NanoBiotechnology/BioNanotechnology

International Technology Service Mission to Japan

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Contents

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Introduction – Aims and Objectives

Global nanotechnology activity and investment is growing rapidly. While it is difficult to provide reliable estimates of absolute expenditure in a field as difficult to define as nanotechnology, it is clear that very significant investments are being made, that these investments are experiencing year-on-year growth, and that relatively new technological powerhouses from Korea to the Irish Republic are responding rapidly and successfully to the diversity of opportunities afforded by encompassing miniaturisation technology.

The UK is not asleep. In 2001 the UK Government funded two Interdisciplinary Research Collaborations[1] and one University Innovation Centre[2] in Nanotechnology with a combined additional funding of ~£25M in the 5 year period to 2006. In June 2002, the UK Advisory Group on Nanotechnology Applications submitted its report[3] *'New Dimensions for Manufacturing: A UK Strategy for Nanotechnology'* to Lord Sainsbury, Minister for Science & Innovation. In his preface to this report, Dr John Taylor, Director-General of the Research Councils and Chairman of the Advisory Group states 'that in order to keep pace with competitor nations we need to recast the scale and nature of our nanotechnology activities. We need to raise awareness in industry of the enormous potential impact that nanotechnology could have and ensure that investment and action by Government, industry and researchers is fully aligned to maximise the benefit for the UK'.

In July 2002, the UK Government published its science, engineering and technology strategy[4], which outlines additional resources for science of £1.25B from FY2002-3 to FY2005-6, including an additional £50M per year by FY2005-6 to support collaborative R&D on key emerging and pervasive technologies such as nanotechnology.

Japan is the world's second largest economy, performing around one quarter of the world's R&D, with its top 10 companies spending more on R&D than the entire UK public sector and industry combined. The Japanese Government has named life sciences, information and communications, environment and nanotechnology as its strategic priorities for the next 5 years. As the most mature economy in a rapidly developing Asian region, Japan recognises a pressing need to move up the value chain, and arguably leads attempts in the region to do so. It increasingly believes that the convergence of biotechnology, information and communications technology, cognitive science and nanotechnology, provides the route to achieve that objective[5]. Shocked by large US increases in both public and private sector investment in nanotechnology, Japan has reacted swiftly and increased its investment to maintain its position as the lead investor in

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[1] IRC in Bio-Nanotechnology (Oxford, Glasgow & York Universities and the National Institute for Medical Research), IRC in Nanotechnology (UCL, Bristol & Cambridge Universities, http://www.nanoscience.cam.ac.uk/irc/index.html)
[2] UIC for Nanotechnology based at the Universities of Durham (nanomaterials) and Newcastle (biomedical nanotechnology, http://www.inex.org.uk)
[3] 'New Dimensions for Manufacturing: A UK Strategy for Nanotechnology', DTI, June 2002
[4] 'Investing in Innovation: A Strategy for Science, Engineering & Technology', HM Treasury, July 2002
[5] K. Omi, Minister of State for Science & Technology Policy, Japan

nanotechnology world-wide, beating both the US and combined European efforts (Table 1). Recent DTI sponsored Missions to the US and Germany have surveyed nanotechnology activity

Table 1: Breakdown of known and anticipated US NNI, EU FP6 and Japanese government R&D expenditure in nanotechnology in the period 2001 – 2003 (*Source:* European NanoBusiness Association[6])

Country	**2001**	**2002**	**2003**	**2002-2006**
US NNI	\$463.85M	\$604.4	\$710.2M	-
EU FP6	-	-	-	€17500M
Japan	\$465M	\$750M	\$1000M	-

in those countries[7]. It therefore appeared timely that Japanese activity in the sector, *particularly in the area of convergence of biotechnology, information and communications technology*, be assessed, opportunities for collaboration identified, and this information more widely communicated to UK industry.

It was in this rapidly evolving, highly dynamic context that the DTI International Technology Service sponsored Nanobiotechnology Mission took place to Japan in the period July 15-19, 2002. The Mission was timed to coincide with the 17th UK-Japan High Technology Industry Forum.

The Mission focussed on biomolecular engineering, surface functionalisation and micro/nano-fabrication technologies which lie at the convergence of biology, chemistry, physics and engineering. These can be directed at harnessing the potential of genomic information through devices and systems providing real-time predictive, point-of-care and personalised health care, and find additional applications in tissue engineering, pharmaceutical screening, environmental and process monitoring, forensics and defence. This focus is aligned with the view expressed in the recent UK Nanotechnology Strategy document[8] that it is simply too late to compete internationally in applications such as semiconductors, but that the strength and health of UK industry in pharmaceuticals and biotechnology presents a particular opportunity.

The key objectives of the Mission were:

- To benchmark and assess the Japanese response to opportunities afforded by advanced miniaturisation technologies, particularly those arising through integration of the biological and physical sciences and engineering.
- To better understand the environment and perceived opportunity that has prompted massive investment in this technology and a shift in focus by Japanese electronics and communications companies and how this impacts UK private and public-sector strategy.
- To assess where Japan expects quick wins, the timescale for them, and the extent of the remaining opportunity.
- To better understand the dynamics of the industry, its likely profitability, barriers to entry, likely manufacturing scenarios, and skills needs.

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[6] 'Its Ours to Lose: An Analysis of EU Nanotechnology Funding and the Sixth Framework Programme', Dr Cristina Román, European NanoBusiness Association, Oct 2002

[7] 'The International Technology Service Missions on Nanotechnology to Germany and the USA', March 2001 (available at www.nano.org.uk and www.dti.gov.uk)

[8] 'New Dimensions for Manufacturing: A UK Strategy for Nanotechnology', DTI, June 2002 (p. 46)

- To explore areas of complimentarily and opportunities for partnerships between Japanese and UK private and public-sector organisations.

The UK delegation represented a breadth of perspectives, across sectors (defence, diagnostics, pharmaceuticals, agrochemical), size (multinationals to university spin-offs), and background (academic, former large corporate, large corporate).

Executive Summary

In June 2002, the UK Advisory Group on Nanotechnology Applications published its report 'New Dimensions for Manufacturing: A UK Strategy for Nanotechnology'. In the preface to this report, the Chairman of the Advisory Group stated 'that in order to keep pace with competitor nations we need to recast the scale and nature of our nanotechnology activities. We need to raise awareness in industry of the enormous potential impact that nanotechnology could have and ensure that investment and action by Government, industry and researchers is fully aligned to maximise the benefit for the UK'.

This strategy should not be developed or refined in isolation from, or ignorance of, international activity and trends. Global nanotechnology activity and investment is growing rapidly. Recent DTI sponsored Missions to the US and Germany have surveyed nanotechnology activity in those countries. As the most mature economy in a rapidly developing Asian region, Japan recognises a pressing need to move up the value chain, and arguably leads attempts in the region to do so. The Japanese Government has named life sciences, information and communications, environment and nanotechnology as its strategic priorities for the next 5 years. And significantly, it increasingly expresses the view *that the convergence of biotechnology, information and communications technology, cognitive science and nanotechnology* provides the route to achieve that objective.

This DTI International Technology Service sponsored Nanobiotechnology Mission took place to Japan in the period July 15-19, 2002. It especially reviews Japanese nanotechnology activity directed at enabling the *convergence of biotechnology, information and communications technology*. It focussed on biomolecular engineering, surface functionalisation and micro/nano-fabrication technologies which lie at the convergence of biology, chemistry, physics and engineering. These can be directed at harnessing the potential of genomic information through devices and systems providing real-time predictive, point-of-care and personalised health care, and find additional applications in tissue engineering, pharmaceutical screening, environmental, food and process monitoring, forensics and defence. The UK delegation represented a breadth of perspectives, across sectors (defence, diagnostics, pharmaceuticals, agrochemical), size (multinationals to university spin-offs), and background (academic, former large corporate, large corporate).

This report details industry activity disclosed to the Mission at NTT Basic Research Laboratories, Olympus Optical Company, Toshiba Corporation, Shimadzu Corporation and Matsushita Electric Industrial Company. In addition, reports on research and strategy in the public sector, derived from discussions with high-profile individuals, namely Professor's Kawai (Osaka University), Baba (Tokushima University), and Namba (Osaka University in collaboration with Matsushita) and members of the National Institute of Advanced Industrial Science and Technology (AIST, Osaka campus) are provided. Brief details, derived from secondary sources, of activities by Canon, Fujirebio, Fujitsu, Hitachi, Hosokawa Micron, Toray Industries, NEC, relevant SME's and other University and public-sector Research Institutes are appended for completeness.

The Mission concluded that technology convergence is indeed recognised to be an opportunity in Japan, but little evidence emerged of a serious attempt to quantify market opportunities and provide commercial focus for R&D activity. At the very least, the scientific teams involved in technology or product development articulated little market awareness. In the clinically related fields of diagnostics and devices there was little evidence of synergistic relationships with the Japanese pharmaceutical sector, or close clinical collaboration to determine end-product value. Little evidence of internationally leading activity in the medical device or therapeutic fields was uncovered, but the Mission was impressed by the clearly evident long-term horizons and commitment of company R&D investment and major strength and activity in both the public and private sector in understanding and harnessing opportunities provided by complex functional biological entities such as biological motors.

The Japanese approach to the protection and exploitation of IP was felt to be out-dated in comparison to that of Japans major competitors. There was no evidence at any of the organisations visited of active IP management, such as attempts to commercialise or license out non-core IP. The academic and public-sector research institutions visited seemed unaware of the financial cost of maintaining a large and unstructured IP portfolio, a situation encouraged by the fact that a government sponsored organisation meets the patent maintenance costs.

The corporate research groups visited appeared to be directed in their choice of programs solely by scientific interest. There was little evidence of the role or integration of criteria like market awareness, manufacturing cost analysis, regulatory requirements and technology development timescales in directing research strategy. In some cases very unrealistic expectations regarding timescales and the investment needed to progress new technology through medical regulatory requirements was shown. It was notable that the industrial researchers we met did not, by and large, view the academic research base in Japan as a source of new technology, preferring if at all, to consider partnering with research institutions abroad. There was a perception in industry that Japanese public-sector funding for research fulfils the interests of academic scientists, not industry.

It was found that spin-out activity from universities is being actively encouraged by central government. It was less clear that there is a corresponding government-supported programme of any sophistication to aid the process. The culture in universities and public-sector research institutes was found to be changing rapidly (or is at least under great pressure to do so), but it was felt that such organisations still have some way to go to become sophisticated players in identifying, protecting, exploiting and pursuing flexible routes to market for new technologies.

The norm in Japan is to pursue collaboration either in-house or with other Japanese companies, however clear evidence emerged that collaboration practices are changing. International technology partnering and R&D collaboration on the development of new technologies, while still in its infancy, is possible. There is complementarity between Japanese and UK strength and expertise.

As noted in the recent UK Nanotechnology Strategy document, it may indeed be too late for the UK to compete internationally in applications such as semiconductors. However, the strength and health of UK academe and industry in pharmaceuticals and biotechnology, the strong decoupling of Japanese electronics and communications companies from the Japanese pharmaceuticals sector, the greater sophistication of the UK in international IP management, and possibly even our record in entrepreneurship and better understanding of spin-off support needs, all present particular opportunities for Japan-UK collaboration.

Mission Focus – Convergence of Technologies

Mission Focus

The Mission focussed on biomolecular engineering, surface functionalisation and micro/nano-fabrication technologies which lie at the convergence of biology, chemistry, physics and engineering. This focus is aligned with the view expressed in the recent UK Nanotechnology Strategy document[9] that it is simply too late to compete internationally in applications such as semiconductors, but that the strength and health of UK industry in pharmaceuticals and biotechnology presents a particular opportunity. For the purposes of this Mission and Report we did not take a pedantic view of the definition of nanotechnology (includes where relevant microsystems and microfluidics), bionantechnology or nanobiotechnology – terms that we will in fact use interchangeably throughout this report. Our pragmatic definition is, like that favoured by the European Commission, a convergence definition.

Importance to UK Industry

The integration of biotechnology, information technology, cognitive science and nanotechnology is viewed in North America[10], the Asia-Pacific Rim[11] and Europe[12] as key for the creation of new scientific and industrial fields, and to enable progression of advanced industrialised nations up the value chain. Mankind's demonstrated ability to completely sequence individual plant and animal genomes may be a major achievement, but is merely an entry into the post-genomic age of applied genomics and proteomics. It is also true that understanding the structure and function of these genes and the proteins that they encode *will* potentially revolutionise our understanding of human, animal and plant disease. However it is the *pervasive real-time application of that understanding* which will revolutionise diagnosis, treatment and prevention. In a still wider context, industry is investing considerable capital with the 'aim of incorporating sensors into everything around us and allowing them to talk to each other and to the internet. This connectivity dynamic is still in its early stages yet looks set to evolve rapidly'[13]. Initial industry targets include health care, the environment (including rapid detection of biological and chemical contamination), food quality and crime-detection. A key prerequisite for many of these ubiquitous systems is the development of devices that enable reliable real-time communication between physical and biological systems. Key concepts include biomimetics, the incorporation of biological molecules into otherwise electronic devices, mimicking biological structures in fabricated devices, and the incorporation of biological signal processing strategies in electronic systems and communications networks.

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[9] 'New Dimensions for Manufacturing: A UK Strategy for Nanotechnology', DTI, June 2002 (p. 46)

[10] 'Converging Technologies for Improving Human Performance: Nanotechnology, Biotechnology, Information Technology and Cognitive Science', NSF/DOC-Sponsored Report, June 2002

[11] K. Omi, Minister of State for Science & Technology Policy, Japan (view expressed e.g. in address to International Symposium: Emerging Fields of Biomedical Research and New Industry by Integrating Biotechnology, Information Technology and Nanotechnology, Institute of Medical Science, University of Tokyo, March 2002)

[12] The European Commission in fact defines nanotechnology in terms of the convergence of physics, chemistry and biology (B. Tubbing, address to NanoBioTec Congress, Münster, Oct 2002)

[13] The X Report, CMP Cientifica, March 2002

The UK has international strengths in biotechnology, pharmaceuticals and some 'front-end' sensor technologies. It is weaker in mass-market electronics and communications technologies. In contrast, Japan is strong in the latter areas and Japanese electronics and communications companies have recognised the huge potential markets associated with ubiquitous sensing capability and the importance within that of information contained within, derived from, or impacting upon biological systems. Indeed, biomedical applications are recognised by most industry analyses as providing, after ICT, the largest and quickest wealth creation opportunities for microsystems and nanotechnology. The recent NEXUS Report[14] identifies the year 2000 world market for biomedical applications as $7.4 billion, raising to $18.5 billion in 2005, with *in vitro* diagnostics and bio-chips taking an increasing share of this market[15]. Japanese giants are therefore establishing strong nanobiotechnology activities (e.g. NTT, Fujitsu, Toshiba and Canon), and there is evidence that they are seeking partnerships with organisations which possess expertise in areas complementary to their traditional focus. It therefore appeared timely that the UK assess both the level and direction of change in Japan, understands the drivers for that change, and identify strategic opportunities for collaboration.

Areas of Japanese Strength & Activity

Japan produces around one quarter of the world's high-technology products, its total R&D expenditure is ~US$90B (most of it in the private sector), it has a larger pool of research scientists than Germany and France combined[16]. Universities and National Institutes dominate Japanese research in nanobiotechnology. An increasing number of firms are actively strengthening their presence in nanobiotechnology, with major electronic companies developing biochip and array technologies, and optical companies entering the field of bioinformatics. There are a growing number of small-scale venture businesses. Japan has particular strengths in understanding the structure and operational principles of bio-molecular motors and their incorporation into man-made devices. Company R&D is characterised by its long-term horizons and substantial financial commitment.

Japanese companies are tooling up for mass production of fullerenes and carbon nanotubes[17], with biomedical applications including pharmaceuticals (anti-cancer, anti-HIV and anti-aging drugs) and cosmetics being explored[18].

Weaknesses

According to a recent analysis by Eurotechnology Japan K. K.[19], Japan's R&D and innovations are still concentrated in large corporations, its economy is characterised by a low number of start-ups and spin-outs, start-ups have difficulty finding top people (CEO's, CFO's), there are low incentives for innovators, and social and legal factors (e.g. little flexibility in capital structures) work against start-ups, and cooperation between industry and universities is more

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[14] 'Market Analysis for Microsystems II 2000-2005' NEXUS Task Force Report, Feb. 2002
[15] increasing from 26% in 2000 to over 50% in 2005
[16] 'Bio-Nanotechnology in Japan – Venture Capital, Public Policy & Results' Gerhard Fasol, Eurotechnology Japan K. K., April 2002
[17] Mitsubishi has a planned production of 1500 tons of fullerenes p.a., Mitsui 120 tons of carbon nanotubes p.a.
[18] 'Bio-Nanotechnology in Japan – Venture Capital, Public Policy & Results' Gerhard Fasol, Eurotechnology Japan K. K., April 2002
[19] *ibid*

difficult in Japan than in Europe and the US. Scientific teams involved in technology or product development articulate little market awareness. In the clinically related fields of diagnostics and devices there is little evidence of synergistic relationships between device developers and the Japanese pharmaceutical sector, or of close clinical collaborations to determine end-product value. The Japanese approach to the protection and exploitation of IP appears out-dated in comparison to that of its major competitors. There is little evidence of active IP management, such as attempts by companies to commercialise or license out non-core IP. Academic and public-sector research institutions seem unaware of the financial cost of maintaining a large and unstructured IP portfolio. There is little evidence of the role or integration of criteria like market awareness, manufacturing cost analysis, regulatory requirements and technology development timescales in directing company research strategy. There is evidence for very unrealistic expectations regarding timescales and the investment needed to progress new technology through medical regulatory requirements.

Government Strategy

Nanotechnology is one of the four key enabling technology areas identified in Japan's second basic Science & Technology plan. In December 2000, Japan's Council for Science and Technology Policy (CSTP) issued a report on the "Strategic Promotion of Nanotechnology/Materials Research". This report identified the following research priorities for nanobiotechnology:

- Development of basic technologies, such as biological functional materials and drug delivery systems to extend healthy living in an ageing society.
- Elucidation of the underlying basic principles for constructing systems using biomolecular mechanisms. Targets include (a) establishment of analytical technologies for collecting data on single protein molecules and protein complex structures, including their motility and their inter-reactions in time and space; (b) establishment of protein handling technology to enable proteins to be equipped with functionality at target sites; (c) developing technology to realise very small and highly efficient energy conversion systems utilising biological reactions, and; (d) developing generic technologies for realising ultra large capacity intelligent memory and ultra parallel processing capability by utilising data processing characteristics of biological systems.

The report also highlighted the importance of

- interdisciplinarity, and
- consolidating infrastructures for R&D promotion including funding opportunities to demonstrate creativity across Ministries, setting targets in considering social needs, strategies for intellectual property rights, and promotion of core nanotechnologies for measurement, evaluation and simulations.

In August 2001, the Ministry of Education Science and Technology (MEXT) published a follow-up report, outlining its proposed plans for supporting research in nanotechnology. This report again highlighted the importance of nanobiotechnology research and reiterated the priorities identified by CSTP. Its projected timescale for the introduction of nano-based medical treatments are indicated in Fig. 1.

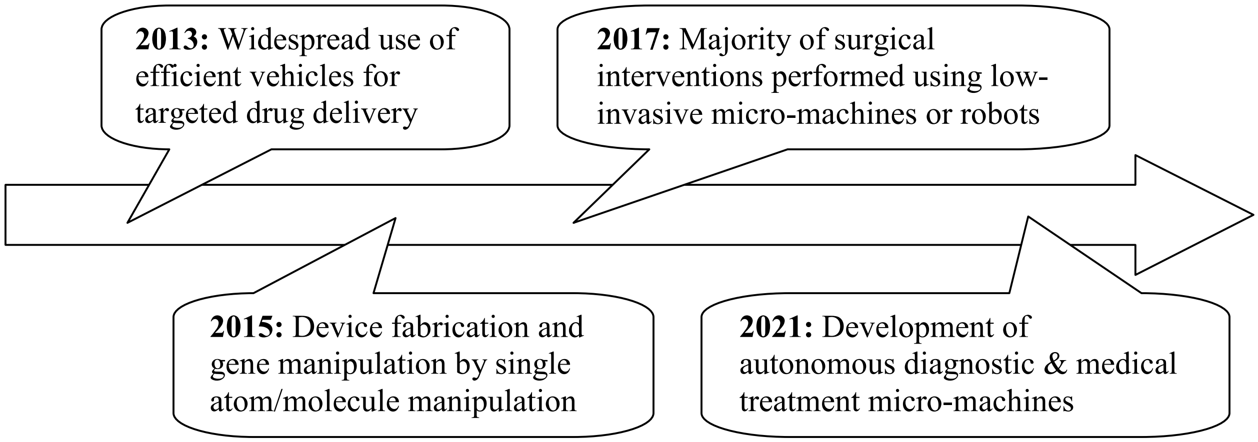

Figure 1: MEXT aspirational timescale for the introduction of nano-based medical treatments (source: Tetsuya Yamazaki, MEXT Nanotechnology Foresight).

Against this background, the Japanese Government is investing heavily in nanobiotechnology, and four Ministries have now launched bionanotechnology programmes (Box 1). Further details on these public-sector programmes are provided in Appendix III. There is generally little coordination between Ministries or programmes.

BOX 1: GOVERNMENT MINISTRY BIONANOTECHNOLOGY PROGRAMMES

Ministry	Focus
Education, Culture, Sports, Science & Technology (MEXT)	Functional materials, molecular machines, biodevices (including DNA electronics), bio-hybrid devices, biosensors, programmed self-assembly
Economy, Trade & Industry (METI)	Analysis and simulation of dynamic networks within cells
Health & Labour (MHL)	Non- and low-invasive medical technologies including single molecule measurements, development of nanodevices to mimic biological functions, tools for minimally invasive surgery, nanoparticle-based drug delivery systems
Agriculture, Forestry & Fisheries (MAFF)	Gene, single molecule and cell manipulation and functional characterisation, biomimetic components and systems, biomimetic materials, nanoparticles, cell culture plates

Public Sector Activity

Researchers at both universities and national laboratories have been playing a leading role in developing underpinning technologies for nanobiotechnology in recent years. Research effort is being focussed in the following key areas:

- Direct observation, imaging and manipulation of biomolecules (especially scanning probe microscopy), the major players being Kobayashi (Tokyo), Kusumi (Nagoya), Kawai (Osaka)
- Molecular motors (especially myosin and kinesin, an area of real strength in Japan), the major players being Uyeda (AIST Gene Discovery Research Centre, demonstrated uni-directional transport of actin filament fragments on microfluidic chips by kinesin motor proteins), Yanagida and Namba (Osaka University), Yoshida (Tokyo Institute of Technology), Hamachi (Kyushu University), Yumoto (AIST Kansai), and Kinoshita (Okazaki National Research Institute).
- Micro- and nano-arrays for genomic/proteomic analysis (especially integration of arrays into micro total analysis systems), the major players being Baba (Tokushima), Kitamori (Tokyo), and Fujii (Nagoya). Research is focused on the integration of a series of analytical processing steps such as extracting DNA from a cell, amplification, separation, hybridisation and detection of DNA for genome analysis on a single chip.
- Biosensors for on-chip applications, the major player being Tamiya (Japan Advanced Institute of Science and Technology, Ishikawa).
- Nanoparticle based drug delivery, the major players being Kataoka (Tokyo), Okano (Tokyo Medical Women's College), and Matsunaga (Tokyo University of Agriculture and Technology).
- Self-assembled biomimetic materials, the major player being Hara (RIKEN Wako campus).
- Tissue Engineering is a major activity at AIST major activity (500 people, $1m pa), using the AIST cell processing centre. The main focal points are in cartilage repair and neurological repair for Parkinsons. There exists a large network of collaboration i.e. Osaka District (SAI-TO), Kobe City (KIKEN CDB), Frontier Medical (Kyoto University) and NCVRU (Cardiovascular Centre).

Detailed visit reports on the work of Professor's Kawai (Osaka University), Baba (Tokushima University), and Namba (Osaka University in collaboration with Matsushita), and of the Osaka campus of the National Institute of Advanced Industrial Science and Technology (AIST) are provided in Appendix I. Further details on the other University and public-sector Research Institute programmes described above are provided in Appendix IV.

Despite all this activity, there is remarkably little contact between universities and the private sector[20], an exception noted by the Mission being the close collaboration between Dr Namba and Matsushita Electric (see Appendix I). Japanese public universities hold few patents, it is difficult to pass those which do exist to the private sector, and investment by state universities in start-ups is impossible. Of note, however, are the Tokyo University spin-out companies 'Micro Chemical Technology Research Inc. and NanoCarrier Co Ltd. Private universities, however, are more active in this arena.

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[20] Until recently, paid consultancy was impossible for Professors in state universities. Acceptance of industry funding for research until recently exposed a state employee to prosecution for bribery.

Private Sector Activity

In March 2001, the Keidanren, Japan's most influential grouping of private companies (the equivalent of the CBI in the UK) publicised its views on nanotechnology development in a document entitled "n-Plan 21". This report highlighted the importance of nanobiological systems research in particular, and called for focused research on the development of "lab-on-a-chip" technology (μ-TAS) and drug delivery systems (DDSs), as well as novel, low cost and low energy consuming bio-chemical processing.

A recent survey of 194 Japanese companies by Eurotechnology Japan K. K.[21] has revealed that 43% have started R&D in nanotechnology, with Fujitsu, HP-Japan, Hitachi, Mitsubishi, NEC, and SONY together estimated to be spending US$770 million p.a.

Japanese industry involvement in the development of nanotechnology in the fields of biotechnology and life sciences is not as advanced as in the IT and electronics field. However, there are a growing number of major Japanese firms and newly formed venture businesses active in nanobiotechnology. In particular, there is increasing interest among IT companies with already active life science businesses. For example, Toshiba, Hitachi and Fujitsu have entered the nanobiotechnology area focusing on the development of "lab-on-a-chip" and DNA chip technologies. Analytical instrument and diagnostic companies, particularly those in the medical equipment and instrumentation business, are also entering the market as they see nanotechnology as vitally important in the post-genomic era. A number of chemicals companies are also investing heavily. But so far there has been little public interest from the Japanese pharmaceutical sector. According to the Japan Pharmaceutical Manufacturing Association, although the Japanese pharmaceutical sector is keeping a "watching brief" on developments, they claim their interests lie in using bionanotechnology, and are therefore unwilling to commit themselves to undertake joint development. But Takeda Pharmaceuticals are members of the newly created Kansai region nanotechnology consortium.

Venture capital is beginning to validate nanotechnology as an area worthy of commercial pursuit. In April 2001, trading house Mitsubishi Corporation established an investment fund targeting start-ups developing new materials, IT equipment, and medical technology based on nanotechnology. This investment fund, in collaboration with Mitsubishi Chemical Corporation set up a new company, Frontier Carbon Corporation, for mass production of carbon fullerene molecules. Construction of their pilot plant in Kitakyushu, Japan is due to be completed this September.

Detailed visit reports on activity at NTT Basic Research Laboratories, Olympus Optical Company, Toshiba Corporation, Shimadzu Corporation and Matsushita Electric Industrial Company are provided in Appendix I. In addition, brief details of activities by Canon, Fujirebio, Fujitsu, Hitachi, Hosokawa Micron, Toray Industries, NEC and relevant SME's are provided in Appendix V.

[21] 'Bio-Nanotechnology in Japan – Venture Capital, Public Policy & Results' Gerhard Fasol, Eurotechnology Japan K. K., April 2002

Sector Specific Observations

Diagnostics

The diagnostics market is often targeted by new areas of research as one of obvious and certain application, however since the growth phase in the 1960s & 70s it is in fact a business of small margins, especially when compared to selling drugs. This traditional scope of diagnostics is typically assay focused, with low technology input. As a result of the recent expansion from genomics, a new area of strong growth is emerging, and this is characterised by its inclusion of new hardware technologies. Perhaps of even greater importance, from a commercial aspect, is the consequential renewed synergy between diagnostics and drugs.

In this discussion *in vivo* diagnostics (medical devices, e.g. imaging) should not be forgotten. In the UK this market is viewed as demanding and complex due to the imposing regulatory and quality hurdles, coupled with often low volumes of eventual manufacture. This is somewhat different in Japan, where there is commitment to long term research - such as in the development of intravascular catheters with actively bending tip by Olympus.

The diagnostics market in Japan is certainly large at $2.9 billion, with a per capita annual spending of nearly $23 on diagnostics (compared to $4 in Taiwan and $10 in Australia). Japan is the second-largest market in the world, after the United States, for nearly every type of *in vitro* diagnostic (IVD) product. Despite the fact that Japanese laboratories pay some of the highest prices in the world for their instruments and reagents, margins in Japan are thin. This is because a huge proportion of the country's outlay for IVDs is taken up by distribution costs and laboratory costs (high labour and property expenses). Wholesalers, who are often non specialists, buy from local subsidiaries of multinational manufacturers. The big manufacturers could service their end-users directly, but they all sell through wholesalers to decrease the need for their own distribution infrastructure. The process of selling to hospitals also is a complex one, which has traditionally been supported by wholesalers.

There are other key market distinctions in Japan. The Japanese regulatory system is complex. It acts as a barrier to entry for smaller international companies, and encourages local manufacture. Reagent rental-instrument placements are not common - laboratories like to pay cash for big, expensive open instrumentation from Hitachi, Toshiba, Shimadzu, Olympus, and Sysmex, and then squeeze their reagent suppliers. Because Japan has well over 100 indigenous reagent suppliers, taking open-system reagent business away from the local firms is nearly impossible for an outsider. This does not equally apply to immunoassays. Here importers command about half of the immunoassay market, but the share of all other IVD product categories represented by imports is very modest.

Japan is an enthusiastic consumer of electronic gadgets and has even been an early (only) user of home diagnostics, an example being sensors for urine analysis incorporated into bathroom fixtures. However their uptake of POC diagnostics in medically supervised situations (such as genetic testing) has lagged behind the US, although this is changing.

There is very little evidence of new nanobiotechnology research being focused towards diagnostics, and most projects reviewed by this mission have targeted considerably longer time horizons. Although not within the scope of this mission, there is much biosensor research in Japan (e.g. NTT enzyme biosensor work), but it should be noted that much of this is academically focused and not relevant to near term clinical diagnostic products. Much of the nanobiotechnology work appears in its early stages to be highly isolated from commercial implications.

Drug Discovery

The drive for developing new nanobiotechnology-based tools for drug discovery appears to be led by the providers rather than the end users. There was little evidence that the Japanese pharmaceutical sector was entering into significant product development relationships with the companies visited. The most notable near-term deliverables were in the area of genomic and proteomic analysis. This was emphasised by the newly established Genome Medical Business Division at Olympus, where a number of such products have reached or are close to market, and by instrumentation under development by Shimadzu.

A number of tools for basic research and compound screening are also under development, examples being the electrophysiological sensor and cellular assay devices described to the Mission by Matsushita. On the more distant horizon, there was evidence that the increased computing power arising from advances in nanofabrication, as well as DNA computing techniques, are being used to model increasingly complex biological systems. Toshiba's analysis of nanoscale DNA dynamics by MO techniques is illustrative, and if progressed to the stated goal of fully describing the behaviour of a living cell could have a profound effect on our understanding of such systems and their potential modulation by drugs.

It is clear that Japanese expertise in optical and electronic device fabrication and mass production is well placed to provide a key component in these applications. The biological expertise appears to be acquired mostly through collaborations and joint ventures, rather than through in-house recruitment, although the latter was evident in some companies.

Therapeutics and Devices

Little evidence of world-class or significant activity in the medical device and therapeutic fields was apparent to the Mission. This could however be due to the Mission emphasis on Japanese nanotechnology, and the clear uncertainty worldwide, in the general medical arena, of an important clinical role for nanotechnology. It may also reflect the companies and institutions visited (i.e. there may be more activity in this area in other centres). The device and therapy related technology that was presented was not specifically nanoscale, but lay more at the nano/micro interface. Some examples included work at Toshiba (in collaboration with Keio University) in robotic surgery (micro suturing and scissors). The medical group at Toshiba are primarily involved in instrument development, but also are developing fuel-cells. Work revealed to the Mission at NTT focused on wearable or implantable devices based on bio-interface research. They described a programme of neuronal/neural stem cell studies investigating behaviour of cells cultured on variously modified surfaces. A detailed study of cultured cells and brain slices and their electrical signal generation, transduction and dynamic networks formed part of this programme. This work reflected NTT's core business interest in robust communications networks and also in futuristic devices for synapse-based human communication. They collaborate with Kings College London in a programme for early detection of heart disease. They indicated that they have no plan to manufacture bio-interfaced devices; all the programmes were directed at proof of principle only. Panasonic (Matsushita) was also engaged in research into brain electro-physiology. The life-science activity at AIST lies at the interface between genomics and materials science. There are groups interested in engineering for manipulation and for measuring cell function; i.e. nanotechnology, tissue engineering, materials, and human interface devices. Tissue engineering is a major activity (500 people, $1million p.a.) at the AIST cell processing centre. The focus is on cartilage repair and neurological repair for Parkinson's disease. They also described a programme using polyelectrolyte activators to develop artificial muscles. This has not reached any clinical application but is being evaluated by NASA for application in wiper blades.

Intellectual Property Rights

Japan uses its patent system to facilitate the transfer of intellectual property (IP) rather than to protect it. The Japanese patent system is meant to educate, as opposed to protect an invention as in the U.S. system. Japanese patent applications are made public and open to rebuttal by competitors. As a result, it is difficult for a firm to exploit its technology. There are many examples of Japanese firms flooding a market with trivial patents around a basic patent, with the purpose of forcing the basic patent owner to cross-license its core technology in order to gain access to that market. A second strategy is to develop a portfolio of related or similar patents that likewise make it difficult for a firm to exploit its core technology alone. IP is regularly traded between established competitors.

The approach to protection and exploitation of IP is out-dated. Both in companies and academic institutions there seemed little awareness of the importance of internationally protected IP. The prime emphasis was on the home market. Unless international applications have been made, the value of the IP to organisations working on a global basis will be low (further filing would be difficult due to the Japanese patents constituting prior art). There was no evidence at any of the institutes visited of active IP management, such as attempts to commercialise or license out non-core IP. The academic institutions visited seemed unaware of the financial cost of maintaining a large and unstructured IP portfolio, a situation encouraged by the fact that a government sponsored organisation meets the patent maintenance costs.

Although there was evidence that the collaboration practices of some companies were changing, the norm was still to pursue collaboration either in-house or with other Japanese companies. International technology partnering and R&D collaboration on the development of new technologies is still in its infancy in Japan, but things appear to be changing. Again there appeared to be no clear strategy regarding IP policy within such collaborations.

In general the industry relating to the management, acquisition and commercialisation of IP is very immature and awaiting leadership. The government, however, has recognised this and is heavily funding a number of initiatives to encourage commercialisation and spin-out of companies. As previously mentioned in this report, this demands a cultural shift due to the natural poor fit of small company management within the Japanese employment and social system (there is a higher social status and perception of security associated with working for established large companies than for a small unknown technology companies).

Market Awareness

Japanese firms are distinguished by the long-term commitments they are prepared to make to the development of new products, components, equipment, and technologies. There are numerous examples of Japanese commitments to long-term developments, such as Sony's 13-year program to introduce charge-coupled device (CCD) image pickup components for the camcorder. Sharp licensed RCA's liquid crystal display (LCD) technology and spent nearly a billion dollars over a decade before its development efforts were brought to market.

Japan has created a major competitive advantage from its development of low-cost, high-volume consumer products, but even in the current economic situation, long term research has not been forgotten. Hence, while the majority of Japanese industry is heavily, and very efficiently, product development focused, there is significant resource reserved in many corporations for a rather protected "blue skies" research activity, the like of which is a distant dream in the UK. The corporate motivation is explained as recognition of the need to diversify core manufacturing capabilities, and maybe also a certain level of corporate qudos. There was, however, limited evidence to illustrate a corporate understanding (within research groups at least) of potential new markets. It is possible that a very different view might have emerged if the Mission had interacted more with company business development and market strategy groups.

The corporate research groups visited appeared to be directed in their choice of programs solely by scientific interest. There was little evidence of the role or integration of criteria like market awareness, manufacturing cost analysis, regulatory requirements and technology development timescales in directing research strategy. In some cases very unrealistic expectations regarding timescales and the investment needed to progress new technology through medical regulatory requirements was shown. The strategy described by the research groups was based on a long term scientific investment, where science would be given a lead and not be driven by market goals. This was particularly noticeable in some companies, where key academics were given free reign to pursue ambitious goals (e.g. Matsushita, molecular motors work of Professor Namba).

Such an approach differs markedly from the "spin-out" culture of the US. In general the groups visited expressed a determination to take technology feasibility projects through advanced stages of product development, prior to (or at least decoupled from) detailed market analysis (market volume, competitors, user and regulatory requirements). Several discussions, however, indicated a change in approach. The collaborations and commercially focused programs at Olympus were based on an efficient process of licensing in technology where it proved beneficial to do so. In discussions with universities and public-sector research institutes, it was apparent that the development of a culture of technology exploitation and the incubation of spin out companies is gaining momentum.

Technology Commercialisation

Routes to Commercialisation of Corporate Industrial and Academic Research

a) Corporate Industrial Research

In a somewhat simplistic analysis the attitudes to collaborations seems to fall into two broad categories.

i) Organisations in this category have long timescales for their corporate strategic research, (>10 year event horizon) i.e. funding in-house work on fundamental research, designed to produce a paradigm shift in their core technology capability and drive concept development and culture shift for the organisation as a whole. They typically publish rather than patent, and hand over research concepts to the business units for research to technology translation. What is somewhat surprising is that there is a relatively low level of collaboration even with academia, particularly with the Japanese academic base. Some organisations see potential in-house venture funds to establish "spin-up" companies to commercialise technologies which are outside the core business units of the corporation. There also seems to be an enthusiasm to identify globally diverse joint venture or strategic collaborations as routes to market for such technologies. However, it seems likely that these corporate research activities will require significant further work to bring the product concepts through into commercialisable property. Therefore, even early stage out-licensing is likely to be problematic unless the recipient is willing to pick up substantial technical uncertainty in progressing the technology to market.

ii) The second category are typically more focused companies, with a narrower range of product offerings or market sectors. In-house research is product-focused, e.g. with a 5 year event horizon. The core competence, business-oriented research is done in-house, but they are keen to collaborate with complementary research/technology providers where needed to bring products forward (e.g. capillary electrophoresis micro-pillars in the Olympus instrument). They are happy to work with small suppliers and co-badge products. Their route to market is via their own or national company distribution marketing. Hands-off out-licensing is unlikely to be a key area for development of partnerships as they are more tied to their core technology and would want to control its entry into the market.

b) Academic Research

There has recently been a 180 degree change in government stance on the role of the publicly funded academic science and engineering base, from a position where it was impossible for academics to receive direct industrial funding and there was little patent activity, to one where industry funding is actively encouraged and targets for the commercialisation of public-sector funded research are mooted or close to introduction. Some universities are being restructured to include Institutes which carry out research driving towards new technologies and commercial opportunities, leaving a core University structure to focus on teaching and fundamental research. The funding mechanisms are being restructured to mirror this framework, i.e. a) strategic, b) grant in aid, c) short term (3 years to market!), or d) mega project ($800 million) half industry funded.

There is also a strong driver to generate start up companies to commercialise new technologies, and out-licensing technology is actively encouraged. The mechanisms and financial support for this process were not clearly apparent to Mission members, and appear to be under development. Mention was made of national spin-off company targets with indicative devolvement to the local and even specific institutional level. It is interesting to note that cabinet-level officers developing this policy view the US and UK as role models.

Routes to commercialisation are varied. Examples noted during visits include direct collaboration with a key manufacturer (e.g. Prof. Baba/Olympus), and academic-led start-up companies (e.g. Osaka), where there is active encouragement of individuals. While this activity is being driven strongly by central government, it was less clear that there is a government-supported programme to aid the process. IP filing is supported, financially and with hands-on expertise, via the Japan Science & Technology Corporation (JST), a government funded organisation, but this is not always seen as being pro-active, so universities are beginning to set up there own technology commercialisation operations.

It was interesting to note that the industrial researchers we met do not, by and large (with Olympus a notable exception) view the academic research base as a source of new technology, and feel that public-sector funding for academic research fulfils the interests of the academic scientists but not of industry.

c) Public-Sector Research Institutes

The position with government-funded research institutes seems to parallel the situation in Britain about 10 years ago (e.g. the Institute of Advanced Industrial Science and Technology (AIST) formed in 2001 in a re-organisation of METI institutes), with the desire from central government that direct government funding should gradually be replaced by private sector funding or self-sustaining commercial research. AIST appears to see the route to market as being dominated by start-up company generation, and appears to be relatively inactive in pursuing other possibilities (e.g. out-licensing, joint ventures, outsourcing manufacture, co-marketing and distribution). They are currently setting up incubator space to encourage start-up companies, and typically are starting a few per year- nowhere near enough to fulfil government targets for the public sector of 300-500 p.a. The culture is changing rapidly, but such organisations still have some way to go to become sophisticated players in identifying, protecting, exploiting and finding flexible routes to market for new technologies.

Conclusions and Recommendations

The integration of biotechnology, information technology, cognitive science and nanotechnology is indeed viewed in Japan as key for the creation of new scientific and industrial fields, and to enable progression of advanced industrialised nations up the value chain. Japanese electronics and communications companies are establishing strong nanobiotechnology activities, and there is evidence that they are seeking partnerships with organisations which possess expertise in areas complementary to their traditional focus. There is a revolution occurring in Japanese universities and public-sector research institutes, which are starting to become more entrepreneurial and are beginning to pursue closer relationships with industry. Relevant government departments are investing heavily in both blue-skies research and R&D projects which link universities, research institutes and companies. Industry R&D is characterised by its long-term horizons and large commitment, and the Mission was impressed by the strength and activity in both the public and private sector in understanding and harnessing opportunities provided by the integration within physical devices of complex functional biological entities such as biological motors.

Taken at face value, this would seem to be an ideal climate for innovation and rapid economic growth. Technology convergence is clearly recognised to be an opportunity in Japan, but little evidence emerged of a serious attempt to quantify market opportunities and provide focus. Much of the work described to the Mission appeared at its current stage of development to be highly isolated from commercial implications. At the very least, the scientific teams involved in technology or product development articulated little market awareness. In the clinically related fields of diagnostics and devices there was little evidence of synergistic relationships with the Japanese pharmaceutical sector, or close clinical collaboration to determine end-product value. There was also an apparent complacency or ignorance regarding regulatory pathways. In addition, there was little evidence of internationally leading activity in the medical device or therapeutic fields.

The Japanese approach to the protection and exploitation of IP was felt to be out-dated in comparison to that of Japans major competitors. There was no evidence at any of the organisations visited of active IP management, such as attempts to commercialise or license out non-core IP. The academic and public-sector research institutions visited seemed unaware of the financial cost of maintaining a large and unstructured IP portfolio, a situation encouraged by the fact that a government sponsored organisation meets the patent maintenance costs.

The corporate research groups visited appeared to be directed in their choice of programs solely by scientific interest. There was little evidence of the role or integration of criteria like market awareness, manufacturing cost analysis, regulatory requirements and technology development timescales in directing research strategy. In some cases very unrealistic expectations regarding timescales and the investment needed to progress new technology through medical regulatory requirements was shown. It was notable that the industrial researchers we met do not, by and large, view the academic research base in Japan as a source of new technology, preferring if at all to consider partnering with research institutions abroad. There is a view in industry that Japanese public-sector funding for research fulfils the interests of academic scientists, not industry.

Spin-out activity from universities is being actively encouraged by central government. It is less clear that there is a corresponding government-supported programme of any sophistication to aid the process. The culture in universities and public-sector research institutes is changing rapidly (or is at least under great pressure to do so), but such organisations still have some way to go to become sophisticated players in identifying, protecting, exploiting and pursuing flexible routes to market for new technologies.

The norm in Japan is to pursue collaboration either in-house or with other Japanese companies, however clear evidence emerged that collaboration practices are changing. International technology partnering and R&D collaboration on the development of new technologies, while still in its infancy, is possible. There is complementarity between Japanese and UK strength and expertise. As noted in the recent UK Nanotechnology Strategy document, it may indeed be too late for the UK to compete internationally in applications such as semiconductors. However, the strength and health of UK academe and industry in pharmaceuticals and biotechnology, the strong decoupling of Japanese electronics and communications companies from the Japanese pharmaceuticals sector, the greater sophistication of the UK in international IP management, and possibly even our record in entrepreneurship and better understanding of spin-off support needs, all present particular opportunities for Japan-UK collaboration.

Appendix I

Individual Meeting/Activity Reports

NTT Basic Research Laboratories

Mission Contact
Dr Masao Morita
Manager, Research Planning Section
3-1 Morinosato Wakamiya, Atsugi-shi, Kanagawa 243-0198

The Company
NIPPON TELEGRAPH AND TELEPHONE CORPORATION
Head Office: 3-1, Otemachi 2-chome, Chiyoda-ku, Tokyo 100-8116, Japan
Paid-In Capital: 937.95 billion yen (March 31, 2002)
Total Number of Shares Issued: 16,134,590 (March 31, 2002)
Number of Employees: 3,165 (March 31, 2002)

The functions of the company are:
(1) Acting as a holding company for shares issued by Nippon Telegraph and Telephone East Corporation and Nippon Telegraph and Telephone West Corporation (hereinafter referred to as the Regional Companies), and exercising rights as sole shareholder and owner.
(2) Providing necessary advice and mediation to the Regional Companies
(3) Conducting research relating to telecommunications technology as the basis of telecommunications
(4) Carrying out business incidental to item (3) above, and other business

Corporate research is structured as follows:

Cyber Communications Laboratory Group
Cyber Solutions Laboratories
Cyber Space Laboratories

Information Sharing Laboratory Group
Service Integration Laboratories
Information Sharing Platform Laboratories
Network Service Systems Laboratories
Access Network Service Systems Laboratories
Energy and Environment Systems Laboratories

Science and Core Technology Laboratory Group
Network Innovation Laboratories
Microsystems Integration Laboratories
Photonics Laboratories
Communication Science Laboratories
Basic Research Laboratories

The Basic Research Laboratories (BRL) group was formed through company reorganization in 1999 and now consists of 3000 researchers with a budget of approximately £1100 million p.a.

Group Visited
Basic Research Laboratories (specifically the Environmental Assessment, Biosensing, and Molecular and Bioscience Research Groups within BRL). The Bioscience Research Group consists of approximately 30 people, with 1% of the BRL budget.

Representatives Present
Dr Masao Morita, Manager, Research Planning Section
Tohru Tanaka, Group Leader, Environmental Assessment Group
Dr Osumu Niwa, Group Leader, Biosensing Research Group
Keiichi Torimitsu, Senior Research Scientist, Molecular and Bioscience Research Group

Technologies Outlined
The NTT long term research strategy is driven from a future vision focused around the concept of a "universal" information network. This is a "living environmental network" in which telecommunications networks are the vehicle to carry information to service every aspect of life, including health monitoring, environmental monitoring, interpersonal communication, entertainment, business information, etc. They therefore see the need for disruptive technologies in two broad areas: enhancing the bandwidth and processing power of the electronics which will provide the technology platform for this new capability, and ubiquitous smart sensors to measure a huge variety of environmental and biological signals.

In the former area, they have active in-house research to understand and manipulate biological signal processing systems, e.g. neural cells. These studies are not, in the first instance, aimed at producing micro/nanoelectronic devices per se, but more to understand the algorithms behind these systems which could then be applied to create a paradigm shift in the design of semiconductor based technologies. In one example, Wistar rat, post natal cortex or hippocampus cells are grown on polysilane surface-modified multi-array transparent electrodes to understand signal and information exchange by detecting both electrical signals and neurotransmitter effects on the pattern of neuron development and activity. Neurotransmitter activity is followed in real time, e.g. glutamate transport and release followed by laser trapping Raman to look at vesicle content. Synapse development across the electrode array is random at first. Etching shallow (10 micron) tracks on the chip enables some degree of ordering of neurites. Surface modification through oxidation alters the degree of cell adhesion. Controlled growth of a network has been achieved on a hexagonal grid which can then be used to measure multi-site electrical activity using an electrode grid array. Using this system they have detected synchronised firing of different cells which depends on strength and frequency of the electrical stimulation. Using different pathways between the electrodes it is possible to get a range of response times between 200 and 300 ms. With repeated firing, pathways become modified to get optimised firing around 200ms.

There may be a biomedical application of this work, e.g. its use in repairing the pathway from the eye to the visual cortex in damaged tissue. By using 300 micron thick brain tissue slices on network electrode arrays and simulating optical stimulation they have observed fast response in thalamus but it takes longer before a response is observed from the cortex. They have shown that the experimental system can be used to measure L glutamate neurotransmitter concentrations at 10 nanomolar and to map the distribution of receptors in different regions of the brain, and to correlate neurotransmitter concentration with cellular activity. In future, it may be possible to use glucose metabolism or ATP to power implanted chips for possible biomedical applications, e.g. in the control of Parkinson disease, or use a CCD as input sensor for treatment of blindness. The impression was gained that these are not current targets, just future possibilities.

There is significant activity in the development of new chemical sensor systems and their incorporation in devices. One technology already on the market is a nanostructured porous substrate (mesoporous silica with mean pore diameter of 6 nm). This is being used to enhance the adsorption of pollutant gases, and supports a dye sensitive to benzene and xylene at sub ppb levels. This has been incorporated into an air quality environmental monitoring system to monitor and control urban traffic pollution. A more generic approach to high sensitivity detection was described which uses surface plasmon resonance plus electrochemical detection to enhance the sensitivity from antibody, DNA or enzyme substrate reactions with short residence times.

Lab-on-a-chip devices are clearly a key target, one example being the development of real time imaging of fluid flow in microchannels by imaging the difference in reflection intensity observed when two different potentials are applied to a channel. This technique has been used to image ammonium ions as initiator of different enzymes. There may be potential to develop miniaturised optical waveguide-based sensors based on polymeric (rather than glass) substrates, for example as *in vivo* bio-sensors.

The company appears to be very well connected with industrial and academic collaborations across the globe, with the partner organisation providing expertise on the biochemical and biomedical application of the technologies being developed in-house.

Market Opportunities from Company Perspective

NTT has a clear and strong vision of the future driven by broad-band, high information-content telecommunications, e.g. for entertainment (music or movie data) and so-called ‘ubiquitous services’ (the concept of a pervasive network of information flow, in which sensors providing real-time interfacing of biological systems with electronic devices are crucial). The extensive work on cultured neural networks should provide insights on the dynamic architecture of the brain and its efficient fault tolerant processing and signal routing strategies with potential benefits for in-silico processor and communications network design. This research may also lead to the development of interfaces to the human nervous system, with the long term vision of in-brain chip implants.

Research within NTT/BRL has a greater than 10 year horizon, and is therefore not actively patented, but valued for the knowledge it will bring to future product design. Results, expertise and whole teams can, however, be rapidly transferred to product development business units with responsibility to transition promising research through to commercialisation, and within which patenting will take place. NTT see themselves first and foremost as a telephone/telecommunications company, so information sharing is key to their business. Fast signal processing and semiconductor improvements (nanometer-size chip features are difficult to fabricate) are key to that business, and by 2010 a breakthrough to non-silicon technology incorporating some bottom-up assembly appears necessary. NTT therefore feel a need to have in-house research on promising new approaches to define and realise this technology.

NTT also have plans to enter the continuous health monitoring market, however it was not clear whether NTT see themselves as a provider of devices for health monitoring, or primarily as a high capacity network/communications provider, with this market (among others) driving the need for increased network speed and capacity.

Approach to In-House Research, Technology Transfer & Collaborations
NTT/BRL see themselves as an open laboratory and welcome scientific exchange with leading academic and public-sector research institutes worldwide. They are clearly pro-active in seeking partners to complement their core skills, which they see as physics and optics based technologies. Collaborations in areas like enzymes, dyes, antibodies, redox systems, etc. seem particularly promising, as such expertise will be required to develop or demonstrate the feasibility of the biosensor component of the ubiquitous information network.

Olympus Optical Co Ltd

Mission Contact
Dr Atsushi Yusa
Director, Senior Operating Officer, Chief R/D Officer
2-3 Kuboyama-cho, Hachioji-shi, Tokyo 192-8512

The Company
OLYMPUS OPTICAL CO., LTD.
Head Office: Shinjuku Monolith, 3-1 Nishi-Shinjuku 2-chome, Shinjuku-ku, Tokyo 163-0914
Capital: ¥40.8 billion (March 2001)
Consolidated Net Sales: ¥466.7 billion (March 2001)
Number of Employees: 4,282 (March 2001) (NB: Olympus Group employees: 19,865)

The company is organised into four main groups, namely Imaging System Group, Medical Systems Group, Industrial Systems Group and the Corporate R&D Centre.

Group Visited
Corporate R&D Centre, Utsugi, Hachoji, Tokyo; one of two Technology Research Institutes. The two institutes employ 2400 staff, more than half the total Olympus Optical Company employees. The R&D spend for 2001 was ¥30.8 billion, approximately 6.6% of net sales.

Project time lines are normally in the region of 3-5 years, with the exception of short life-cycle products such as digital cameras, which are typically less than a year.

The main focus of the visit was the recently established Genome Medical Business Division within the Medical Systems Group. This has the business goal of becoming, by 2010, Olympus' new core business with sales of ¥100 billion. The drive for this new business is the shift in the medical world from observation, where Olympus already had a presence with products such as medical endoscopes and microscopes, towards diagnosis, and ultimately to treatment.

Representatives Present

Dr Takashi Mihara, General Manager, Imaging Technology, Strategy Department
Mr Hiroyuki Yoshimori, Deputy General Manager, Genome Medical Business Division
Dr Sachiko Karaki, Chief Manager, Genome Medical Business Division
Mr Takashi Nagano, Chief Manager, Genome Medical Business Division
Mr Makoto Nakamura, Chief Manager, Genome Medical Business Division
Ms Hiroko Sakamoto, Genome Medical Business Division
Dr Nobuhiku Morimoto, Genome Medical Business Division
Kunihiko Miura, Genome Medical Business Division

Technologies Outlined

The three products described during the visit demonstrated their approach to collaborative research and development. Firstly, a single molecule fluorescence detection system (MF20) for high-speed analysis of protein and DNA interactions, and a closely related product (MF10S) for analysis of PCR products were co-developed with Evotec OAI, Germany.

In a second collaboration with PamGene, Netherlands they have developed a microarray system due for launch in Japan in summer 2002. Key to this technology was a porous inorganic substrate with a very high surface area onto which the microarray was spotted (120 micron spots) with a non-contact spotter. Hybridisation speed was greatly enhanced by repeatedly pumping the analyte through the porous substrate in a procedure referred to as "dynamic incubation".

The third product described was a new biological information analysis system using DNA replication methods ("DNA computing system"), in collaboration with Mitsui Knowledge Industry Co Ltd and Professor Akira Suyama, University of Tokyo. In a change of business model, a spin-out company, NovusGene Inc has been established (50% Olympus, 50% Mitsui) to offer analytical services based on the technology, rather than sale of instruments. The initial application for the instrument is high precision gene expression profiling, with future extensions to SNP analysis and detection of genetic disease.

Market Opportunities from Company Perspective

There is a clear commitment to the further development of the Genome Medical Business over the next decade. Phase I (market assessment) is ongoing, and the business has been launched with an emphasis on the markets of genome-based drug discovery and cancer-related clinical application research. Phase II (establish market presence, 2003-2005) will see construction of a steadily developing business, and accumulation of analytical knowledge at the clinical level. Phase III (business scale expansion, 2005-2010) is targeted towards sales of systems and equipment for cancer-related diseases, and other lifestyle-related areas. As stated earlier, sales of ¥100 billion are forecast by 2010.

Approach to In-House Research, Technology Transfer & Collaborations

Olympus are working hard to develop core competencies in house in areas such as micro-engineering and photodigital. Where a necessary expertise is not available in house (as in the case of the "bio" components), external collaborations with universities and other companies are sought. This was amply demonstrated by the projects presented during the visit. The company will license technologies if required for value-added products. Sources of information on technology developed outside of Japan include, in addition to scientific papers, the Internet and other such avenues, information from venture companies brought via overseas marketing subsidiaries. Evaluation of potential collaborations rests with Olympus scientists whose expert knowledge is seen as critical.

The New Business Division and Intellectual Property Section of the Corporate R&D Centre are responsible for administering collaborations with industry and universities. Currently around 8000 patent rights are in force.

Toshiba Corporation Corporate R&D Centre

Mission Contact

Dr Minoru Saba
Chief Specialist, Strategic Planning Group, Research Planning Office
1, Komukai, Toshiba-cho
Saiwa-ku, Kawasaki 212-8582

The Company

Toshiba Corporation R&D Centre traces its origins to the Matsuda Research Laboratories established in 1899 and adopted its current form following reorganisation in 1999. It has the following major divisions: Information and communication systems (e.g. procurement software), mobile, network and consumer products (e.g. ultra portable computers and projectors), electronic components (e.g. TFT-LCD), medical systems (e.g. CT scanner), power systems and industrial equipment (e.g. Taiwan high speed railway system).

Group Visited

Toshiba Corporate R&D Centre in Kawasaki is working on a wide range of technologies such as; information technology, molecular wires, magnetic RAM, compact methanol fuel cell, robotic control for surgical applications, and recyclable urethane resin. Its DNA chip activity falls within the Business Development Office.

Representatives Present

Nobuhiro Gemma, Group Manager, DNA Chip Project Group, Business Development Office
Shigenori Tanaka, Senior Research Scientist, Advanced Materials and Devices Laboratory
Minoru Saba, Chief Specialist, Strategic Planning Group, Research Planning Office

Technologies Outlined

(i) Electrochemical DNA chip for molecular diagnostics (Nobuhiro Gemma): This technology was presented as an alternative to conventional fluorescence probe hybridisation, which needs expensive laser hardware and dye reagents. The electrochemical technology is a double strand DNA intercollator (Hoechst 33258 minor groove intercollator, Andrews 1990), where a voltage is applied at a gold surface. The current induced by oxidation of the intercolator is measured. The chip aims to be low cost, thus offering further improvements over conventional technology.

Toshiba are developing an instrument around this technology, which they explained has high throughput opportunities, since the hybridisation and detection takes only 1 hour in a single machine. However, it was noted that as with fluorescent hybridisation, sample preparation will be necessary. Toshiba will apply this technology to SNP detection for hepatitis C, of which there are 2 million patients in Japan, 5 million in the USA, and 170 million world-wide. Since interferon is effective in only 30% of patients and has severe side effects, use as a prescription aid for hepatitis C will be an ideal first product for SNP testing. The device is constructed from a silicon chip mounted in an IC board, housed in a plastic holder which also serves to provide microfluidic flow channels and a reaction chamber. The 96 electrode chip uses a 100µl sample.

(ii) Analysis of nanoscale DNA dynamics (Shigenori Tanaka): This is part of a 3 year JST funded collaborative project. A key component is the rational design of conductive DNA wires, achieved by developing state of the art computational tools demanding very large computing resources provided by super computers at collaborating university departments. Topics of study include: calculation of binding energies of nuclear receptors (e.g. ERalpha, RARgamma), which give good correlation with experiment (K Fukuzawa et al., submitted); electron transfer/conductivity in DNA, with applications to on-chip detection of DNA hybridisation, and DNA transistors; and quantum theoretical analysis of photo-induced hole transfer, which fits well with experimental observations of Lewis (JACS, 2000, 122, 12346). The ultimate project goal is the description of living cells by nanoscale molecular simulation, the results of which could be used to interpret and optimise perturbations introduced e.g. by drugs or electromagnetic fields and thus aid medical developments.

Market Opportunities from Company Perspective
Market awareness and knowledge of regulatory processes for the SNP work was not discussed. Regarding exploitation strategies, the key objective is to identify new areas and products for Toshiba. However a spin-off company might be considered if the R&D result does not fit well with Toshiba's core business or manufacturing capability.

Approach to In-House Research, Technology Transfer & Collaborations
The role of the Corporate R&D Centre was discussed and the long term commitment highlighted - for example it took 20 years for Toshiba to develop speech recognition to the point that it could be passed to the product development phase. The R&D Centre has a 5 year horizon, where as Toshiba product companies work to 1 year development plans. The R&D Centre is funded by 10% of the total R&D budget (which itself represents a total of 6% of company sales). An R&D Board defines funding allocations, with currently 40% invested in long term research, and 60% supporting product development. The corporate R&D Centre is tasked with "having a finger in every pie", and "responding to the market". Despite the traditional portfolio of Toshiba products, it was noted that Toshiba has been involved already for 10 years with projects involving biological sciences.

The electrochemical project described above was developed entirely in-house, since 1989. It was explained that Japanese professors are now allowed to take consultancy roles and that this is improving industrial - academic communication. Recruitment in this multidisciplinary area is not easy and comes mainly from Japanese universities.

UK-Japan High Tech Forum

The Mission coincided with the 17th UK-Japan High Technology Industry Forum which took place at Kazusa Akademia Park in Chiba Prefecture, just across Tokyo Bay from Yokohama. Three Mission members were directly involved in the Forum, Professor Terry Knibb as Chairman of the Asia-Pacific Technology Network and UK Chairman of the Forum, Professor Ken Snowdon as UK Chairman of the Nanotechnology & Miniaturisation Session, and Dr Julie Deacon as one of the two UK speakers in that Session. Mission members participated in the *Life Science* and *Nanotechnology & Miniaturisation* parallel sessions on the Tuesday afternoon, the *Forum Dinner* that evening, and the *Report Back* session the following morning. The following paragraphs briefly summarise observations of Mission members relevant to this report.

Nanotechnology & Miniaturisation

The parallel session on Nanotechnology & Miniaturisation was jointly chaired by Professor Hirokazu Negishi (Canon) and Professor Ken Snowdon (University of Newcastle). The breadth of the subject was reflected in the programme composition, addressing areas as diverse as nanomaterials, nanodevices, and nanobiotechnology. The session concluded with a lively discussion on similarities and differences between Japan and the UK in this rapidly evolving field.

In the area of nanomaterials, Dr Koichi Hiraoka of Kawasaki Heavy Industries described work being performed in collaboration with researchers at Kobe University on metal (Au, Ag, Pd, Pt, Ni, AuPd, AuCu) and semiconducting (Cu_2O, CuS, Ag_2S) nanoparticles thermally diffused (~100 ºC, 10 min) into thin polymer films (nylon 11, ~100 nm) formed by vapour deposition. Sandwiched between electrodes very thin films formed in this way exhibit Coulomb blocking and single electron tunnelling behaviour. They are also investigating the photoluminescent behaviour of Si and Ge nanocrystals embedded in a SiO_2 matrix, these films being formed by co-sputtering Si/Ge and SiO_2 and subsequent annealing of the resultant films. Mr Takashi Adachi of QinetiQ Nanomaterials described progress the company has made in developing production capacity (1-10 kg/hr) for powders of most metal oxides.

In the area of nanodevices, Dr Kazuo Eda of Matsushita Electric Industrial gave a wide-ranging presentation describing the technical, resource, population and environmental drivers for the digital and nanotechnology revolutions, the former providing an intangible asset, the second enabling realisation of novel technology within natural resource limitations. He described work by Matsushita on quantum dot fabrication for floating gate multi-value memory devices via self-assembly of nm-scale biomineralised particles, and on biochips for high-throughput drug screening. Further details on these two technologies are provided in the visit report on Matsushita in Appendix I.

In the area of nanobiotechnology, Ms Julie Deacon of CRL described a number of examples of their application of microfluidics expertise to the pharmaceutical sector, including a fascinating description of a 'bio-mimetic' chip for the production of speciality fibers (e.g. spider silk). An important point made by Ms Deacon (and a recurring theme throughout the Mission) was the need in this field to address a high-value market which can withstand the level of investment required to develop such products, which might then find wider application in lower value sectors. Finally, Dr Shouzou Fujita of Fujitsu's Nanotechnology Research Centre described work the company is doing to develop nanowire-based methods of on-chip signal transduction for label-less protein array chips. Fujitsu appear to view technology developments at the interface between human beings and the health-care network as key enablers to increase demand for products and capacity in the ICT sector.

The Session concluded with a general discussion attempting to reveal similarities and differences between public and private-sector experiences. Both countries have identified miniaturisation technology as a strategic priority. There is evidence for quite different company size profiles in the sector, with the UK having much more SME and spin-off activity, but Japan taking clear steps to increase activity and promote a more entrepreneurial climate. Views were expressed on the need for both highly specialised (leading edge) and multidisciplinary skills in this intrinsically cross-disciplinary endeavour. This essentially conflicting requirement is not easy to satisfy in university-level training programmes. Participants were reminded that the elusive definition of nanotechnology can obscure successful existing applications of nanotechnology which are not generally (or prefer not to be) identified as such. The age-old difficulty of identifying likely disruptive winners and killer applications was felt to be particularly acute in this multidisciplinary area.

Shimadzu Corporation

Mission Contact
Mr Kikuno
Shimadzu Corporation
Kuwahara-cho 1, Nishino-kyo
Nakagyo-ku, Kyoto 604-8511

The Company
Shimadzu was formed in 1875 and now is a ¥16.8 billion business, with 8000 employees. The business operates in the following main areas:

- Analytical/measuring instruments (50%): HPLC, UV, scanning microscopes, balances, DNA sequencers, micro chip electrophoresis analysers
- Medical systems (25%): CT, PET scanners
- Aircraft & industrial machinery (25%): Liquid crystal injection system, turbomolecular pumps, Boeing 767 series equipment, head mounted displays for aircraft

Group Visited
Life Science Laboratory, Sangyo Plant, Kyoto Office.

Representatives Present
Osamu Nishimura, General Manager, Senior Fellow, Life Sciences Laboratory, Analytical and Measuring Instruments Division
Shin Nakamura, R&D Manager, Life Science Laboratory, Life Science Business Unit.

Technologies Outlined

(i) MEMS: MEMS technology has a large emphasis and to this end Shimadzu have committed significant resource to fundamental research.

Project areas include:

- Functional devices, such as AFM cantilever and micro valve project (a confidential collaborative area)
- Sensor devices, such as SQUID (superconducting quantum interference device) for brain magnetic field measurements. Laminar flux gate sensor for magnetic field measurement – room temperature operation, ultra-thin layer.
- Micro TAS
  - MCE2010 microchip electrophoresis system. A single channel (50 x 20 micron) quartz device fabricated by lithography and wet etching. Photodiode array detector enables detection along whole channel, to give results similar to gel electrophoresis. Shimadzu have patented micro fabrication techniques (bonding at low temperature, silica substrate, integrated electrodes and optical slit).
  - DNA sequencer which is now in R&D is targeted for launch early in 2003. It is based on collaboration with GenoMEMS (a Boston start-up company) including technology licensed from MIT.
  - Nano-pillars (3 pillars per micron) developed with Professor Horike, University of Tokyo, and Professor Baba. Is used in capillary electrophoresis chips for isoelectric focusing for peptide/protein analysis.
  - Chemical reaction chip (25mm x 200 x 20 micron channel) for "efficient reaction". The project is looking at model chemistry in collaboration with a professor in Tokyo University, and includes liquid-liquid, liquid-gas and liquid-membrane-liquid reactions.

(ii) Shimadzu Biotech: Life science instrumentation for genomics and proteomics (www.shimadzu-biotech.com).

(iii) Reagent Business: An example of this area is Ampdirect™ a PCR buffer for blood samples.

(iv) Analytical Services: In Genomic research centre, to include DNA sequencing, SNPs, peptide and protein analysis.

Market Opportunities from Company Perspective

Shimadzu's current focus is clearly on mass spectrometry, micro TAS and MEMS technologies. These technologies will first be applied to genomic and protein research. However they expect to penetrate the diagnostic market within 10 years. Current applications of interest are: DNA sequencer, DNA fragment analyser, micro reaction system, fluorescent detection system, and point of care diagnostics.

Approach to In-House Research, Technology Transfer & Collaborations

Shimadzu have clear and focused market objectives, for example they wish to focus on microchip detection and so state that they will not consider biosensor development projects. Their IP strategy is traditional and is controlled by the legal department. Shimadzu policy is to put developments into the public domain and indeed base much internal R&D investment directly in areas (such as capillary electrophoresis) where US companies have very strong IP portfolios.

Collaborations are actively considered, as they wish to concentrate their own efforts on core technologies and skills. While they look for external alliances to speed up core projects, they do not consider opportunities to licence out any non-core IP that they generate. Shimadzu take part in government funded programs for basic research only, despite the large nanotechnology budgets that are now available (¥50 billion over the next 3 years). The group visited is not involved in dialogue which might guide government funding policy. Those interviewed feel this is achieved alone through government - academic institution interaction.

National Institute of Advanced Industrial Science & Technology (AIST) Kansai

Mission Contact

Dr Takahisa Taguchi
AIST
1-8-31, Midorigaoka
Ikeda, Osaka 563-8577

The Institute

AIST Kansai is a regional research base for the National Institute of Advanced Industrial Science & Technology (AIST), which begun operations in 2001. It represents the merger of the former Osaka National Research Institute, the Osaka Life Electronics Research Centre, the Osaka Measurement System Centre of the National Research Laboratory of Metrology, and the Osaka Regional Centre of the Geological Survey of Japan. There are nine AIST sites in Japan with life sciences activity, four of which are in the Kansai region. AIST employs some 25,000 researchers throughout Japan, 15% of which are life scientists. It promotes interdisciplinary research actively promotes the integration of biotechnology, information technology and nanotechnology. It defines nanobiotechnology as the discipline bridging biotechnology and nanotechnology.

Group Visited

The key focus of the Kansai bioengineering groups is the area where biology, materials science and informatics overlap. Representatives from three of the four life sciences groups in the Kansai region with nanobiotechnology interests met with Mission members.

The Special Division for Human Life Technology is aiming to develop technologies that will help sustain and improve the self-reliant lifestyle of individuals. It consists of seven research groups involved in protein structure determination, functional characterisation of proteins, monitoring and manipulating the functions of living cells, neuronal networks, and development of mesophase materials for advanced functional biomaterials and medical devices, functional polymers, and biodegradable polymers.

The Tissue Engineering Research Centre consists of six research teams developing technologies for three-dimensional cell culture, genetic technologies and genome informatics, development and differentiation biology, and screening of stem cells. The Centre is addressing the repair and regeneration of tissues and organs, and the replacement of animal testing for the screening of new drug candidates.

The Human Stress Signal Research Centre aims to uncover the biological response to chemical, biological, physical, and social factors induced stress at the molecular, cellular, tissue, and whole body levels and develop sensitive devices to detect stress markers and quantify the extent of stress on human beings and its influence on aging.

Representatives Present

Dr Motoi Suwa, Trustee, Director of AIST Kansai
Dr Takahisa Taguchi, Director of Special Division for Human Life Technology
Dr Noboru Yumoto, Vice Director of Special Division for Human Life Technology
Dr Jun Miyake, Vice Director of Tissue Engineering Research Centre
Dr Shin'ichi Wakida, Team Leader of Human Stress Signal Research Centre

Technologies Outlined

Human Life Technology Group: Dr Yumoto described as an example of work in his area the recent results of Uyeda et al (AIST Gene Discovery Research Centre) where actin filaments (~10 μm long, ~25 nm diameter) where constrained by purely geometrical features (arrow-head structures, fig. 3) to unidirectional motion induced by kinesin motor proteins attached to a glass substrate (1 arrowhead has a direction conversion efficiency of 0.73, so that 4 arrowheads in series achieve a direction conversion efficiency of 0.99). He described current work in his group using cage molecules to block receptor sites on the actin filaments and UV light to cleave the cage-linker and allow loads to be dumped at required locations on a chip.

Dr Taguchi described work on the development of conductive polymer based actuators which are light, soft and flexible, have low energy consumption, low actuation voltage, and are biocompatible. Placed between electrodes, the diffusion of positive ions to the cathode and water molecules to the anode causes local volume changes in the polymer resulting in bending. Such devices can achieve a 2 cm movement at the end of a 2 cm strip of material. The group is exploring catheter applications involving a 4-segment actuator. AIST has spun this technology out into Emex, which is currently seeking regulatory approval for the material. In the meantime it is generating revenues by incorporating the material in toys (artificial fish!) and is exploring its use as an actuator in micro-robots (in collaboration with NASA).

Tissue Engineering Group: This is a large US$130M initiative involving some 500 researchers in AIST, universities and hospitals in the Kansai region alone. Dr Miyake described successful attempts to make artificial cartilage and attempts to develop, from bone marrow, bone coatings on implants. They aim to be making whole organs for implantation by 2020, see the cardiovascular and neural areas as key markets, and recognise that the attitude of health insurance companies to reimbursement will be key to market success.

Human Stress Signal Group: Dr Wakida described progress in his group toward development of a high-throughput assay chip for stress markers. They are using laser beam direct write techniques for flexible chip design (thus avoiding expensive mask fabrication), LIGA to produce stamps for embossing microstructures in polymers, thermal bonding and fluorescence detection. They are seeking to develop a 15 sec. NO_x assay in a separation channel of length a few centimetres.

Approach to In-House Research, Technology Transfer and Collaborations

AIST has considerable flexibility in distributing its operating budget across smaller blue-skies research projects of its own choosing. Larger projects, however, must reflect government priorities. The formation of the tissue engineering consortium in the Kansai region, for example, was encouraged primarily by the National Government. The Institute currently allows researchers with specialist knowledge of a particular sector to define an appropriate route to market for new technologies. AIST is able to contribute to venture funding of spin-offs and derive economic benefit from them. It has a system of 'leave' for researchers to work with a new spin-off venture for a time, before either resigning or returning to the Institute. It is starting to set up a comprehensive spin-off support infrastructure. At present the Institute has few patents, so the cost of maintaining a large patent portfolio is not a policy defining issue. It sees itself addressing a global market and recently showcased 10 of its leading technologies at a technology showcase event in California. The role of the Prefecture Government in establishing and supporting spin-offs is restricted at present to the provision of incubation facilities (i.e. space only). There appears to be no clear strategy at the level of the National Government in deciding the location of new research institutes, implying perhaps that these are not yet consistently recognised at National and Prefecture level as important engines for economic growth in the 'knowledge based economy'. Despite this, the Government expects AIST to take a lead role in the development of the 'knowledge economy', although targets (set by METI) are still soft in economic terms (patents and publications). The Japanese Government would like to see 1000 new companies formed within 3 years, with perhaps 100 of these coming from AIST, although this has not yet been defined as a numerical target.

Institute of Scientific & Industrial Research (ISIR), Osaka University

Mission Contact

Professor Tomoji Kawai
Osaka University, Suita Campus
8-1 Mihogaoka, Ibaraki, Osaka 567-0047

The Institute

The Institute of Scientific and Industrial Research was founded in 1939 with the financial support of Kansai business to promote basic science for the development of industry. It currently has six divisions including twenty four research departments and two centres, one of which is the 'Nanoscience & Nanotechnology Centre', which began formal operations in April 2002. It has a total staff of 151, including 44 academic staff of professorial rank, and 50 research associates, and trains some 217 graduate students. It has a budget (FY2001/2002) of ¥2.5 billion.

Group Visited

Nanoscience & Nanotechnology Research Centre, Division of Nanomaterials & Nanodevices

The objective of the Centre is to develop both top-down and bottom-up nanotechnology and their industrial application. Materials science activities in the Centre have been awarded Centre of Excellence status by the Ministry of Education, with associated funding of $25 million over 5 years.

Representatives Present

Professor Tomoji Kawai (Director, Nanoscience & Nanotechnology Research Centre)

Technologies Outlined

Professor Kawai is a key figure in Japanese nanobiotechnology and was project leader of MEXT's Centre of Excellence (COE) scheme on "atom scale processing for the creation of highly harmonised functional materials" (1997-2001).

At present his research is focused in three areas:

- "artificial lattice science" aimed at control of atomic layers and molecular layers, to enable the creation of novel materials, especially functional lattices with diverse properties for example superconductivity, ferroelectricity, magnetic properties and optical functions;
- "atomic-scale surface science", to build nanoscopic structures and to derive new quantum properties from them, and to manipulate molecules especially DNA, and
- "computational science" to predict lattice and surface properties.

Using scanning tunnelling microscopy (STM), Prof Kawai's group has succeeded in visualising double helix DNA molecules and the processes by which proteins attach to those molecules. Therapeutic applications of his direct imaging work include: (1) manipulation of amyloid fibrils (2) the development of vesicles, with diameters of several hundred nanometers which are able to pass through blood vessel walls to reach target organs for drug delivery systems, and (3) studying the mechanisms of IL-6 blocking.

Prof Kawai is also developing a "high density DNA memory and transistor". He has already succeeded in arranging gold and cobalt, incorporated into self-assembling DNA wires. He is now working on replacing the gold/cobalt with magnetic metals which could then be used as ultra small memory devices.

Further details on Professor Kawai's research activities can be found at http://www.sanken.osaka-u.ac.jp/labs/kawai-lab/english/homee.htm

Strategic Directions & Market Opportunities

Professor Kawai is a member of the Cabinett Office Science & Technology Strategy Board. He indicated healthy debate on strategic directions and opportunities for Japan between academic and industry members of the Board.

Approach to In-House Research, Technology Transfer & Collaborations

The Centre of Excellence currently operates a free foundry service for internal and external customers, with projects chosen for such support by an expert review panel. It is hoped that companies supported in this way will support the work of the Centre in other ways.

Professor Kawai believes the primary role of universities is to pursue 'blue skies' research and training, however Institutes such as ISIS are, and should be, closer to industry. He estimates that ~90% of government research funding is used for 'blue skies' research, with an increasing budget for company-university collaborative research. He indicated that the Government is part funding (50:50) industry-university collaborative research which is very close to market (3 years), including projects with a value of $500 million.

Intellectual property protection is the responsibility of Japan Science & Technology Corporation (JST), a Government Association, with no responsibility to achieve sustainability.

Graduate School of Frontier Biosciences, Osaka University

Mission Contact
Professor Toshio Yanagida
Osaka University
A4, Yamada-oka 2-2, Suita-shi, Osaka 565-0871

The Institution
Graduate School of Frontier Biosciences.

Group Visited
Department of Physiology and Biosignaling

Representatives Present
Professor Toshio Yanagida, Professor & Dean, Graduate School of Frontier Biosciences

Technologies Outlined
Professor Yanagida is one of Japan's leading researchers in muscular motion of actin and myosin proteins. He is the project leader of the ERATO JST "Biomotion Project (1992-1997)" and first visualised the sliding of a fluorescent labelled motor protein (kinesin found in nerve cells) along filaments in real time. He determined how ATP hydrolysis is coupled with mechanical events by combining two technologies (single-molecule imaging and a single motor force measurement) so as to simultaneously measure the ATP hydrolysis reaction and force production.

He described recent work utilising two laser traps to suspend gold beads to which an actin filament had been attached. This arrangement allowed his group to study in detail the mechanism by which myosin moves along actin filaments. In a series of papers from the late '90's to the present his group has shown that myosin walks by biased Brownian motion which an energy conversion efficiency close to 100%.

His interests also lie in the fundamental differences between man-made and biological machines. He sees molecular machines operating near kT (the energy associated with random thermal motion) in a 'fuzzy' manner in a stochastic environment. This is in stark contrast to the deterministic nature of most man-made machines and suggests careful examination of how we should design nanoscale devices to operate in a seemingly chaotic nanoscale environment. His recent work has provided evidence that molecular machines utilise stochastic resonance phenomena to make very small concentration gradients visible.

Faculty of Pharmaceutical Sciences, University of Tokushima

Mission Contact
Professor Yoshinori Baba
1-78, Shomachi, Tokushima 770-8505

The Institution
Faculty of Pharmaceutical Sciences, University of Tokushima

Group Visited
Department of Medicinal Chemistry

Representative Present
Professor Yoshinori Baba, Professor, Department of Medicinal Chemistry

Technologies Outlined
Professor Baba's major areas of interest are analysis of DNA, genes, and the human genome using HPLC, capillary electrophoresis, capillary affinity gel electrophoresis, and MALDI-TOF mass spectroscopy. Current research focuses on micro and nano-fabricated chip technology. Professor Baba's group has succeeded in combining PCR and electrophoresis on one chip to shorten the processing time required. He is currently developing techniques for field-inversion electrophoresis on a chip for high-resolution separation of DNA, SSCP analysis on a chip for SNP analysis, a novel method for stretching the single DNA molecule on a chip for single molecule mapping, and a novel technology for manipulation of a single DNA molecule on a chip for single genomic DNA analysis. His group has recently reported manipulation of DNA strands (creation of knots) using optical tweezers (Appl. Phys. Lett. 80, 515 (2002)).

Strategic Directions in Japanese Universities, Technology Transfer & Collaborations
Professor Baba reported that Waseda University has just started an undergraduate degree in nanotechnology administered by its Institute of Nanotechnology. He sees increasing evidence for entrepreneurship training, especially within engineering faculties. Some two hundred spin-off companies have now been formed from Japanese Universities, but there are very few success stories to report. He believes that Japanese universities are strong in nanotubes, nanomaterials and self-assembly. In addition, Professor Baba observed:

- that Japanese companies are increasingly seeking collaboration with US universities, but not generally with Japanese universities
- total funding for research is increasing rapidly,
- all ministries are prioritising nanotechnology, although some of the 'new' money is derived through re-labelling existing activity,
- that the Japanese Prime Minister attends monthly meetings of the Science Council, at which lectures are given each time on a hot area of science or technology.

Of particular relevance to the theme of this Mission was the information that both NTT and Matsushita are already performing e-health monitoring of whole populations in small villages in Japan.

Matsushita Electric Industrial Co

Mission Contact
Hirokazu Sugihara, General Manager, Bioelectronics and Molecular Electronics Group
Nanotechnology Research Laboratory, Advanced Technology Research Laboratories

The Company
MATSUSHITA ELECTRICAL INDUSTRIAL CO., LTD
Address: 3-4 Hikaridai, Seiko-cho, Soraku-gun, Kyoto, 619-0237
Net Sales: ¥6,876 billion (March 2002)
Employees: 267,196
R&D Expenditure: ¥565 billion (8.2% of net sales) (March 2002)

The Advanced Technology Research Laboratories (ATRL) were opened in 1994 and employ 239 researchers dedicated to basic research (no development). There are three main research areas:

- Mobile Network Laboratory: Adaptive communications, video/speech coding, high-speed wireless network
- Humanware Technology Laboratory: Speech/language processing, cognitive processes, towards the next generation man-machine interface
- Nanotechnology Research Laboratory: Employs about 100 researchers in fields of photonics, brainware, nanostructure devices and bio/molecular electronics. Specific themes within nanotechnology are coexistence with the environment, revolution of production processes, digital networks, biosensors and drug-mining.

Representatives Present
Dr Hiroaki Oka, Manager, Biomolecular Electronics Group
Nobuhiko Ozaki
Dr Ichiro Yamashita, Advanced Research System Theme Leader (present at Embassy reception)
Dr Keiichi Namba, Project Director, Protonic NanoMachine Project (ERATO), Japan Science and Technology Corporation (JST), and Professor, Graduate School of Frontier Biosciences, Osaka University

Technologies Outlined
Biotechnology and nanotechnology are elegantly combined in a biomineralisation project, in which nanoparticles of around 6 nm diameter are manufactured for self-assembly into monolayers on a silicon surface. The technology centred around the use of ferritin 24-mer as a "mould". The recombinant ferritin with modified charges around the interstitial holes allows ingress and accumulation of metal ions (Fe, Co, Ni, Mn) and subsequent heat treatment produces a conductive core. The ferritin particles are self-assembled on an aqueous surface to give a highly ordered monolayer, which is transferred to a silicon surface. Acid treatment removes the ferritin leaving a similarly well ordered structure of 6 nm metallic nanoparticles, for incorporation into semiconductor devices. A basic prototype quantum dot memory device has been produced and a functional device is forecast within two years.

An electophysiological sensor (MED64) for brain systems has recently been marketed for CNS research and drug screening. The multi-electrode device, with 50 micron electrodes in a 400 micron grid, is placed in contact with brain tissue and allows real-time visualisation of electrophysiological changes.

A "drug-mining" chip for cellular assays was also described, which aims to circumvent issues surrounding the use of dyes in indirect screening methods. More direct measurements of cellular activity, such as the use of penetrating electrodes require great skill and are disruptive to the cell. Matsushita have developed a 16 channel silicon prototype device with 20 micron wells. Cells are placed in the wells and form contact with a 5 micron hole in the well base. Current changes across the hole are measured as test compounds are applied to the cell. The effects for single cells are very small and require significant data analysis. Summing signals over many wells increases sensitivity. The goal is a high throughput screening device.

Professor Namba (Osaka University) described his research into protonic nanomachines. Professor Namba has a laboratory at Matsushita and the project has five-year funding from ERATO, JST. The rotation of F1F2ATP synthase and the flagellar motor are both driven by proton flow. A detailed and superbly animated description of the flagellar motor was presented. Professor Namba demonstrated that the range of experimentally observed coiling constructs of the flagellar tail could be explained by a range of supercoils in 10:0 to 0:10 ratios.

Approach to In-House Research, Technology Transfer & Collaborations
An "Advanced Research System" is employed centred on "Themes". These are virtual, collaborative projects, which may include universities, institutes, and national laboratories, and are funded to the tune of $0.42 million per year, for a maximum of five years. The projects are proposed by individual scientists to a Technical Executive Council. The use of spin-up rather than spin-out companies is favoured through in-house venture, and this was exemplified by the MED64 device described above. Collaboration between companies on an international scale was seen as vital.

Appendix II

Attendees at British Embassy Reception

Guests from Governmental Bodies & National Research Institutes

Mr Hiroshi Yoshida	Deputy Director, Nanotechnology and Material Bureau of Council for Science & Technology, Cabinet Office
Mr Yuji Tokumasu	Planning Director for R&D Ministry of Economy, Trade and Industry
Mr Takehiko Yokoo	Deputy Director, Bio-Industry Division, Ministry of Economy, Trade and Industry
Mr Masahiro Uemura	Deputy Director, Bio-Industry Division, Ministry of Economy, Trade and Industry
Mr Iwao Miyamoto	Deputy Director, Bio-Industry Division, Ministry of Economy, Trade and Industry
Ms Naoko Okamura	Deputy Director, Office for Materials Research Development, MEXT
Dr Yuji Kikuchi	Research Leader of Microchannel Array Technology Team, National Food Research Institute
Mr Yoshihiro Nakamura	Research Coordinator, National Institute of Advanced Industrial Science & Technology
Mr Noboru Yumoto	Vice-Director, Special Division for Human Life Technologies
Dr Kenji Sunagawa	Chairman, National Cardiovascular Centre Research Institute
Mr Masami Takayasu	Director General, Medical Welfare & Ergonomics Technology Development Department, NEDO
Dr Masahiko Hara	Laboratory Head, Frontier Research System, RIKEN

Guests from Industry & Industrial Organisations

Dr Shuji Tsuruoka	Chief Technical Liaison, Carbon Nanotech Research Institute Inc.
Dr Walter Blackstock	Vice President - Technology, Cellzome
Dr Koichi Takiguchi	Corporate Vice President & General Manager, Corporate Research Centre, Fuji Xerox Co Ltd.
Dr Yoshiji Fujita	Vice President, Research Division, GlaxoSmithKline
Dr Masumi Motoya	Manager, Production Animal Service & Environment Division, IDEXX Laboratories, KK
Mr Kuniho Nakata	Science and Technology Division, Japan Bioindustry Association (JBA)
Mr Kiyoshi Sato	Secretary General, Japan Biological Informatics Consortium (JBIC)
Ms Yumiko Nakai	Assistant, Planning Department, Japan Biological Informatics Consortium (JBIC)
Dr Akira Horiguchi	Manager, Kyowa Medex Co Ltd.
Dr Ichiro Yamashita	Senior Researcher, Matsushita Electric Industrial Co Ltd.
Dr Ichiro Nakatomi	President & CEO, NanoCarrier Corporation
Dr Lerwen Liu	Managing Director, nABACUS Ltd.

Dr Jun'ichi Sone	General Manager, Fundamental Research Laboratories, NEC Corporation
Mr Masao Morita	Executive Manager, Research Planning Section, NTT Basic Research Laboratories
Dr Keiichi Torimitsu	Group Leader, Material Science Laboratory, NTT Basic Research Laboratories
Mr Hitoshi Yoshino	Principal Representative, QED Intellectual Property Ltd. Japan
Mr Masakazu Kato	General Manager - SMT, Precision Products & Machinery Division, Ryoko Sangyo Corporation
Ms Chitose Nakanishi	Assistant Manager, Intellectual Property Group, Sharp Corporation
Ms Miyuki Nakayama	Assistant Supervisor, Planning & Administration Department, Corporate R&D Group, Sharp Corporation
Mr Shigeru Fukushima	Manager, Life Science Business Unit, Analytical & Measuring Instruments Division, Shimadzu Corporation
Mr Shigeru Kikuno	Assistant Manager, Life Science Business Unit, Analytical & Measuring Instruments Division, Shimadzu Corporation
Mr Masami Yabe	Senior Staff, R&D Planning Department, Toray Industries, Inc.
Dr Shigenori Tanaka	Senior Research Scientist, Advanced Materials & Devices Laboratory, Toshiba Corporate R&D Centre

Guests from Academic Institutions

Prof Masuo Aizawa	President, Tokyo Institute of Technology
Prof Takehiko Kitamori	Professor, University of Tokyo

UK Mission Members

Prof Ken Snowdon	Director, Institute for Nanoscale Science & Technology, University of Newcastle
Ms Julie Deacon	Group Director, Bio & Chemical Instrumentation Group, CRL
Dr David Rodham	Technology Translator, IMPACT Faraday Partnership, Technology Acquisition Project Manager, Syngenta, Consultant, Institute of Nanotechnology
Dr Ian Hughes	Technology Manager, Technology Development, Chemistry GlaxoSmithKline
Prof Christina Doyle	Medical Devices, Drug Delivery, Disposables & Diagnostics, Health, Medical & Bio Technologies, BTG
Mr Shigeru Kakuchi	Interpreter, Simul International

British Embassy Staff

Ms Philippa Rogers	First Secretary, Science & Technology Section
Ms Naoko Takei	Senior Officer, Commercial Section
Ms Yasuko Otsuka	Senior Officer, Science & Technology Section
Mr Ivan Meakin	Senior Officer, Science & Technology Section
Ms Tomoko Watanabe	Officer, Science & Technology Section

Appendix III

Government Initiatives

The Japanese Government is investing heavily in nanobiotechnology, and four Ministries have recently launched bionanotechnology programmes.

1. Ministry of Education, Culture, Sports, Science & Technology (MEXT)

The Ministry of Education & Science has been supporting research relevant to bionanotechnology for a number of years. Most notable was a six-year project launched in 1992 to "develop basic technology for the elucidation of bio-nanomechanisms'. This programme has led to the establishment of centres of expertise in Japan in the direct observation and manipulation of single and complex biomolecules in living cells. The project also led to the development of *in vitro* and *in vivo* experimental systems.

As a follow-up, in FY2002, MEXT funded a major new initiative in nano-scale chemistry and biology aimed at the development of:

- functional materials
- molecular machines
- biodevices and
- biosensors

The initiative is led by Professor Masuo Aizawa (President of Tokyo Institute of Technology, formerly Dean of Life Sciences and a pioneering researcher in biosensors) and comprises six research groups (Box 1).

BOX 1: MEXT NANOSCALE CHEMISTRY & BIOLOGY INITIATIVE

Research Theme	Group Leader
• Development of a "super antibody enzyme" which can function as an antibody but can discompose an antigen like an enzyme.	Professor Taizo Uda, Dept of Biological Production Systems, Hiroshima Prefecture University
• Design and development of a "multi-functional quartz oscillation multi-sensor" for continuous detection of biomolecular interactions.	Professor Yoshio Okahata, Biomolecular Engineering, Graduate School of Bioscience and Biotechnology, TIT
• Build a "mesoscopic structure device of porphyrin" for molecular electronics elements.	Professor Atsuhiro Ohsuga, Faculty of Science Kyoto University
• Development of a "nano structure device which will function as a gene vector".	Professor Kazunori Kataoka, Graduate School of Engineering, Tokyo University
• Development of "nano-tissue engineering" and "next generation of biosensors".	Professor Mitsuo Okano, Advanced Life Science and Medical Research Institute, Tokyo Women's Medical College
• Build a "molecular machine using	Professor Toshihiro Yamase, Chemical Resources

nanocluster polyoxometalates".	Laboratory, Tokyo Institute of Technology

In addition, MEXT has recently issued a call for proposals covering 25 research themes in nanotechnology/materials, four of which are directly relevant to nanobiotechnology, and a further three of which are related, viz.

- "Bio-Molecular Devices" (including DNA electronics, DNA devices and bio chips with nano-scale control functions)
- "Ultra-High Sensitivity Sensing Technology"
- "IT integrated with Medicine: Drug Delivery/Nano Machine"
- "Nano Soft Machine"
- "Single Molecules and their Integration" (by 'bottom-up' assembly approaches, aimed at developing molecular memory, very small one molecular displays, and single molecular sensing elements)
- "Architecture of Nano-Structures by Fusing Organic and Non-Organic Substances"
- "Programmed Self-Assembly"

Successful projects will start from October 2002.

2. Ministry of Economy, Trade & Industry (METI)

In April this year METI launched a new five-year project to develop technology capable of analysing and simulating the dynamic networks within a cell. The project comprises two themes:

- methods to prepare cells for analysis, including labelling technology, and techniques to introduce labelled molecules into cells without damaging other molecules within the cell; and
- development of devices capable of analysing simultaneously the dynamics of high numbers of molecules.

METI plans to launch another new bionanotechnology project in FY2003 and is currently seeking views on the potential themes, in close collaboration with the Japan Bioindustry Association (JBA). The development of "nano machine" technology is one candidate.

3. MINISTRY OF HEALTH AND LABOUR (MHL)

To drive the medical application of nanotechnology, MHL has recently launched a new five-year "Nano Medicine" Programme to develop 'non- and low-invasive' medical technologies. The programme comprises two parts: a "designated project", and a competitive funding stream for relevant innovative research proposals. Total budget for FY2002 is 1.4 billion-yen (£7.7 million), which is split evenly between the two parts.

The "designated project" is lead by Professor Hiroyuki Suga, Director General, Research Center of the National Cardiovascular Centre (NCVC), MHL, and is aimed at addressing four key areas (Box 2).

<u>BOX 2: MHL NANO-MEDICINE PROJECT</u>

<table>
<tr><td colspan="2">A. Nano-Imaging: analysis of molecular functions and structures by imaging at the nano level using AFM and other advanced microscopic techniques, enabling the visualisation of single molecules and helping increase understanding of intermolecular interactions.
Project Leader: Dr Eizo Mori (Director, Department of Cardiac Physiology, NCVC)
R&D Themes:</td></tr>
<tr><td>Circuratory Systems</td><td>• Motion analysis of myosin and actin by applying ‘cell motility assay’ with flourescent labelled actin.</td></tr>
<tr><td>Neuro System</td><td>• Target prion proteins</td></tr>
<tr><td>Molecular Structure Analysis</td><td>• Observation of docking processes of ligand and receptor proteins by STM and AFM</td></tr>
<tr><td colspan="2">B-1. Nano Device Development: To develop devices, which mimic biological functions and structures.
Project Leader: Dr Kenji Sunagawa (Director, Dept of Cardiovascular Dynamics, NCVC)
R&D Themes:</td></tr>
<tr><td>Cardiac Pacemaker</td><td>• Development of “bionic baroreflex system”, consisting of a pressure sensor, microprocessor and nerve stimulator to operate as an intelligent negative feedback regulator (success already in rats).</td></tr>
<tr><td>Artifical Blood Vessel</td><td>• Use nanoscale optical chemistry to induce angiogenesis cells out of embryonic stem cells.</td></tr>
<tr><td>Hemodialysis</td><td>• Build a selective discharging system using nanotechnology</td></tr>
<tr><td colspan="2">B-2. Nano Device Development:
Project Leader: Dr Tadao Kakizoe (Director General, National Cancer Centre Hospital)
R&D Themes:</td></tr>
<tr><td>Forceps & Catheters</td><td>• Development of very small forceps and catheters</td></tr>
<tr><td colspan="2">C. Drug Delivery Systems (DDS):
Project Leader: Dr Kenji Yamamoto (Director, Research Centre of the International Medical Centre of Japan (IMCJ).
R&D Themes:</td></tr>
<tr><td>DDS</td><td>• To develop DDS using semiconductor nanoparticles</td></tr>
<tr><td>Gene Introduction</td><td>• To introduce genes using nanoparticles</td></tr>
<tr><td colspan="2">D. Building database and technology evaluation
Project Leader: Dr Keishige Hasegawa (President, Japan Association for the Advancement of Medical Equipment)</td></tr>
</table>

4. MINISTRY OF AGRICULTURE, FORESTRY AND FISHERIES (MAFF)

In FY2002, MAFF also launched a bionanotechnology project focused on “the development of nanotechnology/materials technology by the evolutionary utilisation of biological functions”. The project will initially run for three years with a budget of 200 million yen for FY2002. The project is being led through the National Food Research Institute, which has been developing, jointly with Seiko Instrument Co and JAERI, technology to directly observe a specific gene on a chromosome using SNOM/AFM. The project comprises five key elements (Box 3).

BOX 3: MAFF BIONANOTECHNOLOGY PROJECT

1. Development of Nano-Structured Cell Culture Plates (suitable for individual cell types)
Project Leader: Dr Yuji Kikuchi, National Food Research Institute (NFRI)
Participating Institutes: NFRI and Hokkaido University

2. Development of Techniques for Manufacturing Nanoparticles with Uniform Diameter
Project Leader: Dr Mitsutoshi Nakajima, NFRI
Participating Institutes: NFRI, Tsukuba University, Kyoto University, Hiroshima University, Hokkaido University

3. Development of New Functional Biomaterials by Molecular Orientation Control Including 'Insect-Originated Functional Biomaterials', and 'Natural Highly Conductive Polymers'
Project Leader: Dr Tetsuo Kondo, Forestry and Forest Products Res Institute (FFPRI)
Participating Institutes: FFPRI, Shizuoka University, Shimadzu, Shinshu University, National Institute of Agrobiological Sciences (NIAS), Kyoto University, Tokyo University, Kyushu University

4. Development of Technology to Analyse and Manipulate Biological Molecular Structures at the Nano-Level (sensing technology mimicking insects and micro-organisms' pheromone and related fabrication/operational technologies)
Project Leader: Dr Yasushi Tamada, National Institute of Agrobiological Sciences (NIAS)
Participating Institutes: NIAS, NFRI, Japan Advanced Institute of Science and Technology, Hokuriku, Kyushu Institute of Technology, Ritsumeikan University, Miyazaki Medical College, Starlight Industry Co.

5. Assessment of Dynamics of Water Molecules and Utilisation
Project Leader: Dr Tomoko Nakanishi, Tokyo University
Participating Institutes: NFRI, Industrial Technology Research Institute, Tokyo University

The Bio-Oriented Technology Research Advancement Institution (BRAIN), a semi-governmental organization jointly founded by MAFF and the private sector to promote R&D in the biosciences and biotechnology through loans and investment, has also, since April 2000, been funding a five year project to develop technology which enables the manipulation of genes at a molecular level. The consortium consists of Professor Masao Washizu, Faculty of Engineering, Kyoto University, Hamamatsu Photonics Co, Shimadzu Corporation, and Kyoto Moritech (a bio-venture) (Box 4).

BOX 4: MAFF/PRIVATE-SECTOR BRAIN CONSORTIUM

Prof Washizu	Using micromachine and 'optical pin-set' (manipulator) technology, to develop single molecule detection and manipulation technology for measurement & analysis.
Kyoto Moritech	Developing a new laser manipulation device, for handling DNA molecules in solution under a microscope, consisting of a high power laser manipulator ('photo pin-set') and a micro chamber for keeping samples, efficient processing and separation
Shimadzu Corporation	Real time high speed detection and recovery of expressed biological

	substances. Developing a chip on which key elements of micro TAS are being integrated, such as functions of handling one cell, cell trapping in a reaction chamber, and supply function of reagents.
Hamamatsu Photonics Co,	Developing an optical analytical system by combining a new immune assay using a capillary electrophoresis method and a functional analytical method by measuring simultaneously active oxygen generated by a cell and calcium iron level in that cell. To be used for the analysis of GMOs and functional foods.

Appendix IV

Other University & Research Institute Activity

The activities of several key players in the public sector (AIST, Kawai, Yanagida, Baba) are described in the Individual Meeting/Activity Reports in Appendix I. Other key activities by category are:

Direct Observation, Imaging and Manipulation of Biomolecules

- **Prof K Kobayashi**, Tokyo University - developed scanning near-field optical/atomic force microscopy which is designed to measure samples by replacing probes with optical fibres.

- **Prof Akihiro Kusumi,** Department of Biological Science, Graduate School of Science, Nagoya University - Project Leader of “membrane organiser” (1998-2003) has developed an ultra-sensitive, single-molecule optical force scanning probe microscope that can measure the interaction force between a single membrane molecule and a component of the membrane/cytoskeleton in live cells. Single green fluorescent protein (GFP) molecules were successfully imaged for the first time in living cells.

Molecular Motors

- **Dr Keiichi Namba,** Osaka University - Project leader of Protonic NanoMachine (1997-2002) which aimed at increasing understanding of the physical processes and mechanisms unique to biological molecular machines, which efficiently transmit, amplify and transform energy and conformational changes through proton exchange. The project especially looked at molecular motor assembly for the flagella of bacteria. The main research themes are (1) energy conversion of a molecular motor, 2)-assembly regulation and (3) polymorphic transition of the protein assembly. Dr Namba was formerly at Matsushita Electric Co Ltd and some of his work is described in the Individual Meeting/Activity Report for the company in Appendix I.

- **Prof Masasuke Yoshida**, Chemical Resources Laboratory, Tokyo Institute of Technology - Project leader of ATP System (2001-2006), which aims to study (1) the detailed mechanisms of the ATP motor system, (2) to find other motor-like enzymes in the biological world (i.e. enzymes handling DNA), and (3) to study regulation of the motor system.

- **Prof Kazuhiko Kinoshita,** Centre for Integrative Bioscience, Okazaki National Research Institute - To image rotation of F_1-ATPase by attaching a tag and the study of how an ATP-driven molecular machine may work and how enzymes convert the energy derived from ATP hydrolysis into mechanical work.

- **Dr Noboru Yumoto,** Special Division for Human Life Technology, Biomolecular Dynamics Research Group, AIST (Kansai) **-** has developed a “speract”’caged peptide’ using sperm flagella as a molecular switching to regulate movements from outside.

- **Prof Itaru Hamachi,** Biofunctional Organic Chemistry Group, Kyushu University - developed a “photosynthesis machine”.

Mirco- and Nano-Arrays for Genomic/Proteomic Analysis

- **Prof Takehiko Kitamori,** Department of Applied Chemistry, School of Engineering, Tokyo University - realised integration of several chemical processes on a chip. Set up spin-out company "Micro Chemical Technology Research Inc". Collaborating with Nippon Sheet Glass Co, and has developed a new type "micro-chemical chip" on a glass substrate using ultra small lens for analysis.

- **Dr Teruo Fujii,** Institute of Industrial Science, Tokyo University - developed a high performance and low cost hybrid type microchip for chemical reaction analysis.

- **Prof Koji Ikuta**, Nagoya University - developed "chemical IC family", lab-on-a-chip.

On-Chip Biotechnology

- **Prof Eiichi Tamiya,** School of Materials Science, Japan Advanced Institute of Science and Technology, (JAIST) in Ishikawa - developed a number of biosensors including an 'immunosensor using micro-antibody bead array' to detect dioxin and human cell-based biosensing of oestrogen. Also developed an 'integrated microchamber array DNA/protein synthesis and cell screening' system.

Nanoparticles for DDS

- **Prof Kazunori Kataoka** of Graduate School of Engineering, Department of Materials Science of Tokyo University - working on the structural design of polymeric nano-capsules (polymer micelle) for entrapping bioactive substances including drugs, genes, and peptides. Also engaged in designing biointerfaces for cellular engineering. Prof Kataoka's DDS technology has been transferred to "NanoCareer Co Ltd" an SME set up in 1996.

- **Prof Mitsuo Okano**, Advanced Life Science Research Institute of Tokyo Medical Women's College - leading biomaterial researcher, looking at 'nano-tissue engineering', using cells as intelligent materials for mounting substrate membranes.

- **Prof Tadashi Matsunaga**, Department of Biotechnology, Tokyo University of Agriculture and Technology - bacterial magnetic particles (BMPs), in particular the elucidation of the mechanism of BMP formation in magnetic bacteria at the molecular genetic level, display of functional proteins on BMPs, mass culture of magnetic bacteria, bioremediation using magnetic bacteria, and application of magnetic particles in clinical diagnostics.

Self-Assembled Biomimetic Materials

- **Dr Masahiko Hara**, Spatio-Temporal Function Materials Research Group at RIKEN's Wako Campus - development of nano-precision materials, focusing on the creation and analysis of molecular organisations that arise from hierarchical structures, and spontaneous pattern generation. At present research is focused on single molecular detection using hybrid probe systems, self-assembling monolayers, and dynamic and transient instabilities of nonequilibrium biomolecular systems. RIKEN is now in the process of forming a virtual laboratory for nanotechnology, a loose network of existing laboratories involved in nanotechnology research, including those involved in nanobiotechnology. Further information on this initiative is available at http://www.riken.go.jp

Appendix V

Other Private Sector Activity

The activities of several key players in the private sector (NTT, Olympus, Toshiba, Shimadzu, Matsushita) are described in the Individual Meeting/Activity Reports in Appendix I. Other key private sector activities by company size category are:

Large Companies:

- **Canon -** the Canon Research Centre develops basic and advanced technologies for future businesses with an eye toward commercialising products five to 10 years down the road. Canon is pursuing a broad range of nanotechnology research through its *NEXT* technology programme. Canon is also active in R&D for environmentally conscious technologies, in particular bio-remediation.

- **Fujirebio -** a leading manufacturer of immunodiagnostics, with an emphasis on infectious diseases, autoimmune disorders and cancer diagnostics (tumour markers). Fujirebio is now exploring new opportunities in the biochip area to fill the demand for order-made medicine and the supply of new types of diagnostic tests. For example, in 2000, they entered into a partnership with Zyomyx, a Californian company to develop protein biochips for applications in the areas of diagnostics and pharmacogenomics.

- **Fujitsu** - opened a specialised nanotechnology research laboratory in December 2000, with three main research groups:
  1. Nanomaterials: Development of nanostructured materials, particularly for semiconductor devices.
  2. Nanodevices and Systems: Development of quantum effect devices for next generation computing and communication networks, including quantum dot memory.
  3. Nanobiotechnology: Combination of extensive background in semiconductor devices with biotechnology for development of biosensors and “lab-on-a-chip” technology.

- **Hitachi -** Hitachi’s Life Science Group (HLSG) was set up in October 1999, to undertake commissioned analytical work and provide bioinformatic analytical services. Through partnerships with overseas biotechnology companies, HLSG has developed SNP discovery, genotyping and gene expression analysis technologies and has now started to provide outsourcing services to Japanese pharmaceutical companies. And in April last year, Hitachi formed a landmark alliance with Myriad Genetics and Oracle to map the human proteome in less than three years. Hitachi also has an active biochip business. Hitachi is funding a considerable amount of research relevant to nanobiotechnology. At its Advanced Research Laboratory a number of projects related to nanoscale atomic and molecular devices, and scanning probe technology for the fabrication of nanostructures are being pursued. And at its Central Research Laboratory, which focuses more on long-term research on new technologies for the coming 10 to 20 years, they have an active life sciences programme, including new techniques for DNA analysis.

- **Hosokawa Micron -** a global firm spanning three different businesses: powder and particle processing; blown film processing; and confectionery and bakery technology and systems, is now developing systems for the production of nanoparticle powers and the stable mass production of composite nanoparticles. The firm have also developed novel "nano activator' technology to bind drug particles to nanoparticles in an aim to develop novel Drug Delivery Systems. The firm is also participating in NEDO's 'DDS development by the use of biodegradable nano composite particles' project in collaboration with Gifu Pharmaceutical College.

- **Toray Industries Inc** – their lead business is in synthetic fibre, textiles and chemicals, but they have a small but expanding medical business which accounts for about 5% of total sales. Toray have developed a low cost synthetic method for carbon nanotubes (CNTs) in co-operation with Prof Hisanori Shinohara of Nagoya University. Toray has also accumulated considerable experience in the biomedical/biomaterial areas, including the commercialisation of interferon beta for treating liver cancer, artificial kidney/catheters for blood purification, and fine chemicals for animal drugs. Toray participated in the government's biomaterial research project (1987-94) and is a participating member company of Protein Engineering Research Inc, a government venture. Toray established their Pharmaceutical Research Laboratories in 1999, which now employ some 500 people. Nanotechnology research is currently undertaken at their Pioneering Research Laboratories, also established in 1999, focusing on speciality polymers. Toray has now invested about five billion-yen (approx £ 30m) in a new research laboratory in Kamakura, due to be opened in May 2003, to focus on biotechnology and nanotechnology research. Toray has not yet revealed its detailed plans but research areas will include gene recombination, production of useful proteins, devices for tissue engineering for regenerative medicine, DDS, cell compatible materials and bioinformatics. They are also developing techniques for biochip fabrication on polymer substrates.

- **NEC** - expanding programme in Micro-TAS

SME's

- **Cluster Technology Co Ltd (Osaka)** - developed substrate for 'nano composite DNA chip' which is "half the price" of glass substrate. Collaborating with Osaka University and Kyoto University.
- **Kyoto Moritech Co -** participating in the "HPLC chip for proteome analysis" project with AIST and Kyoto University.
- **Daiken Chemical Co** - developed cantilever for AFM.
- **NovusGene Co** - set up with funding from Olympus and Mitsui Knowledge Co., SNPs analysis and disease diagnostics by biomolecular computing (DNA computer)
- **Genetic Laboratory Inc (Sapporo)** - developed 'nano-surgery' techniques which enable the handling of mitochondria and other organelles in cell.
- **JUKI** - DNA automated analytical device for genetic disease with application of Prof Matsunaga's magnetic beads hybridization technology.
- **Research Institute of Biomolecule Metrology (Tsukuba)** - visualisation of various biomolecules, designing DNA wire. First bio spin-out from AIST with technology developed through NEDO project "atom and molecule manipulation'. Established December 1999.

- **NanoCarrier Co Ltd** - commercialization of Prof Kazunori Katayama of Tokyo University's high polymer nanometer scale particles to carry pharmaceuticals, genes, diagnostic reagents, and medical instruments.

Appendix VI

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Appendix VII

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NANOMED/INSAT
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