart' way, including releasing specific growth factors or that can be used in cell bioreactors and reconstructive surgery. Much of the work is centred around gelatin matrices and the release of bFGF. There is a strong interest in the application of regenerative medicine in the treatment of diabetes, with, for example, the development of gelatin-collagen based bioartificial pancreas, again involving embryonic stem cells. A number of different cell sources have been used. They have been successful in small animal models with this work, and are planning to experiment with dog models. A further group has been working on peripheral nerve regeneration using collagen nerve guides and the results of clinical work was presented, some 40 or so patients having been treated with their experimental techniques. Their work on collagen has involved prechondrogenic cells which differentiate into chondrocytes following delivery of FGF and IGF-1. The work also involves the study of the role of chondromodulin-1 and its anti-angiogenic action.

Overall the quality of the work carried out in this Kyoto Institute is impressive and the programme is wide ranging but with a reasonably consistent theme. The programme itself is not atypical of university based tissue engineering research, concentrating on cell behaviour and the control of cell function. There was much less emphasis on materials and bioreactors. Interestingly, the teams here had clear clinical objectives and are quite prepared to take their developments to human clinical use after relatively limited animal tests. It was also interesting to note the major emphasis on embryonic stem cells, including human stems cells, even though there is no government approval for their use in clinical medicine. This situation was repeated in a number of other non-university research laboratories.

3.3. Research Centres

The Mission was also able to discuss aspects of tissue engineering research in the Tissue Engineering Research Centre (TERC) of the National Institute of Advanced Industrial Science and Technology (AIST), in the Institute for Biomedical Research and Innovation (IBRI) and the adjacent Riken Centre for Developmental Biology.

3.3.1. Tissue Engineering Research Centre

At TERC (http://unit.aist.go.jp/kansai), the Mission was welcomed by the Director, Dr Jun Miyake, and given presentations by Dr Masato Miyake, Dr Hajime Ohgushi, Dr Gouping Chen, Dr Yonehiro Kanemura and Dr Noriko Kotobuki.. Among the programmes that were discussed was a cell informatics project in which a Genome Network Consortium has been established by TERC and industrial and venture capital members, aimed at the development and

commercialisation of transfection array systems. The medical device group are working on the differentiation of bone marrow mesenchymal stem cells for use in bone, cartilage, liver and muscle tissue engineering. Their work with bone regeneration, involving osteoblasts derived from bone marrow and cultured in hydroxyapatite scaffolds is well advanced and already in clinical use in some patients. The procedures for bone marrow sourcing and differentiation are straightforward, but the process takes up to four weeks and may be inappropriate for acute orthopaedic injuries.

One group was involved with the regeneration of the central nervous system using embryonic stem cells. They are particularly interested in spinal cord injuries. Work on scaffold technology is well advanced, with an emphasis on biodegradable polyesters couple with recombinant proteins. The main clinical focus is on cartilage replacement, with impressive results involving autologous osteoblasts in a dog knee model.

The facilities at TERC are very impressive and the quality of the science is exceptional. The work of the institute is comprehensive, ranging from some high quality fundamental science, to animal models for the evaluation of products and processes, and there is a strong emphasis on commercialisation and clinical strategies in partnership with other organisations. TERC is particularly interested in high level national and international partnerships and there are significant opportunities for UK collaboration.

3.3.2. RIKEN Centre for Developmental Biology

At the RIKEN Centre for Developmental Biology, (www.cbd.riken.go.jp), the Mission was also impressed with some excellent facilities and world-class science. They met with Mr Michio Seki, the Executive Advisor, Dr Shin-ichi Nishikawa, head of the Laboratory for Stem Cell Biology, Mr Naoki Namba, the Science Co-ordinator, and Mr Doug Sipp, Manager of the Office for Science Communications.. RIKEN is the largest publicly funded research organisation in Japan, and was established on the Kobe site during the last year. There are seven core programmes, dealing with (i) cell adhesion and tissue patterning, (ii) stem cell biology, (iii)vertebrate bodies, (iv) morphogenetic signalling, (v) cell asymmetry, (vi) organogenesis and neurogenesis and (vii) evolutionary regeneration biology. Stem cell biology is a major focus, with at least six laboratories engaged in embryonic and adult stem cell work, including developments in circulating endothelial progenitor cells for vascular endothelium regeneration, neuronal induction from stem cells and differentiation pathways and intermediates.

3.4. Comment

Obviously the Mission was only able to visit a few research laboratories in the country and it is not possible to form an accurate impression of the standards of the tissue engineering science in the country as a whole, and no attempt has been made to analyse laboratories that were not visited. This is an important point since the visits were made to laboratories known to be amongst the best. It should be remembered that there are some other world class laboratories in other cities and prefectures, both in academia and government laboratories.

For example, one of the major centres for research is at the Tokyo Women's Medical University, where the fabrication of functional tissue constructs of three dimensional structures is achieved through the layering of two dimensional sheets of cells grown on thermally responsive polymers such as poly(N-isopropylacrylamide). This work has led to the successful use of layers of cardiomyocytes in the treatment of heart failure in animal models, where electrical communication can be established between these layers resulting in normal pulsation, and also in the clinical use of cultured sheets of cells in corneal surgery for patients with severe disease or damage to the conjunctiva. In the same university, there is already clinical experience of tissue engineered arteries using autologous bone marrow cells and biodegradable scaffolds. Once again one can see the combination of high quality basic science and the direct clinical application of these processes to treat patients. Such pathways to the

clinical application of tissue engineering products and processes are not readily seen in the UK, where far more cautious approaches are taken. The Mission was impressed by the urgency in pushing forward with the practical applications, although somewhat nervous that not all of the risks had been identified and addressed, and that the cell biology was not fully understood.

Other universities with significant tissue engineering research programmes include (in no particular order) the Tokyo Institute of Technology, Okayama University, University of Tokyo, Tokyo Medical and Dental University, Osaka University, University of Hokkaido, Kyushu University, Tokai University, Kumamoto University,, Kyushu University and Tsukuba University. It is also recognised that there are other government research institutes with significant involvement in tissue engineering research, particularly in the Greater Tokyo area and at Ibaraki in particular. These include the National Institute of Agrobiological Sciences and the National Institute for Materials Science and also the National Cardiovascular Centre Research Institute in Osaka and the Okazaki National Research Institutes.

No attempt was made, in the time available, to study the education and training programmes within the universities and elsewhere, but such programmes were not in evidence during casual conversations and visits. There must be some concern that the massive investment in tissue engineering and related technologies is not being matched by high level training of scientists and technicians. There is some evidence that Japanese institutions would like to see foreign scientists moving to Japan to take advantage of these new facilities.

4. The Economic & Commercial Base of Japanese Tissue Engineering

4.1. Economy in Transformation

Japan is the world's second largest economy, with a Gross Domestic Product (GDP) of US$3,942 billion. With a population of 127.2 million, the GDP per head is $30,990, while the GDP growth rate is 1.5% per annum and inflation is currently -0.5%. Comparative UK figures are GDP of $1,771 billion; GDP per head of $29,360; population of 60.3m; GDP growth rate 2.1% and inflation of 1.5%[1] .

The Japanese economy is considered to be in a difficult phase, struggling with deflation and the urgent need to move away from the inefficient and outdated economic model based on traditional industries. An added complication is the ever-growing number of companies relocating manufacturing to China in search of lower cost and the need to capitalise on a new and rapidly expanding market.

The need to revitalise and modernise the economy has been recognised by the Japanese Government, who have named Life Sciences (along with information and communications, environment and nanotechnology) as a strategic priority for the coming decade. This underlines a clear desire by the government to move the economy up the value chain and hence strengthen global competitiveness.

The need to focus on life sciences is heightened by the realisation that the Japanese population is aging rapidly. In 1996, 15.1% of the 127 million population were over 65. In 2010 this figure is expected to increase to 22%, and by 2020 reach 27%, the highest anywhere in the world. As the ageing population increases, so to does the demand for healthcare. National healthcare expenditure accounts for 7.1% of GDP (cf. 5.5% in UK; 13.9% in USA) today and is expected to rise sharply over the coming years[2] .

The need to develop technologies that can help address the emerging medical problems associated with these demographic changes is acutely felt at the highest level of Government. Such technologies would need to impact on everything from medical diagnostics and informatics, to pharmaceuticals and the technologies for regenerative medicine, including tissue engineering and cell therapy.

4.2. Government Direction and Incentives

The numerous government agencies have following extensive discussion with the industry sector, developed plans to enhance the technological competitiveness of the domestic industry. Technology has and will continue to be seen as a core factor in driving Japanese economic growth through innovation. In 2000 the Government formulated the Science and Technology Basic Plan 'Millennium Project' as a foundation for future science and technology policies[3]. As a consequence of this initiative, a research project in the area of biotechnology, with a budget of $800 million in 2001, was initiated embracing genome-related research, tissue engineering, research on embryonic stem cells, and bioinformatics.

Unlike previous government initiatives, the Millennium Project is characterised by the collaboration it has engendered among the various government ministries as well as by its clear objective to foster commercialisation of the project results to enable the development of

[1] The Economist: The World in 2003; pp 93-99

[2] Healthcare-Japan profile: Trade Partners UK. www.tradepartners.gov.uk/healthcare/japan

[3] The Government of Japan's Special Millennium Project. Budgetary Framework (January 2000). www.nsftokyo.org/rm00.03 and www.cao.go.jp/cstp/english

new therapies. Indeed, within the government's basic strategy on biotechnology, ambitious objectives have been set to expand from $10 billion (1999) to $200 billion (2010) the biotechnology market and create some 1000 new companies by 2010[4]. The environment for creating biotechnology start-up companies is gradually improving through the provision of necessary venture funding (see Section-Venture Funding), the development of an infrastructure with incubation facilities and equipment, and enactment of new legislation that provide greater flexibility.

The Government provision for research funding in Life Sciences and Biotechnology is, despite the severe budget crises in Japan, set to increase by around 5% in 2003, within most ministries. The Ministry of Economic, Trade and Industry (METI) is mainly focused on health care devices and research instrumentation[5], while the Ministry of Education, Science and Technology (MEXT) expects to spend some $400 million on strategic initiatives to accelerate the translation of research in clinical genetics and tissue engineering into usable products and therapies.

Recent MEXT initiatives[6] include the shift in status, in 2004 of national universities to independent administrative agencies. In addition to reducing government bureaucracy the change will enable individual universities to

- Make profit through their educational and research activities
- Allow faculty members to have posts outside university
- Permit faculty members to choose their status: public servant or not

Incentives for industry to participate are also being put in place by making available $430,000 for each industry derived idea taken up in collaboration with university researchers. Venture companies that are established, based on university research results, will receive funds to the same value ($430,000). The changes will make it possible for venture companies to have their HQ on campus with MEXT providing funds for hiring management and IPR experts.

These initiatives are expected to facilitate university technology transfer activity and counter the continuing trend to confine the output of biotechnology research to university laboratories and institutes.

4.3. Infrastructure Investment

To further facilitate the generation of start-ups, 'western-style' regional bioclusters, previously not common in Japan, are now actively growing especially in Kanto and Kansai areas. These initiatives are part of the Japan Millennium Project.

The Mission focused primarily on the Kansai region with visits to Tissue Engineering Research Centre (TERC) in the Amagasaki Site, Institute of Biomedical Research and Innovation (IBRI) and International Business Centre in Kobe. All of these are key elements of the wider Kobe regeneration programme in the wake of the devastation caused by the earthquake of 1995.

TERC is part of the larger National Institute of Advanced Science and Technology (AIST) set up under guidance from the Ministry of Economy, Trade and Industry (METI). TERC, which today operates independently of METI and derives its strength from a strong multi-disciplinary approach to building technology solutions. The group, under its recently appointed director Jun Miyake, is refocusing efforts into three team areas: bone and nerve regeneration; genetic-

[4] Saegusa, A., Nature 1999 July29; 400(6743): 389

[5] Triendl, R., Nat. Biotechnology 2003 March; 21(3): 21

[6] Monthly S&T Highlights from Japan (Sept.2001). www.arofe.army.mil/NSF

based technologies; and nanobiotechnology. A 10 year programme is built around 1st/2nd/3rd generation tissue engineering products targeting the creation of alternative organs and tissues, the development of technologies that can serve as alternatives to animal experimentation, and the production of physiologically active substances.

A key element of TERC's mission is the building of partnerships between industry and academia through translation of technology into new business. This is built around an investment of $26 million in a new facility (2002), including class 1000 clean room with annual running cost of $10 million. The initiative has attracted an impressive list of industry collaborators including Smith & Nephew (cell sheet engineering), Kaneka (cartilage), Kyowa Hakko (stem cells), Pentax (bone), Dianippon (bone) and Initiam (cell arrays). In addition, the initiative has already generated three start-up companies housed within the TERC facility, indeed reorganising the facility to accommodate new ventures was very evident. High awareness of the challenging target of 1000 biotechnology companies by 2010 was evident here and at most of the centres visited.

The Institute of Biomedical Research and Innovation (IBRI) is another recent investment (on a much grander scale than TERC) located next to the RIKEN-Centre for Development Biology (CDB). The CDB was formed in 2000 at a cost of $53 million in an effort to break with the tradition Japanese academic model by providing a structure within which high-flying scientists can build independent teams that deliver international excellence in science. Today, within CDB there are 7 core programme directors and 23 creative research promotion programmes with a total of 243 researchers and an annual budget of $50 million provided by national government.

The IRBI core facility (figure below) constructed at a cost of $110 million includes:

- Medical Equipment Building (collaboration projects; Medical Imaging MRI/PET/CT)
- Research Building, Cell Processing Centre (Translational Research Facility; Class 100 clean rooms)
- The Clinical Research Centre including hospital wing with 60 beds to open in July 2003, initial focus on cancer

Figure 4-1 Institute of Biomedical Research and Innovation (IBRI)

The running costs of $40 million a year is met in part by contributions from Kobe City ($12 million) and a group of Pharmaceutical Companies ($12 million). The close proximity of the IBRI facility to the CDB's strong basic research programme is seen to offer early opportunity for those entrepreneurs in the facility to commercialise their technology. The IRBI is also focused on attracting external investment from established companies and new start-ups.

Within this Kobe complex, adjacent to the CDB and IBRI buildings is the International Business Centre offering further rental laboratories and offices as well as warehouse, assembly and manufacturing space (total 20,000m^2). This group works closely with the Kobe Biomedical Venture Fund to develop the industrial/manufacturing base within Kobe.

The success of the CBD initiative in attracting world-class scientists to fuel the innovation engine in Kobe remains to be established[7]. However, the Kobe initiative has to-date attracted investment from 32 companies/start-ups (including 19 biomedical companies) with a further 30 under negotiation. The larger pharmaceutical and diagnostic companies are also expressing considerable interest in the Kobe model.

The planned additional investment in a Translational Research Informatics Centre (TRI) at a cost of $4.2 million and a Biomedical Accelerator (Business Incubation) at $38 million and Biotechnology Research and Training Centre on the Kobe site is further evidence of the long-term view taken in establishing Kansai region as an International Hub for regenerative medicine.

The commitment to regional development and the infrastructure investment programme to regenerate Kobe as 'Medical Industry City' is impressive. A watching brief should be adopted by UK Centres focusing on regenerative medicine in respect of developments in the Kansai (and other) region and evolution of the model as much can be learnt from their experience.

4.4. Biomedical Science and Devices Industry Base

Japan is the world's second largest market for medical devices and pharmaceuticals. In both sectors, US firms are the dominant worldwide suppliers of innovative products, holding 12% of Japan's $60 billion pharmaceutical market, and almost 30% of Japan's $20 billion medical device market[8]. Although significant, the foreign company market share is less than those seen in other developed countries This is partly explained by the fact that Japan has a significant number of healthcare companies (particularly pharmaceutical) which tend to operate nationally rather than globally and the difficulty experienced by global companies in penetrating the Japanese healthcare market. Indeed the large home market enjoyed by Japanese companies has fuelled the high national R&D spend when compared to Europe. Japan's share of the total world R&D spend (2000 data)[9] of $700 billion is high at 14% compared to Germany (8%), France (5%) and UK (4%) Within this, 22% of R&D funds come from government the balance (78%) being derived from Industry. In the UK 30% is derived from government.

4.5. Industry Representation at Mission Seminar

Attendance at the Tissue Engineering Mission Seminar and Reception held in Osaka reflected the growing interest in regenerative medicine within the commercial community. Of the 75 organisations represented at the meeting (108 attendees in total), two thirds were commercial organisations ranging from early start-up to large pharmaceutical/medical device companies (see Appendix II).

[7] Cyranoski, D., Nature 2002 Feb.28; 415(6875): 952-3

[8] Healthcare and Medical Products. www.buyusa.gov/japan/en/page88

[9] OECD, Main Science & Technology Indicators 2002. www.aaas.org/spp/rd/pr020603

The Mission team visited two medium-sized companies and two start-up companies. One company, Menicon, withdrew at the last minute from the programme following a company strategic decision to close its in-house skin (autologous) tissue engineering programme. A public statement issued by the company during our visit attributed this decision to a recent statement by the Ministry of Health indicating clinical trial support information would be required for approval of autologous tissue engineered products. This event served to underlined a concern within the tissue engineering community regarding the ill-defined nature of the approval process, in particular for autologous products. A number of organisations in Japan have embarked on an autologous approach to tissue engineering on the assumption that approval would require minimal clinical trial expenditure. Clearly this is not going to be the case.

4.6. Company Visits

4.6.1. Tanabe Seiyaku Co Ltd (www.tanabe.co.jp)

Hosts:

Takatar, Tom; Cancer Surgeon, Head of Regenerative Therapeutics Project
Yoshizawa; Hidetomo; Strategic Research Planning & Management Division
Kondo; Yasushi; Senior Scientist, Advanced Medical Research Dept.,
Discovery Research Laboratory
Matsukawa, Yasuhisa
Michibata, Hideo
Wakimoto; Koji; Scientist, Discovery Research Laboratory

The team visited Tanabe Seiyaku Co Ltd in Osaka. Tanabe is a leading pharmaceutical manufacturer with a history associated with medicine stretching back 325 years to 1678 (in the period of the fourth Tobugawa Shogun). Today it sees itself as an R&D -oriented company with the main laboratories in Osaka. Eighty per cent of its business associated with ethical pharmaceutical products, primarily in areas of the cardiovascular (43%), central nervous (17%) and gastrointestinal systems(10%). It has sales of $1.4 billion; an R&D expenditure of $157 million and employees numbering 4,552 (691in R&D).

The majority of their R&D effort has and will continue to be focused on improving the effectiveness of the established approaches to novel disease-oriented drug discovery. At the same time they are building a capability in genome-based drug discovery as a priority in collaboration with Glaxo Smith Kline.

Tanabe also have a continuing interest in cell-based technologies built around the use of cell based screens as part of their drug discovery programme. The organisation within the basic research laboratories has recently changed to accommodate a human Embryonic Stem Cell programme led by a cancer surgeon Dr. Takatar supported by a team of eight scientists. The programme is undertaken in collaboration (50/50) with a University and receives significant funding through science and technology grants. Within this arrangement Tanabe reserves the rights to exploit the emerging intellectual property.

The company has made an initial 3-year commitment to this programme which will then be reviewed. However, their scientists consider that the project will take at least 10 years to produce a therapeutic product. The team is confident that senior management are aware of the risks and long-term nature of such an investment and will support beyond the initial 3 years.

Tanabe plan for stem cells will follow ministry guidelines for Derivation and Utilisation of Human Embryonic Stem Cells, introduced in August 2001. Six university groups have already had their Human Embryonic Stem Cells Utilisation Plans recognised by the Ministry. Activities within the company are at present confined to studying embryonic stem cell lines from Cynomologus and Japanese monkeys, with plans to progress later this year to identifying

vascular progenitor cells derived from human embryonic stem cells and application for vascular regeneration. There was also reference to early work on stem cell derived neural precursor cells for the treatment of Parkinson's disease.

The absence of clear guidelines on utilising embryonic stem cell-derived products in clinical research and medicine remained a concern for the group. They considered industry had little influence with the Ministry during the setting up of these guidelines. The possibility of having the view of industry reflected in outputs from Government remains difficult, although there was evidence of some improvement. Today organ transplantation projects are under the full control of the Ministry due to issues of transfection. A similar situation was felt likely to emerge for human embryonic stem cell-based products.

Tanabe are currently following what they perceive as more progressive USA (FDA) and UK(CPMP) guidelines for screening and recording history (with respect to gene transfer issues).

Overall the visit proved to be extremely productive and illustrated the desire on the part of some Japanese pharmaceutical companies to embrace regenerative therapeutics through cell and tissue-based products.

4.6.2. Kyocera Corporation Bioceram Division (www.kyocera.co.jp)

Hosts:

Sano, Kenji; General Manager, Bioceram Division
Okimatsu, Hideaki; Deputy General, Manager, Bioceram Div
Nishida, Masaru; Manager, International Support, Development Dept.
Wakebe, Izumi; Manager, Research Department
Yoshihara, Yusuki Manager, Biochemical Research Section, Research Dept.
Muramatsu, Kaxuaki; Biochemical Research Section, Research Dept.
Ohtomo, Ken; Manager, Overseas Business Development, Marketing Dept.

Kyocera is a major ceramic manufacturer providing information and communications components and devices; Global environmental products (e.g. solar panels) and ceramic medical and dental implants. The Kyocera Group employs 44,235 staff in 161 companies. Total sales are $8.6 billion, with 60% overseas, and the total R&D of $333 million (4% of sales).

The Bioceram Division, based in Kyoto, has sales of $83 million (1% of group turnover). The Division's products are composed of hip joints (57%), dental implants (14.5%), knee joints (11.8%), parts OEM (8.6%) and others (8.4%). The business is built around core ceramics technology applied to artificial bone, alumina femoral heads and zirconia components for knee and hip prostheses, and hydroxyapatite-coatings of porous surfaced titanium hip implant stems to improve bone fixation. The main focus is the continued development of new products in their core area of business, to grow their domestic market, and to expand the export market for their products. Within the range of conventional implant systems, they have developed cross-linked polyethylene to reduce wear and generated over 10 years follow-up information on a number of implants.

The R&D team at Kyocera continue to see the need for technologies that improved bone-implant integration, particularly in total ankle joint prosthesis. They are currently evaluating a tissue engineering approach, in partnership with Professor Ohgushi at the AIST Tissue Engineering Research Centre (TERC). This involves coating ankle polyethylene joint prostheses with the patient's own bone marrow derived stem cells[10]. The pilot clinical study undertaken exclusively at TERC utilises their recently built cell preparation and processing facility and is

[10] Ohgushi, H. and Caplan, A., J. Biomater. Res. 1999; 48(6): 913-27

conducted under the physician's (Ohgushi) own authority (no Ministry approval being required). Fifteen patients have received stem cell coated ankle prostheses with no adverse effect, however it is too early to comment on whether such a costly 'osteogenic matrix coating' procedure will lead to improved integration and reduced loosening. Application of tissue engineering in more severe skeletal reconstructive surgery associated with bone tumour excision, are under consideration.

The team had also seen within the academic community considerable interest in applying tissue engineering solutions in the treatment of severe periodontal disease, ranging from the replacement of periodontal ligaments to fully tissue engineered tooth. Kyocera, given their dental interest had no active involvement in such a TE programme at present, but are aware of the possibilities and were maintaining awareness of developments in the academic field.

The group was equivocal regarding the commercial opportunities offered by Tissue Engineering based products. The fact that the regulatory authority is not seen as providing clear guidance was an added complication. However, they were clear in the view that autologous approaches to tissue engineering outlined above would need clinical evidence and Ministry approval for marketing.

Although tissue engineering is part of Kyocera's long-term strategy their commitment is limited at present.

4.6.3. Stem Cell Sciences KK (based in the Kobe International Business Centre).
Hosts:
Nakajima, Kenzo ; President and CEO, SCS KK
Ando, Hidehiro; Director Business Development, SCS KK
Maehata, Toshiro; Medical Industry Development Project,
Kobe City Government

The company is a joint venture between Stem Cell Sciences Ltd (50.8% shareholding), a biotechnology start-up in Australia, and Sosei Co Ltd (30.5% shareholding), a Japanese pioneer in the field with the balance of equity being held by 4 Venture Capitalists (12.4%) and the Researchers (6%). The company has close links with The Institute of Stem Cell Research (ISCR) at the Human Genetics Unit, University of Edinburgh, UK, and has exclusive global rights to IP derived since 1998 from stem cell research at ISCR. The group was attracted to Kobe by the significant knowledge structure that has evolved in regenerative medicine, ranging from basic research to clinical testing within the Kobe City complex. Also the low cost of the facility provided through the investment incentives package was also a factor.

The objective of the company is to develop a leadership position in embryonic stem cell research for gene/drug screening and cell therapy. The core technology derived from SCS Ltd is associated with ES cell sourcing - genetic manipulation - growth factors - cell solution - transplantation technologies, and licences to major pharmaceutical companies are already in place. Strategy for SCS KK is to build on two research collaborations with RIKEN CBD in the development of b-cells and dopaminergic neuronal cells. In these collaborations SCS KK have exclusive rights to RIKEN discoveries. At present two cell lines are ready for clinical trials (β-cells and dopaminergic cells).

The company is looking to secure immediate revenues in Japan from utilising cells for drug screening, to generate short-term revenues in the form of licence fees for growth factor/cell markets, and in the long term to the delivery of cell and tissue products for tissue regeneration. Investment in a new laboratory is planned to strengthen the existing six-strong research team by adding four more researchers in preparation for clinical trials.

An extremely ambitious programme that, with the academic strength of RIKEN CBD and IBRI on their doorstep, may well be feasible.

4.6.4. OsteoGenesis Inc (www.osteogenesis.co.jp)
Host:
Kitagawa, Akira; President and CEO

The team also visited another recently formed small company, Osteogenesis Inc. This is based at Kobe International Business Centre and was formed in July 2001. For Japan this is a unique venture company involving industry, academia and government working together to commercialise the results of the research work of Professor Ueda, Nagoya University, a leading academic expert in Japan in the field of tissue engineering. The research focus of the company is the generation of injectable cell-based bone graft substitute for application in bone supplementation in the mandible and the treatment of severe periodontal disease. During the previous visit to Professor Ueda's laboratory, periodontal disease was highlighted as a significant problem in Japan. An estimated total of 37 million patients per annum suffer from periodontal disease, and with the aging population this is likely to grow. Of these, 35% have severe disease. Although this is not a life threatening condition, it is one that OsteoGenesis feel represents a commercial opportunity for tissue engineering technology.

Building on the research work of Professor Ueda[11] the approach adopted involves isolation and expansion of bone marrow cells, combining this with autologous platelet rich factor (PRF) and adding a matrix of commercial collagen and β-TCP granules, producing a 'cell paste'. In a clinical setting the paste is to be injected into the cavity produced by the destroyed bone around the tooth.

The first proof of concept human trial is however planned in a simpler clinical model of bone cavity augmentation in the maxillofacial region (maxillary sinus floor/alveolar bone/mandibular bone). The ability through this procedure to graft osteogenic cells using a syringe is seen as a significant advantage. Use to reinforce the bone platform around dental implant pegs is also being considered.

As a start-up company within the Kobe Regeneration site, OsteoGenesis can readily secure access to GMP compliant Cell Processing facility at IBRB and will be looking to start clinical studies early in 2004 with market access in 2007/8.

4.7. Prospects for growth in enterprise culture

The drive to grow new business through investment in regional infrastructure projects has already been discussed. This commitment has been underpinned by substantial government spending aimed at stimulating growth. Within this, Science & Technology expenditure has grown each year reflecting the continued expectation at the highest level that future economic success will be grounded on technological advances. Particular focus is being given to life sciences, nanotechnology and information communication. Government S&T spending still only represents 22% of total national R&D spend[12] (UK 30%) the private sector accounting for 78% of the investment. It is therefore extremely important to the Japanese economy that industry continues to keep faith with R&D investment even when profits are under extreme pressure, as they are today for most Japanese companies. The available evidence indicates that industry in Japan continue to see R&D as the route to future prosperity. Initiatives to

[11]Ueda, M., Dentistry in Japan 2003; 39: 199-207

[12]Overview of Japan Economy: www.finstitute.gr.jp/science/reports/innovation_Systemspdf

introduce reforms at all levels that will encourage growth in the national commercial base can be seen and the changes are designed to offer opportunities for investment by overseas companies.

Life science research in Japan is not considered to be at a level that sets the global pace in areas of genomics and cell and tissue engineering. They consider the US and more recently Europe to have taken the investment initiatives necessary for both academic and commercial success. To compete globally the need for partnerships is acknowledged and welcomed and offer a real opportunity for UK academic centres and industry to take advantage of the emerging excellent facilities and incentives to grow life science based business. The high regard for British science in Japan gives the UK a significant advantage. There is every chance that a focus on enhanced Japan-UK collaboration in life sciences would ultimately result in net investment in the UK economy by Japanese Biotechnology companies as a route to access the European market, as has happened historically in the car and electronics industries.

The enthusiasm and desire to build effective global academic-industry bridges is evident within the institutions visited by the Mission and if this sentiment is reflected across all Japanese Universities, then the emergence of Japan as an engine room for enterprise in biomedical science and technology is certain.

4.8. Barriers to Growth

The stated government goal of achieving over 1000 new start-up companies by 2010 is challenging and has many associated risks. These risks, which are not unique to Japan, were touched on in discussion with various hosts, but the detailed assessment was beyond the scope of the Mission. The major concerns surround the following issues.

4.8.1. Availability of Qualified Personnel

In Europe and the USA the availability of scientists, technologists and management expertise to drive the new enterprise culture is recognised. However, the more rapidly aging population in Japan makes this a more critical issue. The Universities are beginning to recognise the need for students to have interdisciplinary perspectives to research and business-orientated skills. However, skill shortfall is anticipated and efforts are being made to address this through encouraging overseas applicants for posts[7]. In addition private corporations employ 70% of all the research personnel in Japan. Therefore it will be essential to mobilise some of this resource as part of the initiative to achieve the desired growth in start-up companies in life sciences and biotechnology. The availability of a suitable number of experienced entrepreneurial management personnel to drive these start up companies may be an even more critical constraint on company formation and growth. There was some examples shown particularly in Stem Cell Sciences KK and Osteogenesis Inc. of energetic entrepreneurial managers but 1,000 companies would create a tremendous demand for such people.

4.8.2. Relaxing the Hierarchy Model within Universities

The Japanese university model, unlike its US and European counterparts, is built upon a departmental structure with academic hierarchy that is considered to constrain rapid development of young academics and entrepreneurs. The general impression from the Mission discussions is that this system remains essentially intact within Japanese National Universities. An initiative such as RIKEN CDB, Kobe is aimed at releasing creativity of young researchers and break the mould. The move to confer independent status on National Universities is also seen as likely to force a culture change and a need to develop commercial links with industry. Although much remains to be done to bring the culture anywhere close to that within US universities, it was evident from the visit to Nagoya University (Prof. Ueda; 50 patents; initiated three start-ups) and Kyoto University, Institute for Frontier Medical Science that technology transition to the clinic is high on the agenda. However it is questionable

whether the major change will occur rapidly enough to bring about generation of the desired number of new businesses by 2010.

An extremely positive aspect of the research undertaken at all the centres was the strong early link between laboratory and clinical research with technologies undergoing early clinical evaluation (anything up to 60 patients) as part of the academic endeavour.

4.8.3. Enhancing Entrepreneurship within Universities

Historically university staff wishing to engage in start-up would have to sacrifice tenure and academic career and re-entry to academic life is difficult. Add to this the reluctance to have industry commissioned research where industry-Professor partnerships are formed and the company has ownership of the IPR, makes the university environment in Japan very different from that in USA/Europe. Removal of these obstacles is essential, but will take time and is unlikely to be achieved in time to enable the university base to make a major contribution to the emerging life science start-up base. Success in achieving the target of 1000 start-up companies will depend upon the willingness of pharmaceutical and medical industry to help spin out their in-house technology loosely linked with universities.

4.8.4. Availability of Suitable Facilities

Although some incubator facilities were seen for the accommodation of new companies, particularly at TERC, little space was seen for growth of companies to the 50-100 person stage needed for sustained operation. Mention was made of land that would be made available for additional facilities adjacent to the RIKEN CDB site in Kobe but no plans were currently in place to build this space out. Considering that GMP clinical manufacturing facilities can take approximately 4 years to design, build and commission then this may cause a gap in the development path unless addressed soon.

4.8.5. Access to Continued Funding

Biotechnology companies typically need to raise some $60 million before they become financially self sufficient from product sales or licensing revenue. The formation of 1,000 companies would create an immense need for capital (some $60 billion over the next 15 years which is a level of investment that surpasses the current US investment in biotechnology after over 30 years of growth and maturation). Although several VC firms are beginning to get involved in this sector, there seemed to be little coherent plans in place to meet this need. This could result in a great deal of waste as companies consolidate to reduce their cash requirements.

4.8.6. Clear Regulatory Routes to Market

The regulatory agencies appeared to be willing to follow the US and Europe in developing and proving a suitable regulatory strategy to support regenerative medicinal products. The example while the Mission was in Japan of Medicon pulling out of the sector because of an adverse change to the regulatory requirements is illustrative of this problem. Without a clear route to market private equity is unlikely to provide the large funds required to develop late stage products into the clinic.

4.9. Comment

Japan, from the Ministry downwards, has understood the importance of translating science and technology into products that benefit the population at large. The significant Government funding of R&D, in absolute terms equivalent to the national UK R&D spend, needs to be seen to provide return to the taxpayer. Government reforms, infrastructure building and a range of incentives are planned to drive growth in new enterprises and jobs. Biomedical sciences, including cell therapies and tissue engineering is at the forefront of these initiatives driven by the anticipated social burden that will emerge as Japan becomes the nation with the highest percentage of over 65 year olds in the world in 2020.

There were signs that encouraged the thought that Japan could develop to be a biomedical science engine room in 2010 and beyond, and opportunities exist for UK industry and academia to further develop partnerships in Japan. Systems have been put in place to create and foster early start ups as spin-outs either from academia or pre-established life-science companies, but little evidence was presented of a coherent plan to encourage these companies to grow to profitability. This could create an opportunity for more mature UK companies to establish links with industrially focussed R+D groups or early start ups in order to bridge this gap and thus access the fruits of the enormous Japanese R+D investment. However, much still needs to change in order to fully realise the potential offered through academic-industry partnerships. Today they remain well behind what has been achieved in USA and slightly behind achievements in UK and Europe.

5. Investment Opportunities

5.1. Sector Overviews

5.1.1. The Japanese Biotechnology Sector

The biotechnology sector appears to have flourished during 2001 in Japan, with over 330 biotechnology start-ups created, compared with 160 in 1998. however, since then the sector has fallen into the same decline as experienced in Europe and the USA. There are, therefore, concerns over the validity of the proposal that the sector will be a major economic driver for the near to medium term. It is noteworthy that that most of the early biotechnology companies were based in the Tokyo region (33%), with half of these being within the developing biotechnology services such as analyses, reagents or bioinformatics. There has been a significant restructuring within and between the administrations of MITI and MEXT in order to create 12 bioscience clusters across the country. Kobe is one of the most significant clusters for regenerative medicine, although there is a certain amount of tension between the broader Tokyo and Kansai prefectures and within the Kansai area itself.

5.1.2. Medical Devices Sector

Japan does not have a strong, global medical device industry despite its leadership in other areas of relevant technology. This has been ascribed to the historically restrictive legislation, high risk of product liability claims, high cost of clinical trials and relatively small returns. Products are imported from the USA mostly, although some European companies also have an established presence in the sector. As a result of the recent government initiatives, a number of companies including Hitachi, Kirin, Toyota, Marubeni, Mitsubishi and Olympus are re-evaluating their strategies for the sector given the size of the market (US $60 billion, EU $41 billion Japan $ 25 billion) and a view that legislation may ease in future. Tissue engineering is seen as one of the developing ‘new’ medical technology sectors to which such companies, and their pharmaceutical counterparts, are attracted.

5.1.3. Tissue Engineering

Tissue engineering in Japan is focussed on the development of tissue and cell systems rather than attempting organ regeneration. To date, the majority of activities have been totally Government funded or conducted within corporate research groups of large pharmaceutical companies. According to Professor Ueda there are currently believed to be approximately 22 companies actively working in tissue engineering in Japan, with the main activities being focussed on first generation cell models and materials which can facilitate biological repair processes and tissue regeneration.

With structural tissues (skin, dental tissues), there are 12 companies with metabolic systems, and another 5 with cellular systems (stem cells, nerves etc) companies.

It appears that Japanese tissue engineering is an emerging sector which is not yet fully defined, and which is evolving rather than being driven by anticipated ‘breakthrough’ scientific discoveries.

5.2. Government Initiatives for Investment in Life Sciences

5.2.1. Policies

The Japanese Government has been attempting to revitalise the national economy with a number of policies and institutional reforms such as privatising public sector entities, reforming the social welfare service and reducing the national debt.

One of the most significant changes has been the active encouragement of cooperation between universities, industry and national research centres, with state funded programmes designed to accelerate the transfer of technology and encourage scientists from academia and public organisations to enter the private sector.

In December 2000 the Japanese Government established a Biotechnology Strategy Council under Presidential leadership, publishing guidelines some short time later. This recognised the significant impact that life sciences will have upon the economic prosperity and quality of life for many industrialised nations over the coming years and was aimed at addressing Japan's competitiveness in this sector.

In particular there is a strong belief that small companies will generate entrepreneurship and risk taking which are considered essential in order to create a new generation of global companies and sustain a new economy in Japan.

Responsibility for the efforts to stimulate the 'bio-economy' are split between the Ministry of sciences, education, & sport (MEXT) and their counterparts in the Ministry of Health, Labour and Welfare (MHLW).

5.2.2. Ministry of Education, Science, Sport & Technology. (MEXT)
This Government department is responsible for the funding and management of State universities and national research institutions. The department has committed 23 billion yen of funding over 10 years ($800 million over 15 years) into basic sciences in support of regenerative medicine and tissue engineering. In particular The Riken Centre for developmental Biology at Kobe has been charged with the provision of a national collection of cord cell derived cell lines as well as programmes into leukaemia, cell manipulation treatments

5.2.3. Ministry of Health, Labour & Welfare (MHLW)
In august 2002 the Ministry of Health, labour and Welfare published a strategic paper entitled 'A Vision for the Pharmaceutical Industry' which directly led to a number of important initiatives to improve the competitiveness of the healthcare sector both in the provision of domestically-focussed services and the development of new biomedical technologies believed to be critical to the long term success of the pharmaceutical industry.

The key issues to emerge from the report include;
- 10-12% of total company R&D expense may be offset against tax.
- R&D spend of bio-industries has increased from 7.2% in the early 90's to 12.4% by the late 90's and will continue to rise.
- A national administrative network will be established to reduce patient recruitment time and costs of clinical trials.
- By 2004 private investment will be permitted into publicly owned research programmes and institutions, with ownership shared between scientists, the academic centres and commercial investors.
- Instigation of competitive performance evaluation at universities and national research centres.
- Individual researchers may apply for funding in addition to those allocated to institutions, and to apply for patents with a view to sharing the benefits 70:30 with their institutions taking the major share.
- From mid 2003 academics will be able to transfer their IP into commercial ventures and work in such organisations for up to 10hrs per week in addition to their academic duties.

These initiatives are designed to stimulate entrepreneurship and an attitude towards greater risk taking by scientists working within the start-up and early-stage private company sector, rather than the traditional corporate employers where most commercial research has traditionally been undertaken. One of the most significant of these initiatives is likely to be the policy that will enable academics to apply for patents and share the benefits with their university by transferring them into a company in which they hold equity or may work part time.

Pharmaceutical product safety regulations will be reviewed in July 2003 to update requirements for biologicals under the prevailing pharmaceutical laws. Although there is recognition that legislation needs to be flexible to encourage companies to introduce new technologies there is a strong practical and cultural preference for autologous cell technologies and non-animal based scaffolds. However, there was no consistent view amongst researchers as to how autologous cells would be regulated. Most think or hope that these products will be regulated as medical devices. Kyoto University sense that the MHLW is more than 2 years away from providing guidelines on the therapeutic use of stem cells in human clinical practice.

MHLW have recently also identified funds for encouraging the development of commercial IPR and funding its transfer into early-stage companies including the provision of management consultancy and project management for early-stage companies. Under this scheme companies are provided with a subsidy of up to 65 million yen for the cost of IPR transfer into the new company which is then repaid to The National Technology Licensing organisation (TLO) through a royalty on eventual product sales.

MHLW believe that Japan has internationally recognised areas of strength, in drug delivery, pharmacogenomics, and biomedical laboratory and production equipment, which can be developed commercially.

Discussion with MHLW identified the skin, bone, the peripheral nervous system, the central nervous system, the eye and cartilage as areas of priority for the application of tissue engineering.

The Government's long term funding commitment to basic developmental biological sciences and an ongoing review of legislative procedures for clinical trials is therefore appropriately supportive given the anticipated 8-10 year timeframes discussed for clinical validation and regulatory approvals of tissue engineering therapies.

5.2.4. Regional Development Funds

In line with most recent government initiatives, there has been a drive to encourage businesses to cluster around the 7 traditional national universities and selected development regions. Here, government funds underwrite much of the establishment cost and associated risks for early-stage companies making these locations attractive for VCs and corporate partners especially since the latter frequently have established links with these institutions .

Kobe is taken as a typical region which has chosen to focus on bio-Industries for it's future development. The initial inward investment has been to establish Government research capability, animal and human cell processing technologies and a clinical research unit. Companies locating here obtain up to 10 years free of ground rent if they construct their own facilities or up to 90% rent free space in the existing incubator for up to 3 years. Kobe development has also established a biomedical ventures fund which is targeted to invest in local start ups as well as offering financing to biotechnology start ups in other regions.

5.2.5. Government Venturing

'Riken ventures' has been established to provide the opportunity for Government scientists working in the Riken laboratories to share the benefit of resulting IPR on a 50:50 basis. Riken allow such staff to work part time for these start up companies and to use Riken space during the early stages, but do not themselves provide equity financing. The group does however, maintain relationships with a number of VCs.

5.3. Private Equity, Venture Capital and Corporate Partnering

5.3.1. Private Equity Financing

The government initiative to encourage spin outs from Universities has led to a rapid growth

in the number of start up companies, many of which fall in the biotechnology sector.
The VC sector has responded with increasing interest during the early 2002 period based upon the following expectations;

- Business model requires validation
- Intellectual property needs protecting and clear ownership. Patents are essential for attracting finance.
- Products need to demonstrate 'proof of principle' early.
- Most foundation money is provided by government and only a small amount is issued by VCs at the stage of 'spinning out'. Their risk seems relatively low.
- VCs are nervous about the lack of clear future regulation and the risk of liability claims for medical devices.
- VCs are seeking international links with investors and experts whilst their domestic sector becomes more clearly defined.
- In general VCs follow the trends that government and US /European investors find attractive.
- The returns from regenerative medicine in Japan and elsewhere are considered to be long term, 10 years for cell-therapies for example. This is determined by the need for a clear regulatory pathway, consensus on ethical and cultural issues and the need for long term clinical trials in many of the target indications.

Discussion with venture capitalists in Tokyo indicated that the central nervous system, the circulatory system, the liver, eyes and bones are the areas of most likely application for tissue engineering. They also recognise that the two most likely routes forward for the establishment of companies in this sector are either based upon significant cell biology which may still require many years of basic funding or may be built around existing drug delivery and biomaterials expertise with nearer term commercial horizons.

VCs have also recognised the strength of Japan's manufacturing and microelectronics sectors and are seeking to create new companies with integrated capabilities including knowledge of biological chemistry and control in order to develop new automated devices for data capture from biological systems such as in vivo monitoring.

The currently depressed investment conditions and economic uncertainty for small companies in particular are considered to be hindering the spin out of additional companies in this and the entire Biotechnology sector. Despite the availability of sufficient government incentives and equity financing therefore such 'start up' activities are seen as too high risk by Japanese academics, compared to the traditional security offered by employment with large companies or academia. Likewise senior executives within the pharmaceutical industry are secure in their present employment and do not wish to take additional risks at a time of economic uncertainty as experienced over recent years.

Recognising this need for both scientists and management and then attracting high quality individuals with international experience and perspectives into early-stage, high-risk companies in Japan will remain a major cultural challenge and probably the single biggest issue facing Japanese Venture Capital Funders and the biotechnology sector.

5.3.2. Corporate Venturing with the Pharmaceutical Sector
One potential way forward to overcome the hesitancy of individuals to join small companies in Japan may be the development of 'corporate venturing'. Several of Japan's large industrial conglomerates have already taken action to establish their own or partnering venture funds to create new businesses for potential acquisition or sale as seems appropriate at the time.

Unfortunately the larger pharmaceutical players seem to be rather negative towards regenerative medicine at this stage, but are taking the opportunity to establish research collaborations in order to learn about cell control and regulation which might then lead to the identification of biopharmaceuticals capable of being isolated and used as drugs. The companies following this strategy at present include Chugai, Kyowa Hakko and Tanabe.

5.4. Comment

The opportunities for venture capital providers to create new companies in tissue engineering in Japan are limited at the present time, largely because of the difficulty in attracting world class scientists and entrepreneurs into small, high risk companies and the time before products can be developed and validated in an as yet unregulated domestic marketplace.

VCs are therefore still investing in the sector, but learning from companies in the USA and Europe in the hope of 'matching' these early investments with Japanese organisations in the coming 10 years, as Japan 'matures' its people, the critical science becomes better understood and perceived technical risk reduced.

The underpinning of significant levels of government, long term funding in the biological sciences during this time and improved coordination of science and medicine in the Government administrations and steps to encourage development and protection of intellectual properties are all well-placed national priorities which will secure the future pipeline of such Japanese companies in future years.

Corporate venturing is likely to expand and succeed as the most effective means of encouraging innovation and stimulating economic growth through the adoption of new technologies and business into the powerful industrial base of Japanese companies in advanced materials, microelectronics and pharmaceuticals. Japan will most likely improve upon research from around the world and increasingly develop a high quality, biomedical technologies manufacturing sector over the coming decade.

6. Reimbursement, Ethics and Regulation

6.1. Introduction

For most industries, the Ministry for Economy, Trade and Industry (METI) provides the lead in policy, economic development strategy, and deliberations on infrastructure change. Because of the tight control of the health market in Japan by the Ministry of Health, Labour and Welfare (MHLW), this is the lead agency in pronouncements about the medical, healthcare and medical device sectors. In areas of activity where the main focus is still research, as is the case with embryonic stem cells, the Ministry of Education, Culture, Sports, Science and Technology (MEXT) provides the lead in funding and guidelines. The new Cabinet Office is responsible for national science and technology policy and reports directly to Prime Minister Koizumi.

METI is the renamed MITI (Ministry of International Trade and Industry). In this context, it has an explicit role of competitive expansion of indigenous industry, through mechanisms such as new approaches to technology and knowledge transfer as well as through directed support. It is also responsible for inward investment. METI's importance in this area is as the key sponsor for AIST and related technology development programmes and projects in tissue engineering and regenerative medicine.

MEXT was created in 2001 by the merger of the Ministry of Education and the Science and Technology Agency. The broad societal role of MEXT was emphasised by referring to culture and sport in its full title. MEXT has significant input into research ethics and, by extension, the bioethics of cell- and tissue-based products, as well as a very important role in funding basic research.

Also in 2001, the Ministry of Health and Welfare (Koseisho) and the Ministry of Labour were merged to form MHLW. In September 2001 and April 2002, MHLW produced its preliminary and second documents entitled 'A MHL Draft Vision for the Japanese Pharmaceutical Industry for Strengthening International Competitiveness.' In this, MHLW recognises that 'increasing costs of developing new drugs, and a worsening of Japan's medical insurance financial system … are resulting in Japan's pharmaceutical industry losing its international competitiveness.' Although the thrust of this document is how to get Japan's indigenous industry to take full advantage of genome based drug discovery, it is careful to promote the position that entry to the Japanese market by foreign companies is welcomed. The main conclusions of the Vision are an opinion that indigenous companies need to merge to compete fully on the world stage (indeed, 2-3 'mega pharmas' are regarded as 'most appropriate') and a series of measures forming a five-year plan 2002-2006.

The Vision recognises that new medical technologies such as regenerative medicine, gene therapy and cell therapy will spread during the next years. A driver for this is the increasing proportion of elderly people in the population. Japan and the UK both face the same problem – that this increase also puts enormous pressure on the ability of the state system (funded through national insurance contributions or by taxation) to continue to provide subsidised medicines and medical or surgical care.

The MHLW also states that 'it is vitally important to consider ethical aspects in dealing with human tissues in advanced medical studies and to gain public understanding…'.

At the present time in Japan, tissue engineering and regenerative medicine are almost synonymous with autologous [stem] cell treatments, and it is stem cells, to be precise the use of embryonic stem cells, that is driving most of the regulatory and ethical impulse at the moment.

6.2. Reimbursement

6.2.1. Ministry of Health, Labour and Welfare and Reimbursement

Reimbursement in Japan for medical products, medical devices, surgical procedures and the use of medical equipment is regulated by MHLW under the Health Insurance Law and the National Health Insurance Law. MHLW sets reimbursement prices for approved products and procedures.

Reimbursement decisions are related to the cost of the product under consideration or a cost for a hospital procedure that is based mainly on length of stay, and not to the cost-efficiency, cost-reduction or benefit-increase produced by use of the product or procedure. Where a product is imported, the base price for reimbursement calculation is a 'foreign average price' that is below an achievable Japanese market price. The MHLW is now considering moving its reimbursement calculations towards a DRG type of system (diagnosis-related groups) that assigns reimbursement value independently of the actual length of time or complexity of treatment at one hospital compared with another.

Health cover provision in Japan is similar to that in UK. It is provided through both public and private routes. Public health insurance contributions of ¥40,000 (£220) per annum are collected from 45.5 million individuals. In addition, employees pay via the Health Insurance Society (32.6 million, mainly in larger companies) or the Government-Managed Health Insurance scheme (37.6 million, mainly in SMEs). The money is pooled into payment agencies such as the Social Insurance Medical Fee Payment Fund. Basic reimbursement covers about 80% of medical and dental fees, up to 100% for the elderly, although some products and procedures are excluded from reimbursement and there is a strong trend to further reductions and exclusion. Where an approved product or procedure is partly-reimbursed, there is co-payment from the patient. Private health insurance schemes are operated by nearly 2000 health insurance societies managed by large corporations and act to offset the impact of co-payment and non-reimbursed treatments.

This system has been under increasing stress. MHLW has recognised the need for major, though painful, reforms. The first moves to keep official prices for medicines and devices as low as possible took place in the early 1990s, through 6-monthly pricing reviews. More recently, the healthcare budget for 2002 required a cut of ¥280 billion (£1.6 billion). This was achieved by a number of measures that have continued into 2003, including:

- Reducing the approved prices of products.
- For the first time, cutting reimbursement of technical fees.
- Reforming structural aspects of the health insurance system including the premium rate for government-controlled health insurance, increased from 7.5% of salary to 8.2%.
- Reducing reimbursement for repeat hospital visits and out-patient procedures.
- Increasing the co-payment charges to salaried workers from 20% to 30% of the cost of medical services as from April 2003.
- Increasing co-payment for the elderly to 10%.
- Encouraging generic products by cutting reimbursement of off-patent original products and branded products for which generics have become available, as well as increasing the per-prescription payments to pharmacists for generic switching.

Such moves restrict growth and innovation in the medical sector, which is in any case more responsive to MHLW controls than to changes in GDP, and the domestic prescription drug market has remained at approximately the same level of ¥6 trillion since 1995. The Japan Pharmaceutical Manufacturers' Association argues that MHLW has applied its reimbursement

decisions arbitrarily and without a consistent rationale[13]. Others point to serious structural impact on sectors, such as psychiatric care, that MHLW is meant to be supporting.

There is a Special Healthcare Expenditure System, in which size of hospital and use of approved products and procedures not yet on published reimbursement lists are taken into account. Long-term hospitalisation has also been added to this system, so that only 95% of the basic costs can be reimbursed, raising the cost of longer-term hospital stays immediately by ¥50,000 (£280) per month; by 2004 MHLW has set the limit at 85% reimbursement. There appears to be some scope for a mixed system in which some elements are eligible for reimbursement and others are paid privately, which will assist the development and uptake of complex treatments such as tissue engineering.

Medical technology, into which category some cell or tissue-based treatments or procedures may be assigned, is reputedly subject to very slow decision-making on reimbursement listing, especially when products are innovative[14]. Individual products and procedures are often very expensive, leading to cost-restrictions on clinical trials; currently, reimbursement for clinical trials samples is not allowed by MHLW.

6.2.2. Reimbursement and Tissue Engineering/Regenerative Medicine

The impact of reimbursement policy on cell and tissue-based treatments is difficult to predict. The currently foreseen uses of regenerative medicine, based as they are on somatic stem cells mainly harvested from the bone marrow, require at least two interventions – one to harvest the cells and the other to reintroduce them in the appropriate place. The second intervention will be equivalent to a standard procedure and there is no reason to suppose at this point that MHLW will offer reimbursement incentives to carry out such procedures simply because innovative regenerative medicine is involved. For example, Osteogenesis, working on cell- and tissue-engineered repair of periodontitis, noted that in the current situation, some dental procedures are reimbursable and others are not. The proportion of non-reimbursable procedures is likely to increase, including dental implants. The clinical target for cell- or tissue-engineered products and procedures in this case may well not be 30 million people in Japan suffering from periodontitis and severe pyorrhoea, but the 200,000 very high income individuals for whom lack of reimbursement is no barrier to treatment[15].

6.3. Ethics

6.3.1. Introduction

Public information or education and ethics are strongly interlinked, because ‘ethics’ is a societal construct. There has long been a strong sense of public education in Japan’s Science and Technology programmes, to which the public has responded[16]. However, there is seen to be still a need to educate and inform the public about new technologies and scientific innovation. The Second Science and Technology Basic Plan, established in March 2001, expresses a ‘Nation’s Vision’ of the creation of wisdom, vitality from wisdom and a sophisticated society. The latter implies an educated society and one that is capable of dealing with ‘ethical aspects’ of technology development. The Plan sets out a number of reforms to the system of science and technology, which address knowledge density, knowledge transfer, reform of the national innovation system and societal accountability (‘Science Technology and Society, Ethics &

[13] source: Japan Pharmaceuticals Manufacturers’ Association, 2002.

[14] M A Searing, AdvaMed USA, Promoting True Healthcare Reform in Japan 2003.

[15] Figures reported by Professor Ueda, Nagoya University, UK Science Mission April 2003.

[16] At BioExpo in Osaka in 1989, one of the best-attended stands was a demonstration of biotechnology in plants, for example, as MLE experienced; and the use of animals for research is accepted by the public in Japan without the kind of demonstrations associated with the UK.

Responsibility')[17]. Incidentally, this plan also calls for promoting public literacy about intellectual property and IP rights. The National Biotechnology Strategy (NBS Meeting December 2002) has public understanding as one of its five main themes. The two elements of this theme are biosafety & bioethics, and education for younger people.

The guidelines for derivation and use of hESCs state that, in principle, the outcomes from the use of hESCs shall be disclosed to the public and, at the same time, the fact that the work has been carried out according to the guidelines is to be confirmed publicly. They also require informed consent to be in place. The revised Pharmaceutical Affairs Law also requires patients receiving any cell- or tissue-based products to have given specific informed consent for the treatment or procedure. This is something that in any case will be essential if the goal of long-term or life-time traceability is put in place.

6.3.2. Bioethics in Practice

Each Ministry of the Japanese government has a 'Deliberation Committee' that looks at ethics relevant to their work, and then recommends whether any legislation, guidelines or other kind of action is required. According to MEXT[18] , review of these issues is the norm; the Law on the Regulation of Cloning Technology will be reviewed in 3 years' time after discussion on the embryo aspects.

The ethics of the use of cells and tissues in the R&D context are mainly dealt with by the guidelines issued by MEXT or MHLW. However, it is notable that, in accord with other bodies round the world, the rights of the embryo to be treated ethically are enshrined in law. The guideline on deriving and using human ESCs states that 'Human embryos and ES cells shall be handled carefully and conscientiously without violating human dignity, taking into consideration that a human embryo is the beginning of a human life and that human ES cells have the potential to differentiate into any type of human cell.'[19] Only married couples may donate surplus embryos[20].

The human ESC Guideline defines Deriving Institutes (DIs), which are approved by MEXT to carry out the work of receiving embryos, isolating ESCs and differentiating cell lines from them, for supply to the institutions carrying out research, the Utilizing Institutes (UIs). An institute will not be accepted as a DI or UI unless it has established rules on ethical and technical matters to be observed in derivation and distribution of human ES cells and sets up an Institutional Review Board (IRB)[21]. The IRB's role for both DI and UI[22] is to review the overall ethical and scientific propriety of derivation or utilization protocols and provide advice on amendments and improvements. In the case of the DI IRB, one of its members must be qualified to give opinions on bioethics and its proceedings must be publicly disclosed[23].

A derivation protocol is submitted by the DI, or a utilization protocol by the UI, to the appropriate IRB for initial comments and revised if necessary, then submitted to MEXT for approval. MEXT consults the Bioethics and Biosafety Committee of the Council for Science and Technology for recommendation on acceptability of either type of protocol.

[17] T Ichikawa, METI, 'Recent Development of Japanese Industrial Science and Technology Policy', to MLE November 2002

[18] UK Science Mission visit April 2003.

[19] Article 3 of the Guidelines for Derivation and Utilization of hESCs.

[20] Article 22 point 1 *ibid*.

[21] Article 9 points 2-3 and Article 30 points 2-3 *ibid*.

[22] Article 33 *ibid*.

[23] Article 13 *ibid*.

Acts specifically prohibited include creation of an individual from hESCs by implantation of a derived embryo into human or animal uterus, introduction of hESCs into a human embryo or foetus and production of germline cells from hESCs [24],[25].

The meetings of the MEXT Committee reviewing stem cell work and research proposals are open to the public and media and the results of meetings are reported on a web-site.

The general supply of human tissues and cells has been dealt with under two initiatives:

- The Human and Animal Bridge Discussion Group (HAB), which imports and supplies human tissues to university researchers and collaborating companies.

- The Health Science Research Resources Bank (HSRRB), an organisation under the Human Science Foundation of Japan, through which Japanese pharmaceutical companies obtain human tissues for research and development; the HSRRB acts as the clearing house for material from collaborating hospitals and started work in 2001 in Osaka.

It is the responsibility of these organisations to assure that obtaining the cells and tissues has been carried out according to an ethical framework.

Continued research may of course throw up findings that have ethical implications. The Institute for Frontier Medical Science at the University of Kyoto has pointed out that the fusion of thymocytes and ESCs produces tetraploid cells, chimeric embryos and teratomata. In this case, further research is needed to decide whether the risk of this occurring is consistent and high enough that the procedure should be banned on ethical grounds.

6.4. Regulation

6.4.1. Ministry of Health, Labour and Welfare and the Pharmaceutical Affairs Law

The [old] Ministry of Health, Koseisho, was responsible for the regulation of medicines and medical devices under the Pharmaceutical Affairs Law (PAL). For most overseas companies and trade organisations, this law and the way it was applied were seen as favouring indigenous companies over foreign companies. Although foreign data has been accepted since the mid-late 1980s, local trials were demanded, often in circumstances where there was no scientific justification. However, there were problems in fulfilling this demand because of the rather stringent regulatory requirements and the relative lack of good clinical research facilities in Japan.

Koseisho took full part in the ICH (International Conferences on Harmonization) process and, as a result, the unification of regulatory procedures and standards in the three major blocs, US, EU and Japan, was agreed by the government in 1993. Implicit in this was a review of regulatory procedures and adaptation to internationalisation of data. Through its intimate involvement in ICH at working party and plenary levels, Koseisho was able to continue the process of accepting overseas data and foreign licence applications on the same basis as local company submissions. It is now not necessary to carry out studies in Japan unless there is a fully-justifiable scientific or medical reason for this.

Major revisions to the PAL were enacted in July 2002. The aim is to achieve unified safety regulations across categories of products including biologicals and newer advanced biological products, such as tissue engineering and gene therapy. The new PAL is also supposed to

[24] Article 27 *ibid*.

[25] According to Professor Nakatsuji of IFMS Kyoto, theoretically, human therapeutic cloning is not illegal but there is a moratorium until guidelines are issued, expected in about 3 years.

facilitate entrance into the market for start-up companies that do not have production facilities in Japan, mainly by allowing outsourcing of manufacturing[26].

The main elements of this revision, as set out by MHLW[27], are:

- Possibility for outsourcing of production.
- Obligation on outsourcing companies to establish quality control divisions.
- Inclusion of ingredients from human or non-plant biological sources, recombinant proteins and gene therapy vectors on the list of 'Biological Products'
- Further division of biologicals into 'Specified Biological Products' and 'Biological Products'.
- GMP as the basis for all biological products.
- Additional requirements for Specified Biological Products including donor eligibility criteria, elimination of disease risk, QC of manufacturing process, more strict attention to labelling and traceability systems (in case of problems).

MHLW recognises that there is a difficult situation in Japan with respect to clinical trials. Factors include low incentives for patients to be involved in trials, low incentives for Clinical Trials Associates and clinicians working on trials and too few centres to carry out studies to GCP. There is also still a requirement for a Chief Investigator who is Japanese, whether or not the data package has been generated outside Japan.

In the area of medical devices, into which category some tissue-engineered products and cell processes may fall, it seems there is still some element of antipathy to foreign applicants. The ICC system (In Country Caretaker) is being revised from April 2003. This used to allow foreign manufacturers to register products in their own name, whilst using a local importer for distribution, by appointing a local company to act in regulatory matters. The revision announced in August 2002 by MHLW requires a local representative company to be appointed, which must be capable of compliance with the relevant GMP, warehousing, testing, tracking and Post-Market Surveillance requirements. The transition period for this is 2003-2006, and it may well affect foreign companies who want to establish cell-processing equipment and procedures in Japan.

The Kobe Medical Industry Development Project, promoted by the Foundation for Biomedical Research and Innovation (FBRI) and financially supported by the City of Kobe, the Government under its Urban Renaissance Program and Kansai prefectural government, includes the Institute for Biomedical Research and Innovation (IBRI). IBRI houses a State-of-the-Art clinical research facility. Kobe justifies this as follows: "With the introduction of new international regulations[28], domestic clinical trials are declining overall, and an environment that is not very conducive to research and development has emerged. Creating an environment that makes it easy to conduct clinical research can be expected to improve the level of medical research, promote the industrial applications of research findings, and accelerate the dissemination of medical services."[29] Amongst other comments from the same source, one stands out:- "The field of cell therapy and tissue engineering is one of the promising fields of medicine, which needs a system for industrialization."

[26] MHLW has noted that by 2002 there were about 3,000 pharmaceutical start-ups in USA but only about 100 in Japan.

[27] UK Science Mission visit, April 2003

[28] This refers to the ICH (International Conferences on Harmonization), which have produced internationally-accepted guidelines stating that, if a trial is performed to GCP (Good Clinical Practice) anywhere in the world, its results should be acceptable to a regulatory authority anywhere else; in practice, this means that the Japan MHL has to accept trials carried out in USA and EU and can demand local trials only if there is a scientific need.

[29] The Kobe Medical Industry Development Project issued by the City of Kobe and FBRI, March 2002.

6.4.2. Regulation and Cell - or Tissue - Engineered Products

The MHLW has responded to innovation in this area by releasing Guidelines from time to time, including guidance on gene therapy, before 1997, a notification on cellular/tissue based products in 1999/2000 and standards for cellular/tissue based products in 2001. As a result of involvement in the ICH process, MHLW has been able to respond fairly rapidly to guidance documents and points to consider coming from the FDA[30]. The revision of the PAL is in many ways a response to the possibility of transmitting unknown infectious agents through new medical technologies. The critical issues for cell- or tissue-based products are the absolute requirement for GMP, strict qualification of source to exclude known pathogens and minimise the risk of disease transmission, validation of the ability of the process to exclude contamination and traceability of product use (which implies long-term if not life-long tracking of recipients[31]). The MHLW's approach in this respect is strong common-sense, especially the recognition that the safety of individual products is affected by the profile of individual donors, where material is harvested from many unspecified persons or animals.

The MHLW regards living cell- and tissue-engineered products as having characteristics of both devices and pharmaceutical products; although it seems that MHLW categorises tissue-based products as devices and live-cell products as 'pharmaceuticals' (i.e. biological products), the regulators would like to see the same degree of safety requirements applied to both. At the moment, dermal and cartilage products are classified as devices. Within the new system, for Biological Products, allogeneic products will be regulated as higher-risk Specified Biological Products but autologous products will be classed as mainstream Biological Products.

In the case of the use of autologous cells, the entire process can take place within a hospital, if it has facilities for cell culture. It is difficult to see how this can be 'regulated' within a framework that is normally expected to deal with products 'placed on the market'. We can envisage that a company gets involved by offering commercial services for isolation, purification, differentiation, enrichment and delivery of cells. In such a case, the company is commercialising a 'product' which is actually a combination of a processing method and a delivery method. The fundamental issues are of course GMP and safety and such a company could be regulated through a type of biologicals establishment licensing procedure, coupled with regular inspections. But this approach is not in place yet, either in Japan or the EU. The situation in the UK at the moment, for example, is that autologous cell procedures taking place entirely within the private sector are completely unregulated. Within the NHS, they are also unregulated, but there are guidance documents covering procedures such as harvesting, expansion, storage and re-implantation. MHLW proposes that each person, company or organisation involved in the generation or use of a product should have their legal responsibilities clearly laid out within a post-marketing surveillance system, so that adverse events can be properly tracked and liability assigned.

Given that the source of material is the patient's own cells, the collection of these should require no greater controls than the collection of blood for transfusion or bone marrow for transplant. Indeed, if innovative approaches to sourcing and de-differentiating adult cells are achieved, the collection method may be no different from taking a mouth-swab. Nevertheless, the patient's own cells may be exposed to contamination during harvesting or processing, or unsafe development (such as expression of cancer-promoting genes) during expansion. Then, the delivery methods should involve the use of approved carriers or generally-accepted

[30] In Mr Hayashi's presentation, no reference was made to EU/CPMP documents – currently, the EU is still discussing how to regulate products containing human cells or tissues, following a public consultation that began in July 2002, and a Proposal for a Directive on quality and safety standards for the procedures involved in cell- and tissue-based treatments, COM(2002)319.

[31] MHLW refers to GPMSP, Good Post-Marketing Surveillance Practice, in this context.

surgical/clinical procedures. It is clear that the whole process should be managed through a defined Quality Management system. Though there is no 'commercialisation' in a wider sense, there is a commercial relationship between the hospital or GP providing the patient's material, the company carrying out the processing and validation of safety and utility, and the hospital or GP that then returns the completed 'product' safely and effectively so that it repairs the patient. MHLW envisages, for Specified Biological Products, that a Risk and Benefit informed consent system is in place for the decision-to-use.

MHLW will be discussing its proposal for the management of cell- and tissue-based devices at the next meeting of the Global Harmonisation Task Force in July 2003. The MHLW has made a firm statement that they want to avoid inhibiting research by over-rigid regulations[32]; it remains to be seen what this means in practice.

6.4.3. Regulation and Embryonic Stem Cells

At this stage, the boundary between ethical constraints and regulation is rather blurred and it is mainly human ethics and research ethics that are driving the management of ESC use. The National Council for Science and Technology set out its thinking on ESCs and their uses in March 2000, in the 'Report on the Human Embryo Research Focusing on the Human Embryonic Stem Cells'. This was followed by a law banning human cloning, but allowing research use of embryos, in November 2000 and publication of the National Council's draft 'Guidelines concerning the derivation and utilization of human embryo stem cell' in December 2000. ESCs can be isolated from spare embryos from IVF, subject to informed consent and some time limitation, but cannot be re-implanted into humans (thus ruling out experimental clinical use). Given that most of the research in Japan has focused on mouse and monkey stem cells, the ability to move ahead with human ESCs has been a very important principle.

The use of ESCs in Japan is still regarded as a research tool and therefore controlled not by the MHLW but by the Ministry of Education (MEXT). MEXT adopted the approach of the Council for Science and Technology and issued 'Guidelines for Derivation and Utilization of Human Embryonic Stem Cells', which came into force on 25 September 2001. So far, one derivation programme operated by Professor Nakatsuji at IFMS University of Kyoto and 6 utilisation programmes have been agreed by MEXT. Prof Nakatsuji's programme began in January 2003.

Institution	Research	Source of ESCs
Keio University	Neural cells	ESC International, WiCell
Kyoto University	Identification of human vascular progenitor cells and vascular regeneration	ESC International
Shinsyu University	Liver and heart muscle cell regeneration	WiCell
Tanabe Seiyaku	Collaboration with Kyoto University	ESC International
University of Tokyo Hospital	Haematopoietic stem cells	WiCell
University of Tokyo, Institute of Medical Science	Haematopoietic stem cells	WiCell

Table 6-1 Approved research projects using ESCs

Source: Tanabe Seiyaku April 2003

[32] Hayashi, MHLW, to UK Science Mission, April 2003.

The guidelines include the following features:

- limit ESC derivation and use to basic research, ostensibly prohibiting clinical research and medical/surgical use until specific regulatory instruments are developed
- nevertheless, allows the use of ESCs to develop new methods of diagnosing and treating diseases
- prevents commercial distribution and sale of ESCs, which have to be provided free of charge[33].
- allows use of ESCs from outside Japan only if MHLW considers that the controls on their derivation are equivalent to those in the Guideline.

Some adjustment of this approach will be required if and when the prospects for commercial ESC-based products become more optimistic.

6.4.4. Comments from Companies and Organisations on Regulation in Japan

According to Professor Ueda, the regulatory framework in general is a barrier for start-ups in new areas of healthcare. In this area of cell-and tissue-based products and procedures, the regulatory situation is still somewhat fluid, but definitely favours autologous products over allogeneic. The current guidelines for human embryonic stem cells do not recognise how advanced the situation is with regard to clinical trials and research, and effectively exclude the use of hESCs in human patients. Because of these two factors, near- and mid-term activity will almost certainly concentrate on the use of somatic stem cells, mainly from bone marrow, that have been persuaded to differentiate into different types of progenitor cells. Autologous cells are already in use in clinical work in orthopaedics, dentistry and nerve regeneration. There is apparently some clinical work underway on allogeneic therapy using cells of bone marrow origin. The lack of clear guidelines and legislation at this stage is certainly hampering commitment by companies to researching and developing ESC-based and allogeneic products. In addition, as one comment put it, though MEXT drives SC research, MHLW is the regulator and has not properly caught up; the Council of Science reports directly to the PM, so this should mean that Ministries talk to each other.

Companies that want to move ahead in this area have decided to exploit autologous cell methods first. This is certainly the approach favoured by Stem Cell Sciences KK, who believe that there are bioethical questions concerning human ESCs that have not been fully-answered and the government still has much to do in developing guidelines. It is seen as likely that the use of somatic stem cells, even allogeneic, will be regarded as a medical device; culture techniques that use serum-free media will make approval easier[34].

Tanabe notes that, because there are currently no regulatory guidelines on preclinical or clinical work with ESCs, it is not at all clear what work will be needed to satisfy safety requirements or how clinical trials are to be structured. In these circumstances, the company has a 'wait and see' attitude and will continue its work with monkey ESCs. Tanabe also sees a likelihood that the Government will handle SC products/procedures in the same way as the highly-controlled transplant chain – perhaps with a single organisation or a consortium that establishes and provides ESCs into a variety of products or procedures; thus the Government will control the supply and the role for companies will be to add IP or know-how to the actual products. However, there are challenges to overcome, especially in the history, characterisation and testing programme for ESCs, that could prove big enough to derail commercialisation of ESC products.

[33] though 'necessary expenses' can be reclaimed.

[34] Stem Cell Sciences KK has taken a licence to serum-free media developed by RIKEN-CBD

Osteogenesis is an example of a start-up that is actively seeking to develop cell-based products and it expects to spend much money on satisfying regulatory requirements. Because of the way in which MHLW has redefined what falls within the Pharmaceutical Affairs Law, even if the company calls what they are doing a 'process' it will still be regulated under PAL. MHLW's position at the moment is that the autologous procedure and the company's product should be regarded as a medical device. It is expected that MHLW will add Guidelines for Cell Processing to the Medical Devices regulations; however, in the near future MHLW will consolidate the Medical Products and Medical Devices regulations and it is most likely that GMP will then form the basis for control of cell products. Osteogenesis believes that big hospitals should be able to build in systems to comply with any MHLW controls on this type of process and procedure. This might be a significant disincentive for further commercial activity in this area, if the entire process can take place within the hospital setting.

7. Regional Developments and Biotechnology Clusters

This section explores the Japanese Government's national and local initiatives for the support and promotion of the bioscience industry in Japan. In particular the measures enacted to encourage spin-out company formation and the attraction of foreign direct investment (FDI). The Japanese Government has identified bioscience as an area of potential future economic growth, predicting that the market will be worth 25 trillion yen by 2010. This growth is partly predicated on increased demand due to a rapidly ageing population. As a result, the Biotechnology Strategy Council drew up guidelines in December 2002 to promote biotechnology.

7.1. Strategy

The Japanese Government's Biotechnology Strategy is based on three basic principles, with fifty courses of action and two hundred practical action plans, which can be summarised as follows:

7.1.1. Principle One – Development of R&D Capabilities

- Development of R&D Capabilities
- Increase in government expenditure for biotechnology -related R&D programmes
- Strategic budgeting and efficient implementation
- Developing human resources to support biotechnology

7.1.2. Principle Two – Improvement of Commercialisation Environment

- Provide incentives for commercialisation and develop the necessary systems and rules
- Nurture leading companies, revitalise start-ups and promote cooperation between industry, academia and government
- Develop R&D infrastructure and systems connecting research with business, create an IP strategy and industrial centres

7.1.3. Principle Three – Promotion of National Understanding & Support

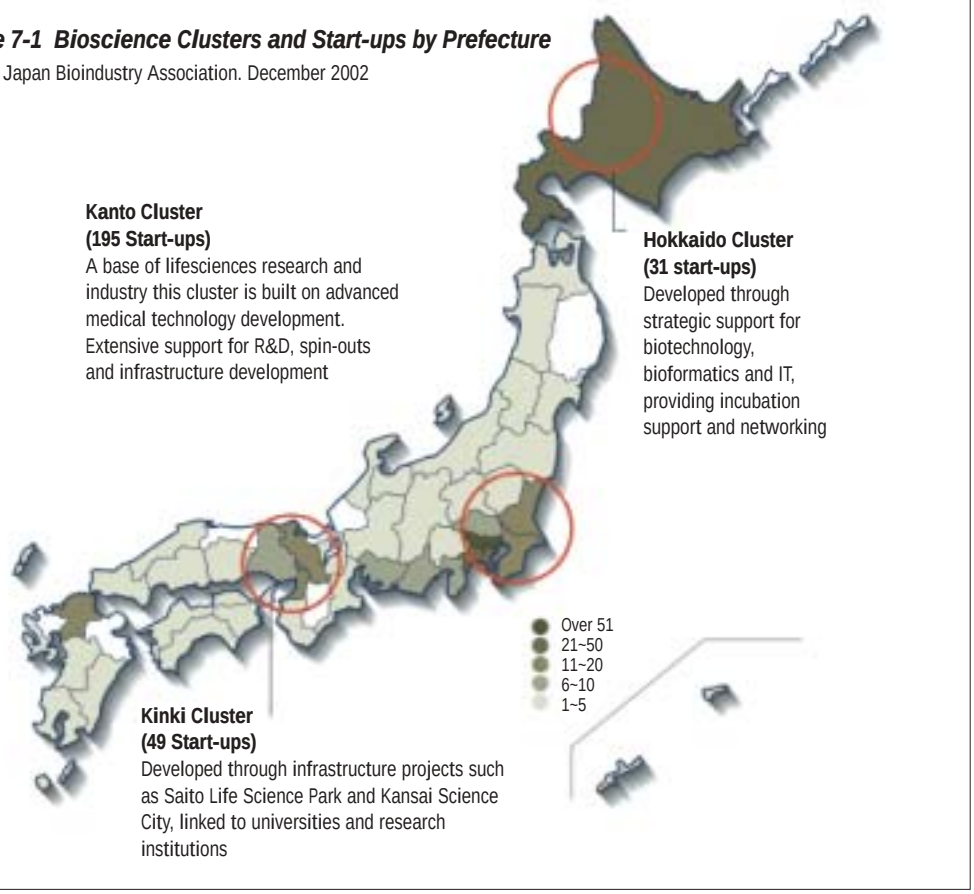
- Improvement of disclosure and supply of information (with the public)
- Demonstrate the Government's solid stance toward safety and ethical issues in a visible manner
- Upgrade school and adult education in biotechnology

Despite being drawn up as recently as December 2002, this strategy already seems to paying dividends with 300 bioscience start-ups being claimed by Spring 2002. An additional catalyst for this spin-out activity seems to have been the removal of rules in 2000 that had hitherto prevented university professors from serving as company executives. It is claimed that this step 'greatly improved the environment for commercial exploitation of world-class technologies developed by state-run universities'.

The government's plans are designed to create 1,000 spin-out bioscience companies by the end of fiscal 2004. The budget for fiscal year 2003 is 72 billion yen (£380 million @ ¥190).

Figure 7-1 Bioscience Clusters and Start-ups by Prefecture

Source: Japan Bioindustry Association. December 2002



7.2. Financial Support

Between 1995 and 2000 the Japanese government doubled expenditure related to life sciences and now intends to grow this expenditure further, focussing the spend on basic research, building world-class research facilities for strategic distribution of resources.

There are increased tax incentives for R&D – increased from 15% of the increase in R&D spending from the previous year, to 12% of overall R&D spending. This applies to all industries and is expected to translate to 100 billion yen in tax cuts for the biotechnology sector.

It is worth noting that there are also various other measures that also support the development of infrastructure and company development.

For example Osaka Prefecture, Kobe City, Ibaraki City, to name but three have extensive incentives schemes to promote the development of industry in those locations. These schemes have been stimulated by the creation of laws designed to balance the high concentration of businesses in Tokyo, and redevelop the Kobe area after the Great Hanshin Earthquake of January 1995.

In Osaka Prefecture the levels of financial support can be summarised as follows:

- Capital subsidies for lease or freehold purchase of land
- Subsidy ceiling raised to 1 billion yen for bioscience, IT and nanotechnology
- Maximum 50% R&D subsidies
- Property tax incentives
- Low interest loans for capital equipment and operating capital

In Kobe City the incentives are as follows:

- Property tax reduction by 50% for 3 years
- Real estate acquisition tax reduced by 50%
- 60,000 yen – 100,000 yen subsidy for employing residents from Hyogo Prefecture
- Feasibility study subsidy – 75% (max 3 million yen) for domestic companies, and 92% (max 5.5 million yen) for overseas companies
- Office rent subsidy of 2,500 yen/m^2/month (max 5 million yen per annum)
- Additional subsidy of 1,000 yen/m^2/month for three years (max 36 million yen) for foreign companies who take space in the Kobe International Business Centre
- Subsidy 10% of design & build costs (max 1 billion yen) until March 2007
- Subsidised loans up to 80% of capital expenditure

In addition to the above very comprehensive system of grants and financial incentives, there are various plots of land on the Port Island site that qualify for preferential rates and preferential loans. For example, a bio-medical business locating on the Port Island Second Stage Enterprise Zone would be eligible for a free land lease programme is they commit to 20 years, employ at least 50 people per 5,000 m^2 land or 100 people for 10,000 m^2, and 150 for 20,000 m^2.

7.3. Facilities

Within the overall strategy for the development of bioscience there is a project for the specific development of tissue engineering. Known as the Millennium Tissue Engineering Project, it runs from fiscal year 2000 to 2004 and has a budget of 10.8 billion yen. Within this project there are various sub-projects under the Ministry of Health & Welfare, Education Ministry, MITI and Science & Technology Agency.

These are detailed in report compiled by the British Embassy Science & Technology Section dated March 2001.

In summary however this Project has already created several centres of excellence that can serve as either generators of spin-out companies, or as hubs for the location of companies wishing to exploit technologies or engage in collaborative research.

For the purposes of tissue engineering the institutions and universities that are participating in the Millennium Tissue Engineering Project are:

- Kitasato Universities and others, Tokyo Metropolis
- Tokyo University Institute of Medical Science
- Various Ministry of Health & Welfare institutes including the National Cancer Centre, Tokyo
- Okazaki National Research Institutes
- J-TEC
- Institute for Frontier Medical Sciences, Kyoto University
- AIST Tissue Engineering Centre, Osaka (TERC)
- Osaka University
- Kobe City – Advanced medical Research Complex, Kobe Port Island
- Regenerative Medical Research Centre, Kumamoto University

In addition to these facilities, there are a number of science parks being established across Japan that can accommodate bioscience start-up companies of various disciplines and who also offer business incubation support, financing and mentoring.

7.4. Cluster Development in Kobe

The Mission looked in particular at the developments in Kobe and the activities there for cluster development.

As mentioned above, the Kobe area was already the beneficiary of special assistance measures following the Great Hanshin Earthquake. The additional measures that were put in place by the Japanese Government following the Biotechnology Strategy Council decision in December 2002 to promote biotechnology have served to strengthen the development of the Port Island Development, in particular for the support and development of Tissue Engineering and the attraction of FDI.

The Port Island Second Stage development covers an area of 390 hectares that is being developed as follows:

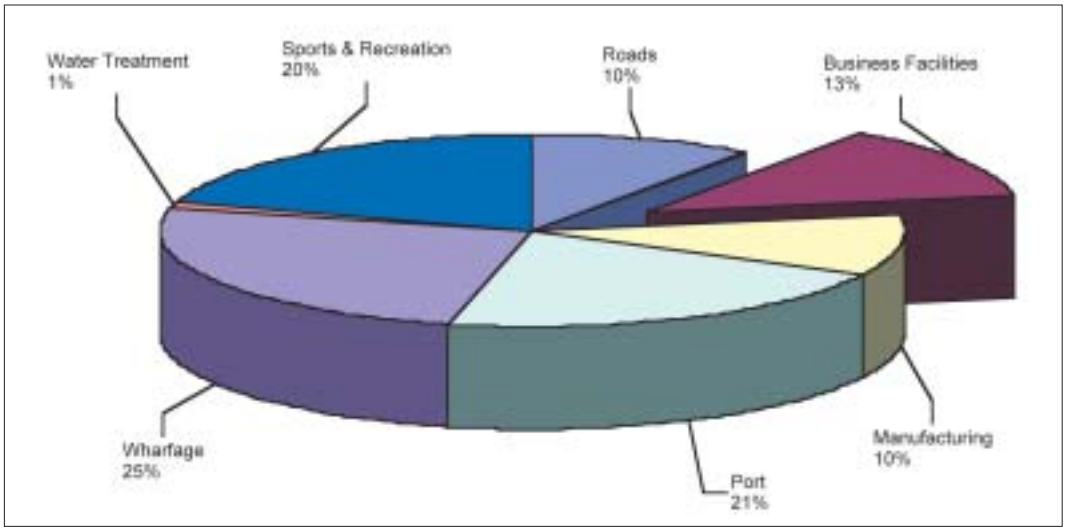


Figure 7-2 Port Island Second Stage, land usage (hectares)

The Port Island Project is projected to run until 2005, culminating with the opening of Kobe Airport – at this stage it is unclear whether further support will be available after this date, but already the extent of development is impressive and there is a clear impression that financial support will continue beyond 2005.

Facilities that have been established on the site are:

- RIKEN Centre for Developmental Biology
- Institute for Biomedical Research & Innovation
- Biomedical Accelerator
- Translational Research Informatics Centre
- Kobe KIMEC (Kobe International Multimedia Entertainment City) Centre
- Kobe International Business Centre (KIBC)
- Kobe Incubation Office

The strategy for developing a bioscience cluster is centred on R&D and the medical industry. The Institute for Biomedical Research and Innovation (IBRI) is seen as the focus for this activity,

supported by business incubation services at the Medical Business Support Centre and by skills development at the Training Centre.

The approach taken by Kobe was to establish a series of working groups under the auspices of The Council for Science & Technology as indicated in Figure 7-4 below. The various working groups mentioned in that group were established between 1999 and 2000 so are well established. They bring together expertise from over 60 companies including names such as Takeda, Fujisawa, Tanabe, Dainippon, Shionogi, Yamanouchi, Daiichi, Chugai, Banyu, Sankyo, Eli Lilly and Eisai; and 50 academics and medical doctors from the Kansai medical schools and local medical doctors association. In total over 370 companies contribute to the working groups.

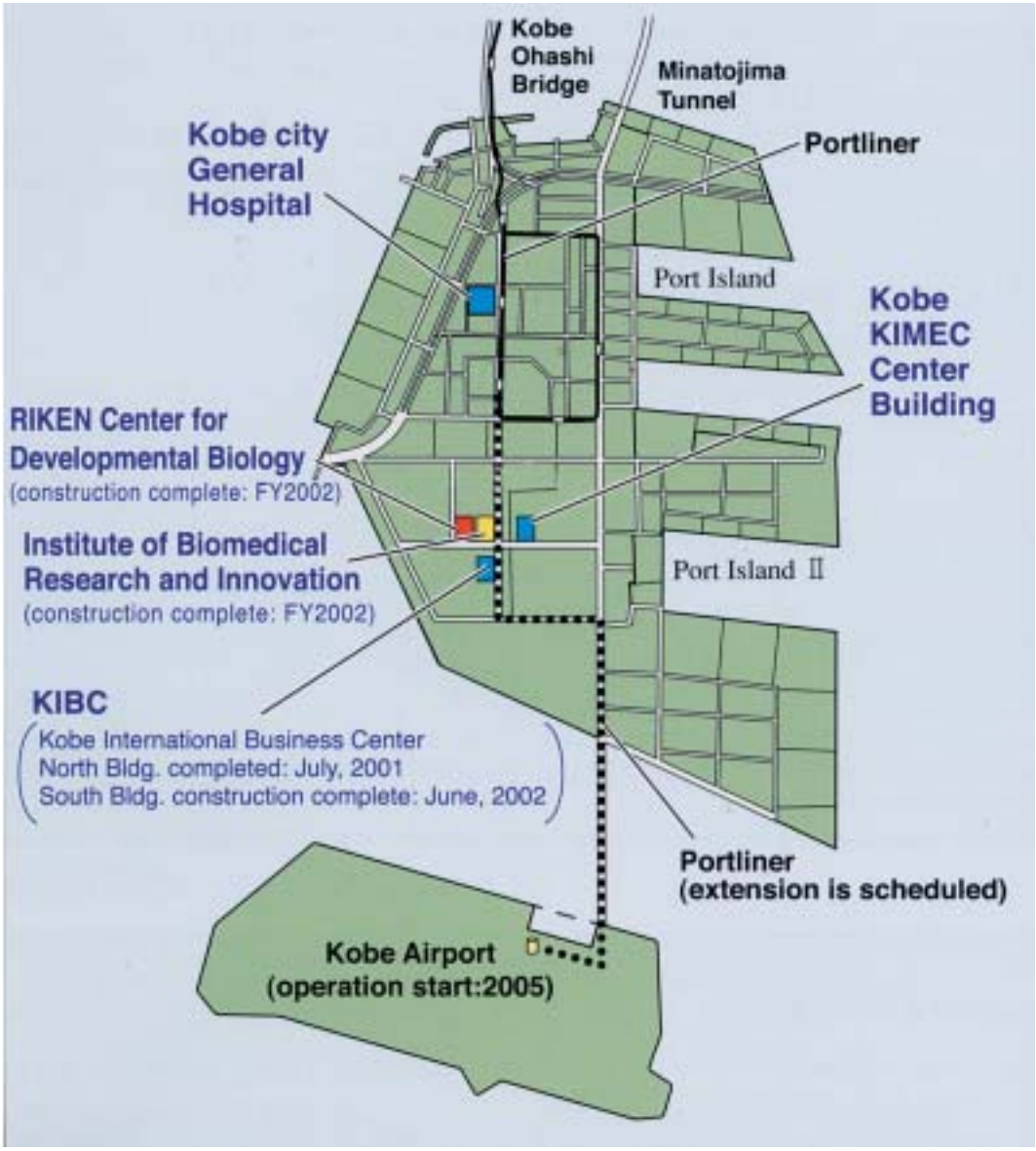


Figure 7-3 Port Island Project

The various facilities in the development currently accommodate 30 businesses, of which 15 are biomedical related. There is a total capacity for around 60 companies, will full support ranging from animal facilities, data centre for informatics, IT companies, cell processing

companies and business support facilities. In addition, it is planned to move the Kobe General Hospital from the north of the island to the location within the next 5 years. This facility will provide 1,000 hospital beds facilitating clinical trials and supporting large-scale clinical research.

An important part of the Kobe project for the purposes of incubation is the development of the Biomedical Accelerator (BMA). This is being developed at a cost of 4.6 billion yen funded by METI (1.8 billion yen), the City of Kobe (1.8 billion yen) and private companies (1 billion yen).

The objective of this incubation facility is to shorten the time from R&D to commercialisation through the provision of subsidised accommodation, business support and venture capital funding via the Kobe Biomedical Venture Fund.

The facility will occupy some 10,000 m^2 housing an animal and laboratory facility, data centre, radio isotope facility, cell processing centre and general laboratory facilities for biotechnology companies. Completion is scheduled for December 2003.

The entire project is projected to create 23,000 jobs and generate 530 billion yen in the Kansai region; of this 18,000 jobs will be in Kobe City generating 330 billion yen over the next 20 years. The overall aim is to create a Medical Industry City, linking research institutions and universities across Kansai, creating new companies, attracting overseas investment and creating collaborative links across the world.

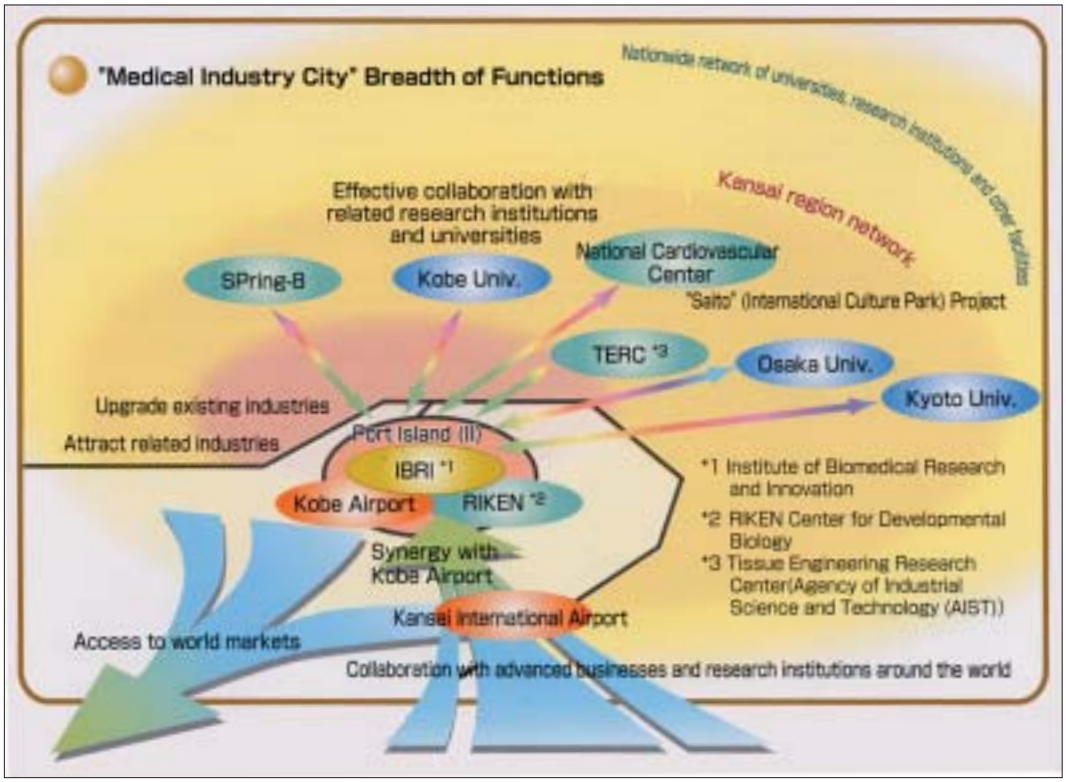


Figure 7-4 Kobe City Medical City Vision

7.5. Venture Capital

In addition to substantial investment in infrastructure, a venture capital fund has been established to support unlisted biomedical venture companies who seek to locate in Kobe. The fund, established by Sumitomo Mitsui Bank in January 2001 is structured as follows:

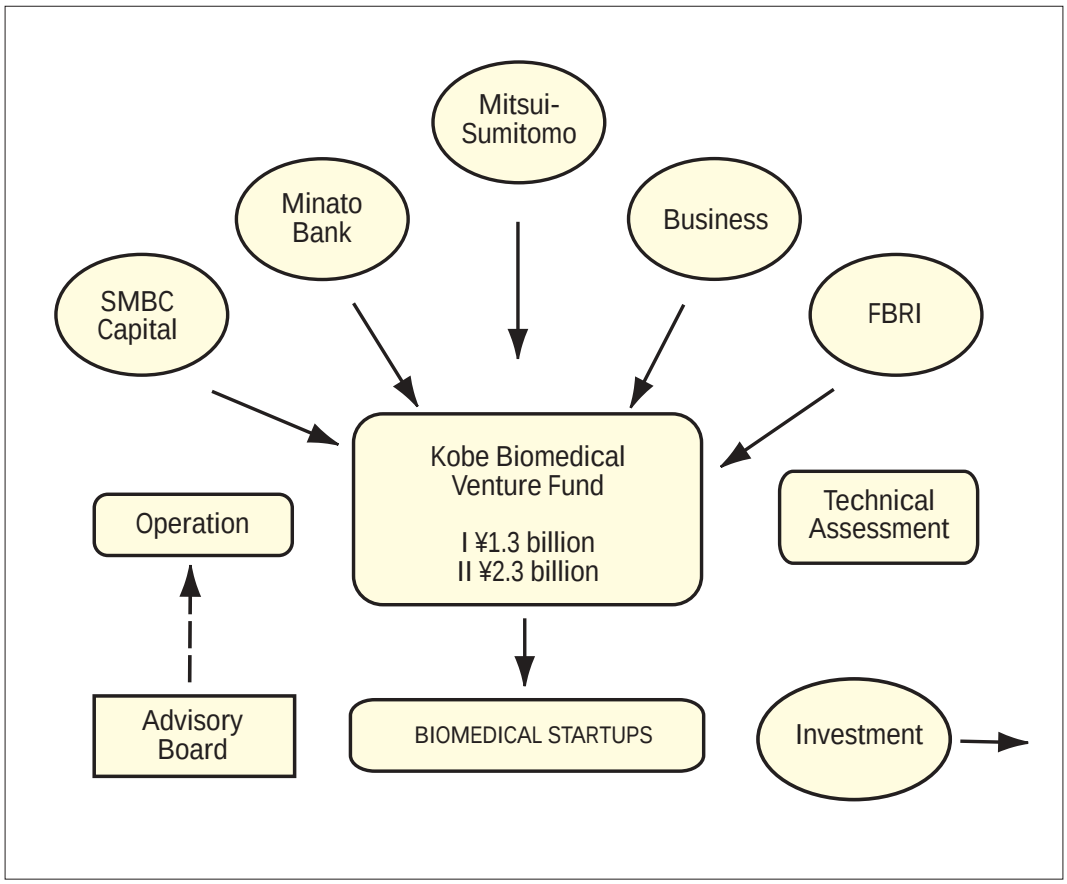


Figure 7-5 Kobe Biomedical Venture Fund – Scheme

Technical assessments are made by the Technology Assessment Board as follows:

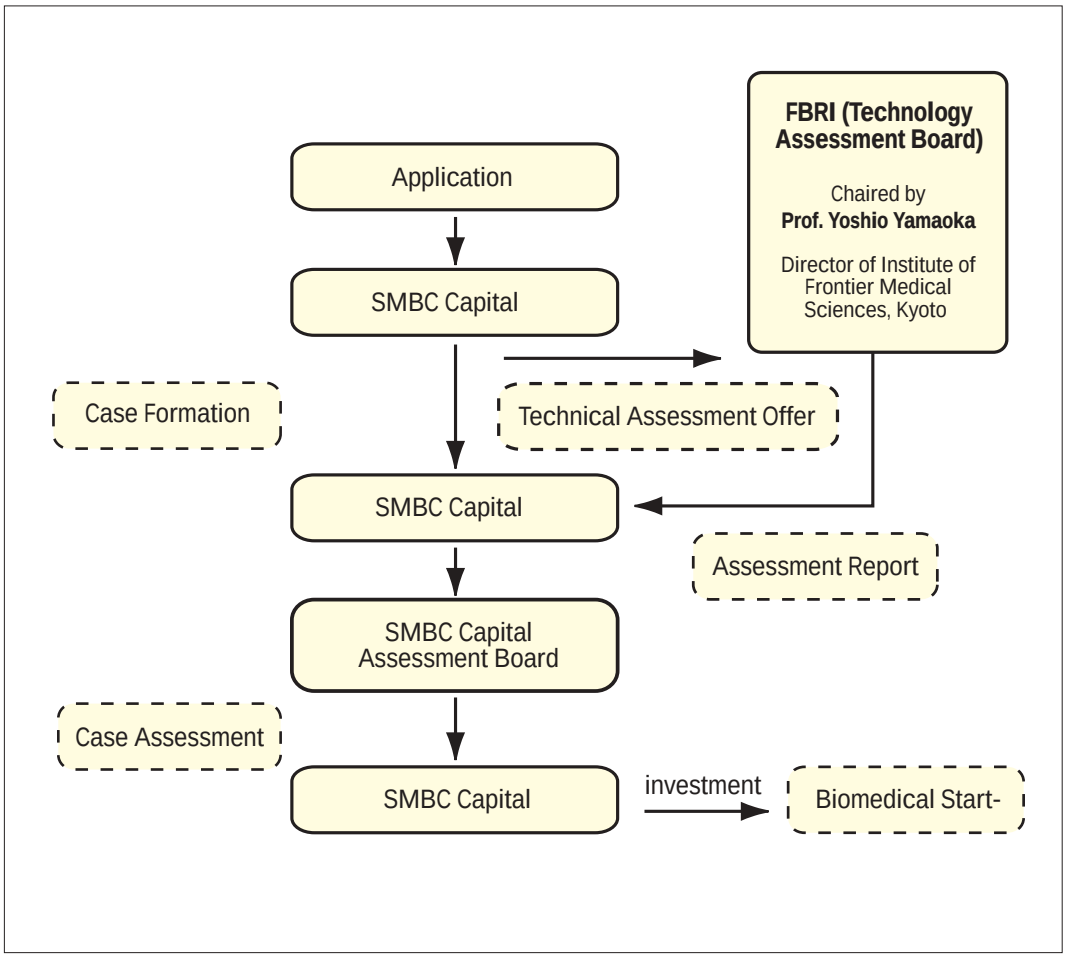


Figure 7-6: Kobe Biomedical Venture Fund – Investment Flow

7.6. Skills

The Kobe project will also make provision for the development of appropriate skills for the developing cluster. A Biotechnology Research & Training Centre is planned for completion by the end of fiscal year 2003.

A 3,000 m^2 building will house a centre for advanced human resource development specifically for the biotechnology industry. The building will also house the Kobe University Incubation Centre providing incubation support to businesses through joint research projects and specifically provide support for spin-out companies from Kobe university faculties of Medicine, Engineering, Agriculture & Science, and Science & Technology. This will be further supported by the Kobe University MBA programme.

The facility will be managed by Kobe University.

7.7. Comment

The extent of infrastructure development in Japan is enviable. The quality and quantity of facilities, especially in the Kansai area are of the kind that could attract investment from overseas and stimulate spin-out activity. However it is evident that the level of regional subsidy has already resulted in some instances where companies have been drawn from one region to

another, chasing the best levels of subsidy, rather than necessarily to the most appropriate location for their business. The evidence for this comment is based on one example given to the group and further research would need to be carried out to identify the full extent of this problem.

What is less obvious is the level of 'soft' business support, through mentoring and Business Angels for example. There is considerable evidence of VC activity and this appears to be accelerating, no doubt spurred by the government's activities to encourage company generation. The establishment of regional venture funds such as the Kobe Biomedical Venture Fund further bolsters VC activity.
There is evidence of a substantial number of start-up companies emerging from the universities, and that a number of these companies have been prompted by a number of particularly entrepreneurial professors. There is also clear evidence of the support from industry for these initiatives shown by the involvement of key sector companies in facilities and project management. What is less evident is where the professional managerial skills for these start-ups will be sourced, although linkages to the MBA programme at Kobe University may help in that location.

What is less clear however is how foreign direct investment will be attracted to Japan to increase competition and diversify the cluster that is emerging.

Whilst there are very substantial incentives available to companies who commit to long-term investment in areas such as Kobe, so far the foreign owned companies that have established a presence have mostly been as a result of partnerships with Japanese organisations. This may reflect the perceived difficulty of locating in a country as Japan. Kobe City however is making great efforts to provide 'soft' support to potential investors through the Hyogo Prefectural Government and with initiatives run by JETRO. The latter service will provide support on all aspects of location in Japan from office location to fund-raising, including day-to-day matters such as banking and visa application.

There would appear to be substantial opportunities in Japan, and these are being made easier to access by the concerted efforts of both regional and national governments.

Background material for this section was obtained from a variety of sources[35].

[35] Presentation from City of Kobe, April 2003, Invest in Japan, Volume 2, 2003, JETRO, Tokyo, www.jetro.go.jp/investjapan/, The Kobe Medical Industry Development Project, City of Kobe Foundation for Biomedical Research & Innovation (IBRI), March 2002, RIKEN Centre for Developmental Biology, Kobe, April 2002, Access to Success Kobe – A Guide to Industrial Sites in Kobe, City of Kobe, 2002, www.city.kobe.jp/cityoffice/39/040/english/index_e.html, Attractive Sectors – Biotechnology. JETRO Invest in Japan. March 2003, Tissue Engineering in Japan. Yasuko Otsuka, British Embassy Science & Technology Section, Toyko, March 2001, Kobe International Business Centre (KIBC). City of Kobe Urban Development Corporation, Various meetings with ministry representatives, academics and companies on the Mission

8. Conclusions

Overall the members of the Mission were impressed by the quality of the basic science that is underpinning Japan's tissue engineering programmes and the extent of government and institutional support for the emerging tissue engineering industry. There is no doubt that Japan faces very similar barriers to the successful commercial introduction of tissue engineering products and processes to those experienced in the UK and elsewhere. The solutions to the problems associated with these barriers are not obvious and it would appear that the tissue engineering community in Japan is not necessarily in any better position to resolve these issues. Indeed some of these issues may well be more difficult to resolve in Japan because of long established traditions in universities, investment communities and government institutions. Nevertheless there are several signs of significant changes in recent years with respect to these traditions and it is possible that Japan will emerge as a leading force in the globalisation of tissue engineering. We would like to point to a number of very important issues that reflect the current directions of the scientific, clinical, industrial and economic practices.

First it is evident that the Japanese government at both national and prefecture levels decided that regenerative medicine in general, and tissue engineering in particular, constitute one of the major technology platforms for the medium and long-term, which should form the basis of the re-emergence of a strong Japanese economy. The investment that government departments are making in the infrastructure for the biotechnology and medical technology industries is massive and it is clearly the expectation that this investment will be rewarded by major industrial innovation and increased employment. Members of the Mission were duly impressed by the scale of this investment but it has to be said that this policy is not without risk. The withdrawal of one major Japanese company from the tissue engineering industrial sector during the period of the Mission on the basis that they could not identify a clear pathway to commercial exploitation under the present uncertainties over the regulations surrounding regenerative medicine, underlined the nature of the risks involved.

In the context of this investment, government institutions have set very high targets for the emergence of new companies and new commercial initiatives. Although there has been an interesting start to this process, these targets appear to be unreasonably high. Local governments appear to be very keen to play a significant role in this new industry, especially by the provision of very favourable investment and manufacturing opportunities. There was some evidence that the benefits of these attractive policies may only be transient, as some companies fail to grow at their expected rate, and as differential policies between different cities and prefectures may only result in the perpetual movement of companies around Japan on the basis of the best financial incentives.

It was evident that the Kansai area, and especially Kobe, are amongst the frontrunners in this field with considerable investment in new world-class facilities. In many ways there was the appearance of biotechnology clusters in these areas although this is probably as a result of these financial incentives in this sector rather than because of any serious technological strategy. The facilities that were evident in Kobe included very impressive cell biology research laboratories, the manufacturing infrastructure for start-up companies and a major clinical facility for the purpose of clinical trials of pharmaceuticals and the products of regenerative medicine. There was a feeling that as impressive as these facilities were, they may have difficulties in attracting the appropriate number of world-class scientists and clinicians that would be necessary for economic success. We were also concerned that little attention appeared to have been paid to the availability of skilled technicians and scientists that would be necessary for these extensive operations.

Through visits to a few large companies and a couple of very small companies, and also through discussions with venture capitalists and various delegates from industry at the seminar, it became clear that there was much interest in funding tissue engineering research from private equity and venture capital. The amounts involved are still fairly small in view of the uncertainties in this market but it is possible that this will increase in the medium term if the market is able to mature. Corporate venturing is also evident and may well become the more important route for resourcing these developments. In general large pharmaceutical companies are not heavily involved themselves, but expect that ventures with small biotechnology start-ups will provide their most effect route to this market, a situation very similar to that which prevails in Europe and USA.

It should also be said that the impressions of the members were dominated by these facilities in Kobe, Osaka and Kyoto, as there were no opportunities in the time available to see other major centres. It is obvious that equally good science is performed in other areas of the country and especially it is noted that the Tokyo and Ibaraki areas have some extremely productive and high quality institutes and universities.

The Mission was only able to visit two universities, in Nagoya and Kyoto. It was clear that some very interesting quality science was being carried out in these institutions, and in some cases notwithstanding an apparent lack of investment in comparison to some of the government funded research institutes. It is also noticeable from many conversations that the universities are undergoing significant change, first in respect to the status of national universities as they become somewhat independent agencies and secondly in the light of a changing view on the ability of professors to undertake entrepreneurial activity and become engaged in spinout companies. This is an interesting experiment and it is unclear just how fast and effective this change in culture will be. It was never too clear exactly how the financial arrangements were put in place with respect to these university-originated spinout companies but there was some evidence that professors carry little risk in this process, which may not be the best basis for commercial success. In general the quality of the science being performed in university laboratories is very high and probably comparable to the general level in the UK.

It is interesting to note that research in tissue engineering, which is multi-disciplinary by definition, is carried out in many different types of university departments, ranging from mainstream engineering to molecular biology. In Japan, which does have a long tradition of biomaterials science research, the evidence would suggest that tissue engineering developments are not being derived from this tradition but rather emanate from cell and molecular biology, genetics and clinical medicine. Much of this science of extremely high quality. We were surprised to see so much work on embryonic stem cells which, although interesting and rewarding from a scientific point of view, cannot lead to any commercial or clinical advance in the foreseeable future since Japanese regulations do not allow the therapeutic use of these cells.

The regulatory environment in Japan appears to be as confused as it is elsewhere in the world. In most jurisdictions, commercial products used in healthcare have been regulated as either pharmaceuticals or medical devices. In a few countries there is also a third category that deals with substances of biological origin. Tissue engineering products fit none of these categories and, for various reasons, the regulatory agencies have been slow to accommodate these new products within a legal framework, with clearly identified protocols. Whilst this is understandable to some extent in the light of the rapidly evolving scientific and clinical dimensions of regenerative medicine, it is also unfortunate since companies are not able to predict regulatory positions or follow established methods for approval. Japan, in principle, is no different to any other country and although work on new guidelines and legal frameworks is in progress, these are not yet in place and considerable uncertainty faces Japanese and

overseas companies alike. We enquired about the role that industry and academia had in the development of new regulations. Although it was unclear exactly how expert opinion was brought to bear on these procedures, we were left with the impression that those most actively engaged in this technology had little influence over the regulations being drafted.

These regulatory issues also have an impact on reimbursement. This report has demonstrated the difficulties that healthcare reimbursement agencies have in Japan concerning the ability or willingness to pay for new treatment regimes that are as yet unproven and not well established. Again this is similar to the situations that prevail in the USA and the majority of European countries. Without satisfactory resolution of these problems, tissue engineering companies find that they have to sustain the heavy costs of the treatment of patients themselves, increasing the development costs of products and potentially extending the period of time before there is any return on their investment. We did not see any evidence that Japan had fully grasped the importance of this situation.

The clinical areas that are attracting the attention of tissue engineering research in Japan deserve comment. The majority of developments in Europe and the USA are concentrated on diseases and conditions for which there is currently a lack of effective treatment modalities. Thus early tissue engineering products have focused on problems with skin, for example chronic ulcers, where only palliative measure have been previously available. Major initiatives are underway with respect to the treatment of nerve injuries and degenerative diseases of the nerve tissue. There is little interest in the development of tissue engineering products that would have to replace very successful existing procedures, such as in total hip replacement. Although in general the approaches to tissue engineering in Japan are also directed to major diseases that require innovative treatments, it was also obvious very significant investment was being made in some less glamorous areas such as periodontal surgery. Indeed it was evident that many research groups and start-up companies were directing their efforts toward the regeneration of periodontal tissues and teeth. There is no doubt that dental diseases are still far more prevalent in Japan than in the UK, but nevertheless members of the Mission were surprised at this emphasis within tissue engineering.

It was also interesting to note that, in spite of a lack of a regulatory approval pathway for the commercialisation of tissue engineering products, a number of procedures had found their way into clinical practice. We were provided with evidence of the clinical use of tissue engineering processes in the treatment of nerve injuries and in periodontology. It is also evident from various publications that Japanese clinical investigators are using tissue engineering products in the treatment of cardiovascular disease and ophthalmological conditions in human patients. These procedures appear to be carried out under the medical license of the clinicians themselves rather than through any regulatory process associated with the product. The ability to carry out such clinical investigations on patients is obviously dependent on cultural and legal conditions.

In summary therefore we found more commonality than differences between the tissue engineering industry in Japan and the UK. The general economic situation prevailing in Japan is clearly a major factor in the establishment of a tissue engineering industry but the confidence placed in the potential for tissue engineering and associated technologies to underpin the future financial health of the country by government is acting as a major stimulus. On the basis of this investment, a number of world-class research facilities have been established although these are as yet not fully populated by groups of world-class scientists. For the moment Japan is leading the tissue engineering field within Asia but they will have to capitalise on the opportunities provided by these investments if they are to maintain this position. We saw many potential opportunities for the involvement of UK companies and academics in joint ventures and collaborations with these laboratories and institutions.

9. Appendices

9.1. APPENDIX I - PRIVATE EQUITY AND VENTURE CAPITAL PROVIDERS

NIF Ventures
20 employees plus advisors.
39 biotechnology investments, with 14 successful exits. Have only made 2 investments since 2002 neither in Japan.(Intercytex and AGY Therapeutics)

Diamond Capital. (Mitsubishi)
Entered into biotechnology sector 2 years ago and now 375 of new investments are in this sector. Work with a number of European and US investors including Merlin in order to gain exposure to companies and ideas internationally. Current Japanese portfolio includes companies in biomaterials, drug delivery, bioinformatics and autologous skin culture.

Itochu Ventures.
Invested in Biotechnology since 2000 including partnering with MPM Bioventures in Boston. USA.

Marubeni Ventures
Marubeni invest into ideas and people at an early stage with the hope of creating companies which can be acquired by the parent group in 3-5 years. Their portfolio includes life sciences, nanotechnology and biomedical technologies. They also operate JVs in Japan with several of their investee companies leveraging their corporate operations locally.

Investment partners in Europe include Merlin and Critical technology fund, Orbimed, Morgan Stanley and Bear Stearns.

Summit Pharma Ventures
Formed through a JV between Sumitomo corporation and Sumisho pharmaceuticals the group has 43 employees and operates as a technology licensing business liasing between Japanese Pharma and the rest of the world as well as using its contacts and expertise to provide sector specific fund management services for others as well as running its own Life sciences venture fund.

Mitsui Ventures corporation (MVC)
The group is a large investor with $40 million invested to date in Asia, $20 million in North America and currently seeking partnering opportunities in Europe. In the US the group have targeted healthcare industries for 60% of their fund and expect to make 10 investments 5 in medical technologies and 5 in Biotechnology.

9.2. Appendix II:
ORGANISATIONS ATTENDING THE MISSION SEMINAR (NOT IINCLUDING THOSE VISTIED BY THE TEAM)

Company Location	Annual Turnover $	Medical Products/Evidence of TE interest	www
Asahi Intecc Co Ltd, Nagoya	(200 employees)	Catheters and guidewires with thin film resin technology	www.asahi-intecc.co.jp
Aslan Tec Inc	?	?	?
As-one Corp, Osaka	$241m	Research Equipment - proteomics robots, hybridisation systems	www.as-1.co.jp
Astra Zeneca KK, Osaka	$17.8bn (plc) (Japan; 2000 employees)	Pharmaceutical	-
Cardio Inc	Start-up 2001	Cell and gene therapy in cardiovascular systems for regenerative medicine. Cells sheet patch for heart muscle/ cardiovalve for aorta	
C-design Corp, Kyoto		Regional development/industrial promotion/corporate planning.	www.c-design.jp
Chugai R&D Co Ltd, Kyoto	-	Bone ceramics/ pharmaceuticals/ diagnostics: molecular biology	www.chugai-pharm.co.jp
DIA Research Martech Inc, Tokyo	$1.6bn	Contract Research – Science & Technology	www.drmi.co.up
Espec KK, Osaka	$200m	Manufacture, controlled environment research/equipment	www.espec.co.jp
Fujisawa Pharm.Co Ltd, Osaka	$3bn	Pharma, molecular biology/gene manipulation	www.fujisawa.co.jp
Gunze Ltd, Osaka	$1.4bn (plc) (2780 employee)	Artificial dermis (Pelnac); testing skin model (Vitrolife); manufacture bio- degradable material. Regenerative Medicine Facility in Kyoto	www.gunze.co.jp
Hitachi Medical Corp, Kyoto.	$1bn	Medical equipment & systems to hospitals	www.hitachi-medical.hbi.ne.jp
Japan Chemical Res. Co	(2236 employees)		
Japan Tissue Engineering (J-TEC), Gamagori City		Focus on cultured skin/ cartilage using autologous sourced cells. Products in clinical trial in Japan	www.jpte.co.jp
JCR Pharmaceutical Co Ltd, Ashiya	Founded 1999 (19 employees)	Pharmaceutical - interests in bioengineered products rh hGM	www.jcrpharm.co.jp
Kaigen Co Ltd, Osaka	$68m (200 employees)	Pharmaceutical marketing company	www.kaigen.co.jp
Kaneka Corp, Osaka	$100m (200 employees)	Chemicals/ pharmaceuticals	www.kaneka.co.jp
Kurabo Industries Ltd, Osaka	$3bn (6726 employees)	Diverse textile manufacturer/bio-medical interests	www.kurabo.co.up
Marui & Co Ltd		Retail company	
Matsushita Electric Industrial, Osaka	$52bn (267000 employees)	Electronics brands include Panasonic/JVC/ Technics. Biomedical interest sensors for bioactivity patents in living tissue. Link with Tensor Bioscience	www.matsushita.co.jp
Meiwa Shouji Co Ltd	$160,000 (67 employees)	Distributor of scientific instruments	www.meiwanet.co.jp
Minolta Co Ltd, Osaka	$3.8bn	Optical equipment/ imaging technology	www.minolta.com
Mitsubishi Pharma Corp, Osaka	$1.9bn (9000 employees)	Pharmaceuticals/ Biopharmaceuticals manufacturer w.m-pharma.co.jo	
Mitsui & Co Ltd	$95bn	Services and products conglomerate	www.mitsui.co.jp

Company Location	Annual Turnover $	Medical Products/Evidence of TE interest	www
Nagase Chemtex Corp, Osaka	$180m (500 employees)	Pharmaceutical/ chemicals/ polymers	www.nagasechemtec.co.jp
Nippon Cable Systems Inc, Osaka	$618m	Metals/plastics/ lubricant based business. Medical arm specialising in remote manipulation/endoscopes/catheters/ guidewires	www.hi-lex.co.jp
Nippon Zoki Pharmaceutical, Osaka	Private	Pharmaceutical/ manufacturing/ marketing	www.nippon-zoki.co.jp
NTT Basic Research Lab	(100 employees)	Independent research lab focus on device physics, functional material science & quantum electronics	www.brl.ntt.co.jp
Ohashi Kasuga Tsusho Inc			
Oriental Yeast Co Ltd, Tokyo	$3.2bn	Manufacturer of yeast and food products(4%) and biochemicals (19%). Focus on medicinal products from yeast.	www.bekkoame.or.jp
Otsuka Pharmaceutical Co Ltd www.otsuka.co.jp	28bn (5224 employees)	Manufacturing, distribution of pharmaceuticals, clinical testing equipment, medical equipment.	
ProPhoenix Co Ltd, Hiroshima		Analytical service, proteome, mass spec. electrophesis	www.prophoenix.co.jp
Sekisui Chemical Co Ltd, Tokyo	$2.5bn (21500 employees)	High performance plastics/composites Research into sensor/ human sensitivity tech	www.sekisui.co.jp
Senju Pharmaceutical Co Ltd, Osaka drug products moving in veterinary ethical products		$150m www.senju.co.jp	Specialise in ophthalmic
Shimadzu Co	$1.4bn	Scientist 'Koichi Tanaka' 2002 Nobel Prize in Chemistry. Medical systems and equipment etc. New business biotechnology unit incorporating kratos analytical	www.shimadzu
Shionogi & Co Ltd	$3.5bn (9000 employees)	Pharmaceutical products/diagnostics/ industrial chemicals	
Smith & Nephew KK, Tokyo	$1.6bn (plc)	Medical Device company. Ortho/ Wound Management. Marketing tissue engineered products.	www.smith-nephew.com
Sumitomo Seika Chemicals Co Ltd, Osaka	$340m (900 employees)	Fine chemicals and functional polymers company	www.sumitomoseika.co.jp
Sysmex Corporation	$396m	Hospital analytical/ diagnostic equipment manufacturer. Committed to post genome science/technology	www.sysmex.co.jp
Taiho Pharmaceutical Co Ltd	$800m	Pharmaceutical company with established market in oncology and branching into urology and autoimmune disease	www.taiho.co.jp
The Nikkan Kogyo Shimbun Ltd	(1300 employees)	Press publishing business	www.nikkan.co.jp
Toppan Printing Co Ltd, Tokyo	(12700 employees)	Printing & packaging company with a contract R&D centre (Life Technology Partnership UK)	www.toppan.co.jp
Unitika Ltd, Osaka		Textiles/polymers/ advanced materials/ home care medicines (chitin based wound dressing)	www.unitika

9.3. Appendix III: Team Members

Professor David Williams FREng
Professor of Tissue Engineering and Head of the Department of Clinical Engineering, University of Liverpool.

Mission Leader

Professor David Williams is Head of the Department of Clinical Engineering at the University of Liverpool and Deputy Director of the UK Centre for Tissue Engineering jointly run from the Universities of Manchester and Liverpool. He also directs the MRC sponsored interdisciplinary research programme in Liverpool.

Professor Williams trained as a materials scientist and is a chartered engineer, but has worked in medical devices, biomaterials and tissue engineering for 35 years, being a Professor of the Medical School for twenty years. He is best known for his work on biocompatibility of implantable materials, with over 300 scientific papers published in this area. He has published over 30 books, including the seminal treatise on biomaterials (Implants in Surgery, 1973) and the recent Williams Dictionary of Biomaterials.

Professor Williams is a long term advisor to the medical device and tissue engineering industrial sector, with involvement in aspects of materials selection, biological testing, product liability litigation and regulation. He has been Vice Chair of the Scientific Committee on Medicinal Products and Medical Devices of the European Commission for the last five years and has written many scientific opinions that underpin European legislation in these areas. He is currently Editor-in-Chief of Biomaterials, the world's leading journal in this field. Professor Williams was elected a Fellow of the Royal Academy of Engineering in 1999.

Professor Gareth Lloyd-Jones – Director, Group Research Centre, Smith & Nephew plc.

A chemist by degree and with a PhD in Organic Chemistry and three years post doctoral experience (two years spent in USA at Worcester Foundation, Mass.) linking chemistry, biochemistry and biology, Gareth has spent 21 years in the pharmaceutical industry, initially 4 years at Sterling Winthrop, Newcastle-upon-Tyne, before moving to Reckitt and Colman Pharmaceutical Division, Hull, progressing to Divisional R&D Director.

In February 1992 he joined Smith & Nephew, a global healthcare business, as Director of Research at their purpose-built facility on the University of York Science Park and subsequently (1996-2002) became Managing Director of the York site with overall responsibility for the Group's Research Centre. In these posts Professor Lloyd-Jones took personal responsibility for ensuring the overall R&D climate was conducive to the introduction of new product opportunities and building more effective systems of progressing projects from concept to market.

in January 2003, he formed a 'sole trader' advice and consulting business for the healthcare industry.

Gareth is a Fellow of the Royal Society of Chemistry, Royal Society of Arts and an honorary Professor in the Department of Chemistry at the University of York.

External to Smith and Nephew, he has significant professional involvement with a number of organisations:

- Medilink (Yorkshire & Humberside) Board member (1995)
- Nominated Programme Management committee MedLINK; Government new market investment programme, sponsored by DoH (1995)
- Director, York Chamber of Commerce (1997)
- Member of Advisory Board - Institute of Bioengineering and Biosciences, Georgia Institute of Technology, Atlanta (1998)
- Member of Yorkshire Forward's Regional Bioscience Group (1999)
- Member of Advisory Committee to ESRC/MRC Innovative Health Technologies Programme (2000)
- Chair, Science City York Board(2002)

Elected Chair Medilink (Yorkshire & Humber) effective Feb. 2003

Dr Paul Kemp – Chief Executive, Intercytex

Paul Kemp initially studied Biochemistry at University of Wales graduating in 1978. He then went on to University of Leeds to research the Organisation and role of Glycosaminolycans and Proteoglycans in mammalian skin, obtaining his PhD in 1981.

After spells at both British Leather Research and The University of Manchester, he joined Organogenesis Inc in Canton, USA. Between 1987 and 1997 Paul occupied various posts including Vice President: Connective Tissue Science and was one of the principle inventors of the manufacturing system for Apligraf which was the first medically approved manufactured human organ system. He also designed and implemented the Company's collagen production facility and scaled up the process to meet the Company's Research and manufacturing programs.

In 1997, Paul founded Intercytex, of which he is currently Chief Executive Officer, which is devoted to developing cell based systems to induce tissue and organ formation. Intercytex currently employs 45 staff in Manchester and Boston and has programs in skin, hair and kidney regeneration. The company is funded by a consortium of European, US and Asian venture funds.

Dr Mike Hudson – Managing Director, Health Ventures Ltd.

Following a B.Sc., Ph.D, DIC & ARCS in Life Sciences from Imperial College Mike has devoted much of his career to initiating, building and managing ambitious, high growth ventures within both large and small organisations.

He has led a significant number of acquisitions and strategic initiatives as well as founding and holding board positions with a number of small companies. In these capacities he has seen both success and failure, as well as faced the challenge of raising finance as well as negotiating the purchase of businesses.

Mike represents the investor community on the Department of Health's steering committee responsible for the 'Health Technology Devices programme', and has close working relations with providers of Venture Capital, Private Equity and Corporate Finance as well as with a diverse array of corporate clients.

Adam Getliff – Bioscience and Chemicals Cluster, Yorkshire Forward

After a varied a vibrant career, Adam graduated as a mature student from the University of Wales, College of Cardiff in 1995 with a BSc in Business Studies and Japanese. During the course he spent time at Kitakyushu University in Kyushu, Japan and on industrial placement at Sapporo Beer, Kyushu.

On graduation he returned to Japan to take up a position as Coordinator for International Relations at Ukiha Town, Fukuoka Prefecture, Kyushu, on the Japanese government JET Programme.

During his three years on the JET Programme he improved his Japanese, becoming fluent, and gained an in-depth insight into Japanese business and culture, working with the local government to establish a programme of internationalisation and regional development through 'Green Tourism'.

In September 1998, at the conclusion of his contract in Japan he returned to the UK and found employment with the West Midlands Development Agency (now Advantage West Midlands, the West Midlands Regional Development Agency) working with Japanese companies to attract inward investment to that region.

In January 2000 he moved to the Yorkshire & Humber Regional Development Agency, Yorkshire Forward, to head up their Asia Pacific Desk, focussing again on attracting inward investment from Japan in particular.

Since 2001 he has been working in the Yorkshire Forward cluster development programme, in particular in the areas of bioscience and chemicals.

He has experience in the development of infrastructures for the growth of competitive and vibrant clusters, in particular the needs of bioscience companies, and the strategies for the attracting Foreign Direct Investment (FDI).

He is married with a young daughter and speaks fluent Japanese.

Meredith Lloyd-Evans – Managing Partner, BioBridge Associates

Meredith Lloyd-Evans was educated at The Manchester Grammar School, the University of Cambridge, 1967-73 (Medical Sciences, History Of Art, Veterinary Medicine) & the University of Guelph, 1973-1974 (Intern, Ontario Veterinary College). He is married with 2 daughters and enjoys cycling, sailing, walking, scuba, gardening, art, eating and drinking and the culture and life of Japan.

After graduating, he spent 15 months in Canada, worked 4 years as a general veterinary surgeon in the UK and joined SmithKline Animal Health, where he piloted a number of innovative veterinary medicines to the market. He founded BioBridge® Associates, an independent consultancy, in 1989, working in biobusiness development, technology issues and regulatory affairs in biotechnology, animal health, human health, biomaterials, medical devices and agro-food. He is Managing Partner.

Since 1988, Meredith has visited Japan many times and has represented UK mission groups in Japan and Canada. He has a number of Japanese clients in healthcare, animal health and chemicals sectors. From 2000-2002 he was involved as a regional co-ordinator in the Japan 2001 festival in the UK. He is now learning Japanese and, after some months, recognises that he has probably reached a level equivalent to a 3-year old Japanese child in vocabulary and word-recognition.

The Royal Academy of Engineering

The objectives of The Royal Academy of Engineering are to pursue, encourage and maintain excellence in the whole field of engineering in order to promote the advancement of the science, art and practice of engineering for the benefit of the public.

The Academy comprises the United Kingdom's most eminent engineers of all disciplines. It is able to take advantage of their wealth of knowledge and experience which, with the interdisciplinary character of the membership, provides a unique resource with which to meet the objectives.

Its activities include an extensive education programme, research chairs and fellowships, visiting professorships, industrial secondments and international travel grants. It provides expert advice on engineering matters to government and other bodies and awards the UK's premier annual prize for innovation in engineering, The Royal Academy of Engineering MacRobert Award.

Election to The Academy is by invitation only. Up to sixty Fellows may be elected annually, together with Honorary Fellows and Foreign Members who have made exceptional contributions to engineering. All are elected by their peers for personal achievement of exceptional merit and distinction. Fellows are distinguished by the title "Fellow of The Royal Academy of Engineering" and use the designatory letters "FREng".

The Academy was founded in 1976 as The Fellowship of Engineering on the initiative of HRH The Duke of Edinburgh and a group of distinguished engineers. It was granted its Royal Charter in 1983 and, with the consent of HM The Queen, adopted the present title in 1992.

UK Focus for Biomedical Engineering

The UK Focus for Biomedical Engineering was established in 1993 under the auspices of The Royal Academy of Engineering. Its origins date back to 1987 when The Academy was invited to submit evidence to the House of Lords Science and Technology Committee enquiry into priorities in medical research. This led to the formation of a working party to investigate the role of engineering in medicine and launched The Academy's involvement in the field. The working party concluded that a focus for biomedical engineering in the UK was necessary to assist developments in policy and to co-ordinate activities and so the UK Focus for Biomedical Engineering came into being.

Membership comprises a range of professional groups involved in the field, Research Councils, medical charities and trade associations. The Royal Academy of Engineering provides a number of representatives, including the Chairman, Professor Peter Wells FREng FRS.

dti

The DTI's International Technology Service (ITS) provides a suite of programmes dedicated to helping British businesses increase their productivity and competitiveness by learning about and accessing innovative technologies and practices in other countries. The suite includes:

www.globalwatchonline.com - a revolutionary internet-enabled ITS service delivering immediate and innovative support to UK companies in the form of fast-breaking worldwide business and technology information plus unique coverage of DTI, European and international research and business initiatives, collaborative programmes and funding sources.

GlobalWatch - the website's sister publication, showcasing innovation in action. Distributed free to UK high-tech organisations, the magazine features the latest technology developments and practices gleaned from ITS activities around the world and now being put into practice for profit by British businesses.

UKWatch - a quarterly magazine, published jointly by science and technology groups of the UK government. Showcasing British innovation and promoting inward investment opportunities into the UK, the publication is available free of charge to UK and overseas subscribers.

Overseas Missions – short fact finding overseas visits by small group of technical experts from UK companies, and academia, to investigate innovation and its implementation at first hand. Overseas Missions allows entire UK sectors and individual organizations to gain international insight to guide their own strategies for success.

International Secondments - provides financial and practical assistance in inward and outward secondments of individuals from any discipline to and from any country, for periods of three to twelve months, to learn best practice, understand new developments in technology and develop overseas links.

The International Technology Promoter (ITP) programme - providing free, flexible and direct assistance from commercially-aware technology specialists to raise awareness of, and provide access to, technology and collaborative opportunities overseas. Delivered to UK SMEs by a team of 16 ITPs, the programme provides support ranging from information and referrals to more in-depth assistance with, for example, licensing arrangements and technology transfer. The ITPs cover North America, Europe and Asia and specialize in key disciplines.

For further information on the DTI International Technology Service please visit www.globalwatchonline.com