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BRIEFING

# Health and Medical Research in Japan

## Health Research Observatory

James R. Burgdorf

Prepared as part of RAND Europe's Health Research Observatory
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RAND EUROPE

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# Preface

This documented briefing provides an overview of health and medical research in Japan. The report is part of a series of country-specific reports available from RAND Europe's Health Research Observatory, funded by the UK Department of Health.

The report is divided into three parts. In the first part, the *Structure of the Japanese Health Research System*, including funding sources, sectors performing health and medical research, and health research priority setting, is presented. The second part, *Processes and Performance of the Japanese Health Research System*, focuses on the types of funding available and how funding activities are conducted, and provides exemplars of the system's performance. The third part presents an *Outlook* and considers current and emerging health research issues in Japan.

The report is based on desk-based document review and will be updated on a regular basis. It does not attempt to discuss current policy options, or make recommendations for future strategy. The report will be of interest to government officials dealing with health and medical research policy, medical research councils, health and medical research charities, public and private institutions engaged in health research, and researchers.

The use of ¥ throughout this report stands for Japanese yen, unless stated otherwise.

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# Summary


## Summary: Key Points

- Most important sectors: private industry and universities
- Government funds universities, research institutes, and research funding agencies; life sciences are a perennial priority area in R&D promotion
- Historically weak ties between basic and applied researchers, but efforts are being made to promote cooperation between universities and industry
- Health and medical research underperforms compared to other R&D areas in Japan and compared to other countries
- Pharmaceutical industry faces challenges
- Recent reforms aim to improve Japan's national contribution to health and medical research

Despite Japan's well-deserved reputation for technological research and development (R&D), its performance in the area of health and medical research compares unfavourably with many of its peers. Fortunately, the Japanese government, faced with the rapid ageing of society and anxious for an additional source of economic growth, recognises the problems and has initiated significant reforms designed to improve the nation's standing in this area.

In Japan, health and medical research is performed largely by universities and private industry, which are dominant in terms of expenditure and number of employed researchers. Public research institutes play a smaller but significant role within the system. Funding for these players comes from private industry, which funds its own research activities, and government, which provides the vast majority of funding to the universities and research institutes through its education and health ministries. The central government also oversees the national university system, as well as the development of drugs and medical devices.

Unfortunately, a lack of communication between the academic and private sectors has hindered Japan's industrial success in the area of health and medical research. Universities in particular have been criticised for being too rigid and unresponsive to the nation's economic and health needs: too often, the innovative discoveries of Japan's universities have not been applied or commercialised. Meanwhile, Japan's relative level of investment in this area of research lags behind other nations. Other problems include a general lack of

skilled clinical researchers (preferably speaking English) and quality facilities, and the high cost of conducting research in Japan.

The result is an undersized contribution to the world's medical knowledge base, despite Japan's strength in some areas of basic biomedical research, such as regenerative medicine. The pharmaceutical industry also faces serious difficulties related to the high costs and slow pace of development, and a declining share of domestic and global markets. Recognising the problems, the government has reformed the universities, making them more independent and competitive, and has introduced new incentives for cooperation with industry. Like the universities, it put its own public research institutes through a similar process of "agencification", granting them greater managerial and budgetary independence. Both universities and research institutes have been made to rely increasingly on competitive grants for their funding. New funds have been made available to local areas for the development of world-class research and educational centres in health, medicine, and other areas, in the hopes of catalysing new industrial clusters. Finally, in its current and previous five-year plans on science and technology, the Japanese government has declared life sciences to be one of its four priority areas for promotion.

Although it is still too soon to judge how successful these new measures have been, some of the early signs have been encouraging. Cooperation between universities and industry is growing. The increased dependence on grant funding seems to have given universities and research institutions a more competitive orientation. The number of new clinical trials has begun to increase, while the rate of clinical trial cost increases has levelled off.

# Acknowledgments

The author would like to thank the valuable input of Observatory team members, particularly Amanda Scoggins, as well as careful editing by Lucy Bailey. Further constructive comments were provided by Quality Assurance reviewers Jonathan Grant and Charlene Rohr.

# Abbreviations and Terms

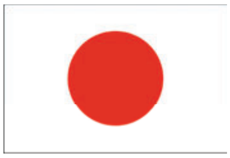
| | |
|---|---|
| Agencification | The conversion of government departments into semi-independent public agencies |
| COE | Centers of Excellence |
| CSTP | Council for Science and Technology Policy |
| GDP | gross domestic product |
| IAI | Independent Administrative Agency |
| IMCJ | International Medical Center of Japan |
| JFCR | Japanese Foundation for Cancer Research |
| JFY | Japanese fiscal year (April1–March 31) |
| JSPS | Japan Society for the Promotion of Science |
| JST | Japan Science and Technology Agency (also known as the Science and Technology Agency) |
| METI | Ministry of Economy, Trade, and Industry |
| MEXT | Ministry of Education, Culture, Sports, Science, and Technology |
| MHLW | Ministry of Health, Labour, and Welfare |
| MIAC | Ministry of Internal Affairs and Communications |
| NCC | National Cancer Center |
| NCCRI | National Cancer Center Research Institute |
| NCCHD | National Center for Child Health and Development |
| NCVC | National Cardiovascular Center |
| NIHN | National Institute of Health and Nutrition |
| NIPS | National Institute for Physiological Sciences |
| NIRS | National Institute of Radiological Sciences |
| NRICHD | National Research Institute for Child Health and Development |
| PMDA | Pharmaceutical and Medical Devices Agency |
| R&D | research and development |
| RERF | Radiation Effects Research Foundation |

| | |
|---|---|
| RIKEN | *Rikagaku Kenkyujo* (Institute of Physical and Chemical Research) |

# Introduction

## Health and Medical Research in Japan

### Observatory on Health Research Systems


James Burgdorf

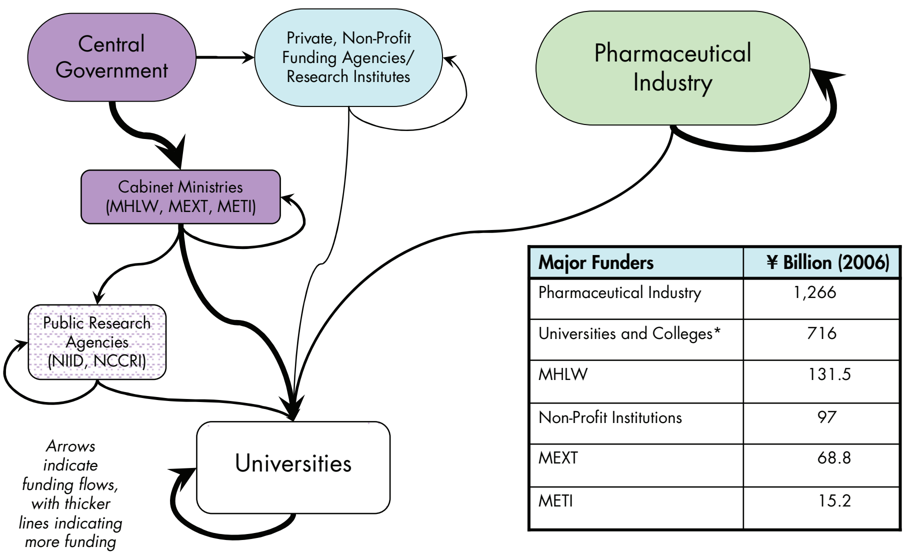
October 2008

This report provides an overview of Japan's health R&D system. Given Japan's reputation for discovery, innovation, and their commercial applications, the nation's underwhelming performance in health and medical research may be surprising to some. Within the Japanese research community, however, the diagnoses are well known: some mixed success in basic biomedical research, a weak tradition of clinical research, and a pharmaceutical industry beset with challenges related to drug development. Fortunately, having held the health and medical research sector up to its own country's high standards, the Japanese government has made reforms over the past decade to help the country compete and contribute globally. So, although it may be true that Japan has a bit of "catching up" to do in this area, there are some recent and encouraging signs that it is doing just that.

This report is divided into three sections. The first section describes how the health R&D system in Japan is organised and coordinated, and describes health research expenditures. In addition, a brief overview of the mission and governance arrangements of the key health R&D funding organisations is provided. The second section describes how the health R&D system carries out its activities and provides exemplars of how the system is performing. Finally, a brief account on Japan's current and emerging health research issues is provided.

# Structure of the Japanese Health Research System

## Funding Flows for Health and Medical Research




| Major Funders | ¥ Billion (2006) |
|---|---|
| Pharmaceutical Industry | 1,266 |
| Universities and Colleges* | 716 |
| MHLW | 131.5 |
| Non-Profit Institutions | 97 |
| MEXT | 68.8 |
| METI | 15.2 |

*Funds from Universities and Colleges may be counted twice, because they themselves are largely funded by MEXT

Source: MAIC (2008); Burrill and Company (2007)

The Japanese health and medical research system is dominated by the pharmaceutical industry, which spent ¥1.3 trillion (£6.5 billion)[2] on health and medical research activities in the 2006 Japanese fiscal year (JFY). Also important are universities and colleges, which spent ¥716 billion. In a distant third place, the top three ministries of the central government involved in health and medical research spent a total of approximately ¥215.5 billion. The central government is followed by private, non-profit research institutions and funding agencies, which spent approximately ¥97 billion on health and medical research in 2006 (Ministry of Internal Affairs and Communications [MIAC], 2008). In 2004, Japan's total expenditures on health and medical research were ¥2 trillion (MIAC, 2008).

From the central government, funding flows down to ministries, agencies, and universities. Private non-profit institutions usually fund their own research efforts, but may also fund universities. Similarly, pharmaceutical companies spend most of their research funds on their own researchers, but they also contribute to research done at universities. Most researchers work in universities or in private industry, with slightly more working in universities than in industry, but the researchers in private industry are better funded. This section describes these basic relationships in further detail.

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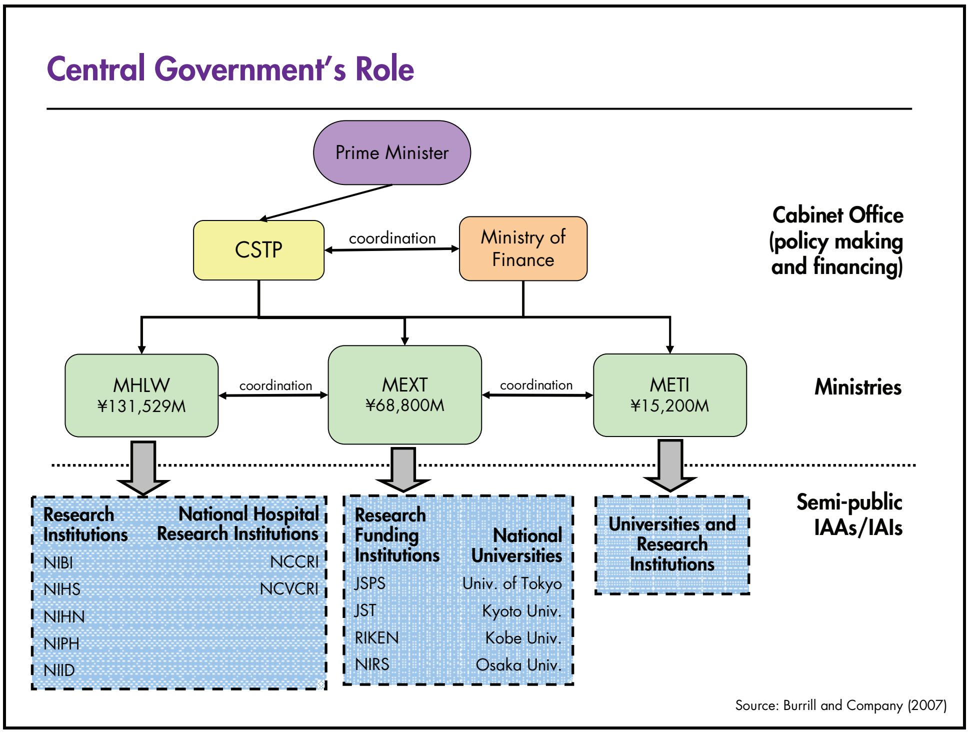
[2] Based on the Feb 17, 2008 exchange rate of ¥212 = £1.




The Japanese government's health and medical research budget stood at approximately ¥215.5 billion in 2007, representing an approximate 1.5 percent increase over the previous year (Burrill and Company, 2007). This increase occurred despite general budgetary belt tightening, thus demonstrating the importance the government places on this area. The health and medical portion of the research budget is divided among three cabinet-level ministries: the Ministry of Health, Labour, and Welfare (MHLW), the Ministry of Education, Science, and Technology (MEXT), and the Ministry of Economy, Trade, and Industry (METI).

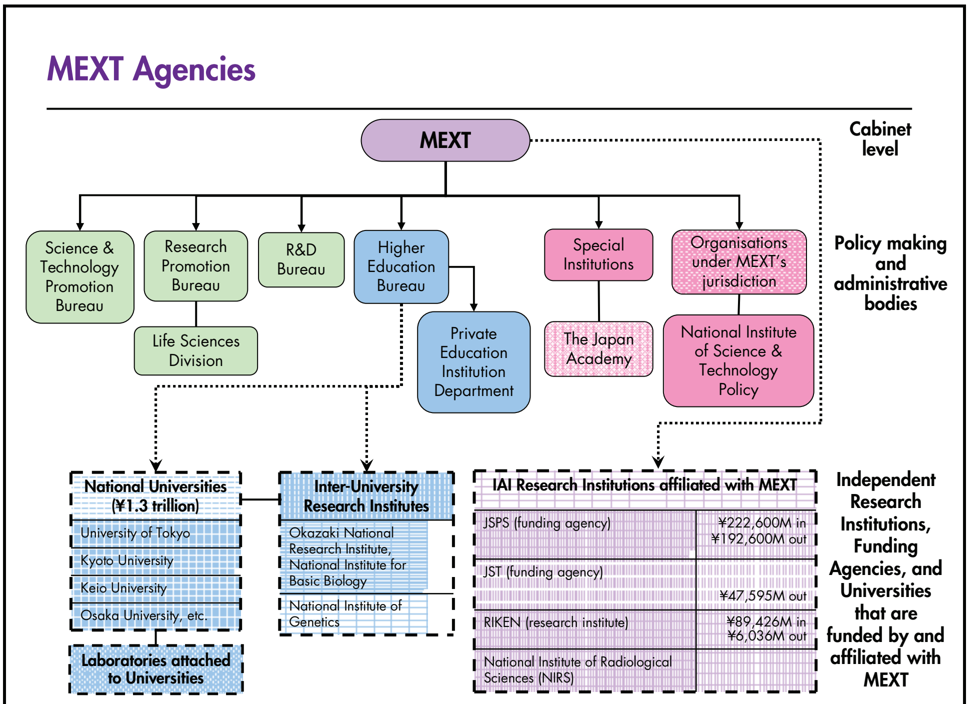
The Council for Science and Technology Policy (CSTP) is Japan's premiere policy-making body for science and technology. It was created in 2001 to coordinate science and technology policy between different ministries of the central government; previously, it was felt that the different ministries were not acting in a cohesive manner. The CSTP is comprised of 14 members plus the Prime Minister, who acts as its chair. The 14 members include six cabinet members who sit at the head of ministries, seven executives from academia and industry, and the president of the Science Council of Japan (an interest group for scientists). It operates at a level above the ministries to plan strategy, design policy, decide resource allocation, evaluate projects, and generally, to coordinate ministerial science and technology activities.

The CSTP's domain covers all ministries and agencies involved in science and technology, including MHLW, METI, MEXT, the Ministry Internal Affairs and Communications, the Ministry of Land, Infrastructure, and Transport, the Ministry of the Environment, and the Ministry of Agriculture, Forestry, and Fisheries. However, only the first three of these have a large involvement in health and medical research.

At the beginning of this decade, the Japanese central government began a process of reforming its administrative structure by converting certain departments or agencies into a new type of public entity called independent administrative institutions (IAI) or independent administrative agencies (IAA). The transformation of a traditional government agency to an IAA is undertaken with the aim of making that agency as nimble and responsive to public needs as a private sector business would be. While high-level ministries are still responsible for planning activities, semi-autonomous IAIs underneath them may take on operational functions with considerable control over the budgets they receive from their ministries. Instead of having their policies set *ex ante*, IAIs are evaluated *ex post* by a ministerial evaluation committee (Organisation for Economic Co-operation and Development [OECD], 2005, p. 160; Pharmaceutical and Medical Devices Agency [PMDA], 2006). IAIs are intended to be managed in a flexible style similar to a private corporation. Although their activities are funded by the government through ministries, activities performed by IAIs are not necessarily considered as having been performed by the government. Employees of IAIs may be considered either public or non-public officials (OECD, 2005, p. 161).

Some of the first IAIs in 2001 were research institutes, which have been the main target of so-called "agencification" (OECD, 2005). Most funding agencies in Japan are also now IAIs, whose resources come from the ministries and agencies that set up the competitive R&D programmes (Shinohara, 2006a). Although agencification among IAI research institutions and funding agencies is widespread, as of 2005, not all research institutes in MHLW had yet been agencified (OECD, 2005, p. 161).

A similar process of agencification has been played out in other areas of Japanese government, such as national universities, which were made separate from MEXT in 2004 (OECD, 2005, p. 142, p. 162).



Source: JSPS, http://www.jsps.org; RIKEN, http://www.riken.go.jp (see footnotes for details); Shinohara (2006a)

MEXT is Japan's lead agency for R&D. It absorbs approximately 65 percent of the central government's science and technology expenses and plays a substantial role in health-related research in Japan.[3] MEXT is a large agency, and its JFY 2005 budget of ¥5.7 trillion accounted for 7.0 percent of the national government's general account budget.[4] However, only 14.5 percent of MEXT's budget is used for the promotion of science and technology (41.9 percent of this is funded competitively), and only a fraction of that amount is used in the area of health and medicine. Another 23.8 percent of MEXT's budget is used to fund national universities, which are also involved in health and medical research (among many other types of research and activities).

MEXT also provides some funding for education and research in basic science at private universities, including a relatively automatic infrastructure portion (¥117 billion in JFY 2006) and a variable, reviewed portion related to research funds (¥48.8 billion in JFY 2006) (Shinohara, 2006b). Of course, these funds are not entirely devoted to health and medical research.

Within MEXT, the National Institute of Science and Technology Policy helps plan and implement long-term science and technology policy.[5] Another policy-oriented division of

[3] MEXT, "Promotion of Science and Technology," http://www.mext.go.jp/english/org/struct/024.htm (as of April 14, 2008).

[4] MEXT, "MEXT's Budget," http://www.mext.go.jp/english/org/struct/004.htm (as of April 14, 2008).

[5] Cordis, ERAWATCH Research Inventory for Japan. Link to "National Institute of Science and Technology Policy" under "Structure of the Research System." http://cordis.europa.eu/erawatch/index.cfm?fuseaction=ri.content&topicID=35&countryCode=JP&parentID=34 (as of April 21, 2008).

MEXT, the Japan Science and Technology Agency (JST), is an IAI funding agency that works to implement Japan's Science and Technology Basic Plan (OECD, 2005, p. 162).[6] It distributes competitive grants for basic research programmes (OECD, 2003a); in JFY 2005, JST distributed ¥47.6 billion in grants (covering many fields of study) (Shinohara, 2006a). In JFY 2006, about 91 percent of JST's revenues came from government, with almost all of the rest coming from its own operating income (JST, 2006).

The Japan Society for the Promotion of Science (JSPS; also known as *Gakushin*) is an even larger R&D funding agency under MEXT (OECD, 2005, p. 162), and promotes itself as "Japan's lead funding agency".[7] JSPS was established by an endowment from Emperor Showa in 1932, but has been a quasi-public IAI since 2003.[8] It receives over 99 percent of its funding from the national government, with some private contributions as well.[9] In JFY 2007, JSPS had a budget of ¥222.6 billion, of which it distributed ¥192.6 billion in grants, although most of these grants were not for health and medicine (Shinohara, 2006a). In addition to administering research grants, JSPS sponsors research fellowships, international exchanges, cooperation between academia and industry, and "social enrichment research" in the humanities and social sciences in service of Japan's Science and Technology Basic Plan.

To build Japan's basic research capabilities, MEXT, through JSPS, has sponsored various efforts to promote high-quality research sites and clusters. One of these, the 21st Century Centers of Excellence (COE) Program, fosters domestic education and research centres to help them become world-class leaders.[10] Funds from the programme help encourage a competitive atmosphere among universities by offering targeted support for building and improving research capacity. In 2002, 28 COEs in the life sciences were established at various universities with another 35 in medicine in 2003.[11] Some universities were the site of multiple COE awards. The University of Tokyo, for example, won three grants each for life sciences and medicine. The former 21st Century COE Program has now transitioned to the Global COE Program, with a similar purpose and an added international flavour (Shinohara, 2007a). In JFY 2007, 13 university research efforts in the life sciences were funded by the Global COE Program. The Global COE Program's 2008 budget stands at ¥34 billion, but only a fraction of this money is destined for research in health and medicine (Shinohara, 2008).

The National Institute of Radiological Sciences (NIRS) is a MEXT-affiliated research agency that studies the effect of radiation on health. Despite the existence of the Radiation

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[6] JST, "Mission of JST," http://www.jst.go.jp/EN/about/mission.html (as of April 14, 2008).

[7] JSPS, "About JSPS," http://www.jsps.org/aboutus/about_jsps/index.html (as of April 14, 2008).

[8] JSPS, "Purpose and Functions," http://www.jsps.go.jp/english/about_us/purpose.html; JSPS, "JSPS's Mid-term Objectives and Plan," http://www.jsps.go.jp/english/about_us/mid.html (as of April 14, 2008).

[9] JSPS, "Budget," http://www.jsps.go.jp/english/about_us/budget.html (as of April 14, 2008).

[10] JSPS, "Global COE Program," http://www.jsps.go.jp/english/e-globalcoe/index.html (as of April 14, 2008).

[11] JSPS, 21st Century COE Program, "Selected Programs (FY2002)," http://www.jsps.go.jp/english/e-21coe/04_A.html, and "Selected Programs (FY2003)," http://www.jsps.go.jp/english/e-21coe/04_F.html (as of April 14, 2008).

Effects Research Foundation (which is more focused on the after-effects of nuclear war), the NIRS claims to be, "the only institution in Japan dedicated to comprehensive scientific research for radiation and health".[12] NIRS's JFY 2005 budget of ¥17 billion included ¥13.3 billion in management expense grants, ¥290 million in facilities maintenance grants, ¥1.64 billion in income from its own operations, and ¥1.8 billion in income from government operations (NIRS, 2006a). Although it seems that most of NIRS's government funding comes from MEXT, the Ministry of the Environment and others also contribute (NIRS, 2006a). NIRS collaborates internationally with researchers from around the world and assists radiation workers in developing countries (NIRS, 2006b).

The Institute of Physical and Chemical Research (known as RIKEN), a prominent national research institute, is described later in this section.

[12] NIRS, "Greetings," http://www.nirs.go.jp/ENG/outline/greeting/index.shtml (as of April 14, 2008).

## Selected MEXT Activities in Health and Medicine R&D, 2007

| Ministry/ Agency | Programme/Project | 2006 Budget (M¥) | 2007 Budget (M¥) | Change Amount (M¥) | Change (%) |
|---|---|---|---|---|---|
| MEXT | National Bio-resource Project | 0 | 1,776 | 1,776 | New |
| MEXT | Comprehensive Database Project | 290 | 1,600 | 1,310 | 452% |
| MEXT | Translational Research | 900 | 2,175 | 1,275 | 142% |
| MEXT | Molecular Imaging (New Research) | 0 | Part of 1,355 | | |
| MEXT | New and Recurring Infectious Diseases Research Centers | 2,600 | 2,750 | 150 | 6% |
| MEXT | Analyses of Genomic Functions | 2,310 | 2,301 | –9 | 0% |
| MEXT | Materialisation of Regenerative Medical Care | 1,077 | 970 | –107 | –10% |
| MEXT | Personnel Fostering for Particle Beam Cancer Treatment | 0 | 40 | 40 | New |
| MEXT | Molecular Imaging (Ongoing Research) | 1,001 | Part of 1,355 | | |
| MEXT | Medical Care Based on Genomic Information | 3,130 | 2,568 | –562 | –18% |
| MEXT | Cell/Bio Function Simulation Project | 704 | 542 | –162 | –23% |
| MEXT/JST | Bio-informatics Promotion Center | 1,809 | 1,682 | –127 | –7% |
| MEXT/JST | Brain Science and Society | 1,536 | 997 | –539 | –35% |
| MEXT/NIRS | Heavy Particle Beam Cancer Treatment | 5,510 | 5,537 | 27 | 0% |

Source: Burrill and Company (2007)

The chart above details some specific health and medicine R&D programmes funded by MEXT. A good deal of the research that MEXT funds is directly administered by the Ministry itself, whereas other portions are first routed through IAIs associated with MEXT, such as JST. New projects for JFY 2007 include a national bio-resource project to supply research materials to Japanese researchers and additional funds for translational research to bring basic science into clinical practice. Some continuing programmes include the creation of a genetic database, infectious disease research centres, and studies in genomic science, regenerative medicine (one of Japan’s areas of strength), molecular imaging, cell function, bio-informatics, brain science, and the treatment of cancer with particle beams.

## RIKEN Groups

| Parent Institute | Suborganisation | Functions | Budget JFY 2007 (M¥) | No. of Personnel |
|---|---|---|---|---|
| Wako Institute | Brain Science Institute | Undertakes research activities in three particular areas: understanding the brain, protecting the brain, creating the brain, and nurturing the Brain. | 9,191 | 513 |
| Tsukuba Institute | BioResource Center | Provides external organisations resources, such as cultured cell lines, DNA, plants and animals for experiments, and information. | 2,393 | 88 |
| Harima Institute | RIKEN SPring-8 Center | Undertakes physical science and structural biology research. | 2,269 | 117 |
| Yokohama Institute | Genomic Sciences Center | Researches genes, the genome and proteins, ranging from their molecular level to an individual level. | 5,330 | 322 |
| | SNP Research Center | Focuses on the relationship between differences in the genetic code and individual-level diseases. | 1,590 | 112 |
| | Research Center for Allergy and Immunology | Investigates causes of conditions, such as allergy, to clarify immunological mechanisms and functions from a genetic level to immunity, with the aim of developing methods of establishing medical treatments. | 3,456 | 211 |
| | Center of Research Network for Infectious Diseases | Supports the Program of Founding Research Center for Emerging and Reemerging Infectious Diseases, which is promoted by MEXT. | – | 11 |
| Kobe Institute | Center for Developmental Biology | Established three research fields: Mechanism of Development, Mechanism of Regeneration, and Application to Medicine, on which the researchers are concentrating in these comprehensive projects. | 4,802 | 322 |
| | Molecular Imaging Research Program | Seeks to support the discovery of new drugs through its Molecular Probe and Drug Design, Molecular Probe Dynamics, and Functional Probe research programs. | – | 29 |

Source: RIKEN Web site, http://www.riken.go.jp; LATEC Network Web site, http://www.latec.jp/private/middle4_9.html

RIKEN is a national research institute (as opposed to an R&D funding agency) (OECD, 2005, p. 162), which conducts various types of science and technology research, from the basic to the applied level. Its name is a contraction of *Rikagaku Kenkyuudjyo* (Institute of Physical and Chemical Research). Once a private institution, RIKEN was placed in MEXT as an IAI in 2003. It is home to five separate research institutes. Of its ¥89.4 billion budget in JFY 2007, it redistributed ¥6 billion in grants, and spent most of the rest on its own research institutes and activities.[13]

One of these institutes within RIKEN, the Wako Institute, is engaged in embryonic research and brain science. Wako houses the Brain Science Institute (¥9.2 billion budget, 513 personnel), which classifies its research into four areas: understanding the brain, protecting the brain, creating the brain, and nurturing the brain.[14]

The Tsukuba Institute conducts gene-related R&D, and runs businesses related to bioresources. It is home to the BioResource Center (¥2.4 billion budget, 88 personnel), which provides external organisations resources such as cultured cell lines, DNA, plants and animals for experiments, and information.

RIKEN's Harima Institute studies radiation light and does joint research with external research institutions, such as universities; it is home to the SPring-8 Center (¥2.3 billion

[13] RIKEN, "Budget (Fiscal Year 2007)," http://www.riken.jp/engn/r-world/riken/personnel/index.html#budget (as of April 14, 2008).

[14] RIKEN, "Programs for Junior Scientists," http://www.riken.jp/engn/r-world/research/research/index.html (as of April 14, 2008).

budget, 117 personnel), which conducts research in physical sciences and structural biology with the aim of developing cures for disease.[15]

The Yokahama Institute is heavily involved in life sciences. It hosts the following centres: the Genomic Sciences Center (¥5.33 billion, 322 personnel), which researches genes, the genome, and proteins, from an individual to a molecular level; the SNP Research Center (¥1.59 billion budget, 112 personnel), which studies genetic causes of disease; the Research Center for Allergy and Immunology (¥3.46 billion budget, 211 personnel), which focuses on the causes of allergy and immunological mechanisms, in the hopes of developing treatments; and the Center of Research Network for Infectious Diseases (11 personnel), which supports MEXT's Program of Founding Research Center for Emerging and Re-emerging Infectious Diseases.

RIKEN's fifth institute, the Kobe Institute, studies regenerative medicine, in cooperation with external research institutes and medical organisations. It is the home of the Center for Developmental Biology (¥4.8 billion budget, 322 personnel), which works in the fields of mechanism of development, mechanism of regeneration, and application to medicine, as well as the Molecular Imaging Research Program (29 personnel), which seeks to discover new drugs by way of molecular research.

[15] RIKEN SPring-8 Center, "Research Activities," http://www.harima.riken.jp/eng/labo/index.html (as of April 14, 2008).

## Universities and Colleges

**National Universities in Health and Medicine**

- University of Tokyo (Institute of Medical Science)
- Tokyo University of Science (Research Institute for Biological Science)
- Kyoto University
- Kobe University
- Osaka University
- Keio University

**National Inter-University Research Institutes**

- Okazaki National Research Institutes
  - Institute for Molecular Science
  - National Institute for Basic Biology
  - National Institute for Physiological Sciences
- National Institute of Genetics

**Private Universities**

- Kitasato University (Kitasato Institute for Life Sciences)

*Number of health and medical researchers work in Japanese Universities and Colleges (2006)=104,804*

*Intramural expenditures on health and medical research and development in Japanese Universities and Colleges (2006)=¥893 billion (¥716 billion self-financed)*

Source: MIAC (2008); National Science Foundation, http://www.nsftokyo.org/japansources.html

Japan's university system is an important component of its health and medical research system. University researchers made up almost 80 percent of Japan's 131,581 health and medical researchers in 2006, and universities were the final destination of over 43 percent of Japan's research investments in that field (MIAC, 2008).

Although MEXT funds Japan's National Universities, it is not in direct administrative control of them, because they have been agencified into National University Corporations, which compete against each other for funds and students (OECD, 2005, p. 162). Each of the 88[16] National Universities are now independent and autonomous,[17] and 42 of them have schools of medicine.[18] Employees of the National Universities are not considered public sector employees (OECD, 2005, p. 142). From MEXT, they receive annual operational block grants equal to about ¥1.3 trillion, which cover salaries, facilities management, research and other costs (OECD, 2005, p. 162; Shinohara, 2007b). Through their laboratories, National Universities are directly engaged in health and medical research. Some of the most important National Universities in health and medicine include the University of Tokyo, Tokyo University, Kyoto University, Kobe University, Osaka University, and Keio University.

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[16] Conversation with Dr. Kyoko Koishi, Dept of Anatomy and Structural Biology, University of Otago, Dunedin, New Zealand.

[17] MEXT, "School Education: Incorporation of National Universities," http://www.mext.go.jp/english/org/struct/020.htm (as of April 14, 2008).

[18] Conversation with Dr. Kyoko Koishi, Dept of Anatomy and Structural Biology, University of Otago, Dunedin, New Zealand.

National Inter-University Research Institutes are also important within the larger Japanese R&D system. These institutes are designed with the intent of fostering cooperation between researchers at different universities, although few are concerned with health and medicine. Two exceptions are Okazaki National Research Institutes and the National Institute of Genetics.

The Okazaki National Research Institutes, which consists of an Institute for Molecular Science, a National Institute for Basic Biology, and a National Institute for Physiological Sciences (NIPS),[19] works closely with universities across Japan to conduct fundamental research. Of Okazaki's JFY 2002 total budget of ¥10.4 billion, ¥825 million went to NIPS, with an additional ¥1.21 billion going to all research facilities. The NIPS budget can be broken down further by its sources, with ¥368 million from MEXT's Grants-in-Aid for Scientific Research programme, ¥86 million from the Research for the Future programme, ¥133 million from contracts, ¥15 million from cooperative activities with industry, and ¥55 million from donations. Of the 406 employees of the Okazaki National Research Institutes, 96 work in NIPS, in which there are 14 professors, 17 associate professors, 33 research associates, and 31 technical staff.[20] The Okazaki Institutes are also active in international cooperation, with NIPS working with 128 foreign researchers in 2002. Organisationally, NIPS has also been placed within Japan's National Institutes of Natural Sciences, which groups together five inter-university research institutes.

The National Institute of Genetics, founded in 1949, became an inter-university research institute in 1985. The Institute's departments cover nearly every aspect of genetic science, spread over 39 laboratories.[21] Although much of the activity is related to human health, such as developmental biology and the human genome, other areas are not so closely related, such as plant biology and evolutionary biology.[22] The National Institute of Genetics also runs a graduate education programme, which hosts both domestic and international students.

Although they are not nearly as prominent, private universities also make contributions to health and medical research in Japan. One of the best examples is Kitasato University, which runs the Kitasato Institute for Life Sciences. The Kitasato Institute was founded in 1914 by Shibasaburo Kitasato, an eminent physician and bacteriologist. The Institute eventually grew into Kitasato University. The Kitasato's mission, which involves "research on the causes, prevention and treatment of various diseases," is supported by 1,361 members and an annual budget of ¥27.5 billion. The various laboratories at Kitasato University study organic chemistry, tropical diseases, infection control, advanced medicine,

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[19] Organisationally, NIPS has also been placed within Japan's National Institutes of Natural Sciences, which groups together five inter-university research institutes. See http://www.nins.jp/english/index.html.

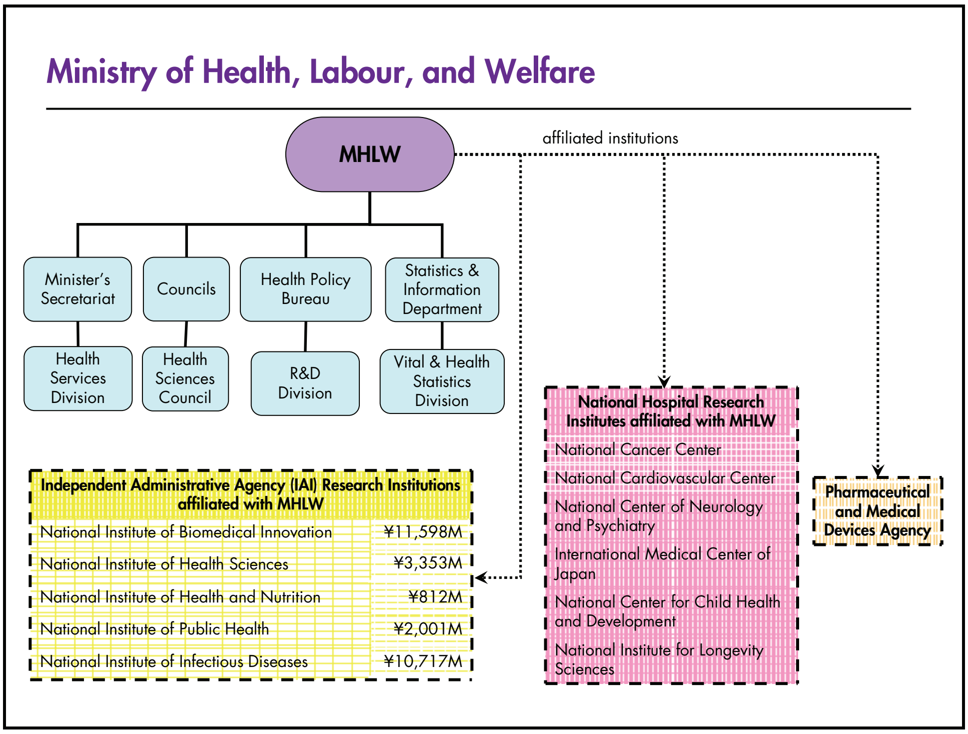
[20] Okazaki National Research Institutes, "Message from President," http://www.orion.ac.jp/data_e/frame/a1_1.html (as of April 14, 2008).

[21] National Institute of Genetics, "Organization," http://www.nig.ac.jp/section/index-e.html (as of April 14, 2008).

[22] National Institute of Genetics, "Research at NIG," http://www.nig.ac.jp/section/research-e.html ( as of April 14, 2008).

animal experiments, liver diseases, and anti-infectious drugs.[23] Kitasato was the site of the first 21st Century COE Program in a private graduate programme in pharmaceuticals.

[23] ReaD, "The Kitasato Institute," http://read.jst.go.jp/public/cs_kkn_004EventAction.do?action5=event&lang_act5=E&kcd1_act5=9417000000&judge_act5=2 (as of April 14, 2008).




The MHLW is engaged in many activities outside of health and medical research, but it may be considered the most important ministry related to health and medical research in Japan's central government. Although it funds less research overall than MEXT, the research it does fund is almost always directly related to health and medicine. In JFY 2006, its health and medicine-related research budget of ¥131.5 billion was over 90 percent larger than MEXT's. By JFY 2008, that budget had grown to ¥136.4 billion (Shinohara, 2008).

MHLW is affiliated with 76 national hospitals,[24] some of which are paired with research institutes to create national centres of medicine. Many of these prestigious research institutes are considered Japan's leading scientific organisations in their respective fields.[25]

One of the oldest of these research-centre–hospital combinations is the National Cancer Center (NCC), which was founded in Tokyo in 1962. It now pairs two research-oriented national hospitals with the NCC Research Institute (NCCRI), which studies prevention, detection, and treatment of cancer.[26] Like the other MHLW-affiliated research institutes that are linked to hospitals, the NCCRI receives most of its funds from the MHLW. In the case of NCCRI, some of those moneys have been received under the grants-in-aid for the Cancer Research Program, and the Third-Term Comprehensive 10-Year Strategy for Cancer Control. Over time, the NCC has grown into two hospitals, with the first in

[24] MHLW, "Organization of the Ministry of Health, Labour and Welfare," http://www.mhlw.go.jp/english/org/detail/index.html (as of April 14, 2008).

[25] NCCRI, "Director's Message," http://www.ncc.go.jp/en/nccri/about/preface.html (as of April 14, 2008).

[26] NCCRI, "Overview," http://www.ncc.go.jp/en/nccri/about/overview.html (as of April 14, 2008).

Tokyo being joined by Hospital East in Kashiwa. Likewise, the NCCRI has grown as well, with an East wing in Kashiwa working with the Hospital East. Currently, the NCCRI employs 130 staff scientists, 100 research assistants, 90 research residents and other fellows, and an unspecified number of foreign guest scientists within nearly 30 research divisions.[27]

Similarly, the National Cardiovascular Center (NCVC) pairs the NCVC Hospital with the NCVC Research Institute, which were founded together in 1977.[28] It employs 98 full researchers, 65 domestic and 15 foreign postdoctoral fellows, and 60 technicians, and has an annual research budget of approximately ¥2.5 billion. The NCVC Research Institute has departments of aetiology and pathogenesis, biochemistry, cardiac physiology, molecular physiology, epidemiology, pharmacology, structural analysis, bioscience, and comprehensive experiments, plus three laboratories for comprehensive medicine, animal research, and biomedical instruments. In addition, there are five departments and one laboratory devoted to advanced medical engineering, which studies artificial organs, regenerative medicine, etc. This part of the NCVC Research Institute is intended to accelerate research translation from academia and government to industry. The NCVC Research Institute boasts that it publishes nearly 800 scientific journal articles each year, with 250–300 in English.

The National Center of Neurology and Psychiatry unites Musashi Hospital, the National Institute of Neuroscience, Kohnodai Hospital, and the National Institute of Mental Health. The National Institute of Neuroscience is composed of seven sections for basic research (molecular biology, biochemistry, morphology, embryology, neurobiology, etc.) and seven for clinical research (neurodegenerative diseases, multiple sclerosis, schizophrenia, muscular dystrophy, etc.). The National Institute of Mental Health is composed of eleven departments, focused on such topics as drug dependence, psychosomatic research, child, adolescent, adult, and elderly mental health, social psychiatry, psychophysiology, developmental disorders, psychiatric rehabilitation, and forensic psychiatry.

The National Research Institute for Child Health and Development (NRICHD), within the MHLW-sponsored National Center for Child Health and Development (NCCHD), has departments of developmental biology, endocrinology and metabolism, allergy and immunology, genetics, infectious diseases, innovative surgery, pharmacology, maternal and child health, reproductive biology, and health policy. Each of these departments has two laboratories and works in cooperation with NCCHD's children's hospital (NCCHD, 2002). Some of the specific research efforts currently conducted at NRICHD include fetal medicine, gene therapy, pharmaceutical development, and stem-cell research. NRICHD's maternal and child health department cooperates internationally to bring down child mortality rates and support maternal health in the developing world. Although NRICHD's annual budget of approximately ¥1 billion is mostly funded by MHLW, it also receives funds from other sources (NCCHD, 2002).

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[27] NCCRI, "Overview," http://www.ncc.go.jp/en/nccri/about/overview.html (as of April 14, 2008).

[28] National Cardiovascular Center, "Research Institute," http://www.ncvc.go.jp/english/res/rese.html (as of April 14, 2008).

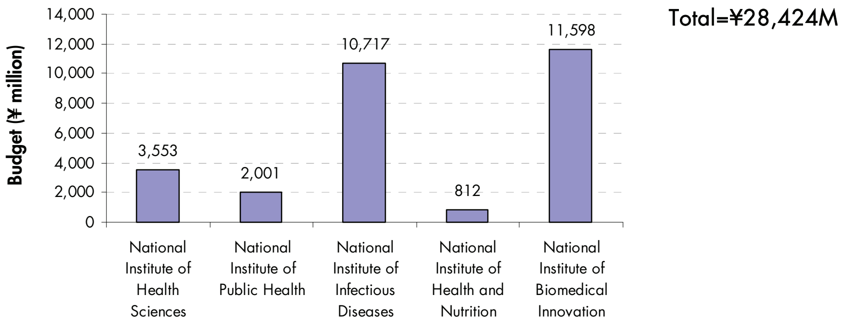
The International Medical Center of Japan (IMCJ; formerly the 4th National Medical Center) also has its own hospital research institute, which is engaged in a wide range of medical research and works with international partners to combat infectious and lifestyle diseases.[29] It hopes to increase Japan's global contribution to medical science. It is also tasked with providing medical aid to developing countries. It has twelve departments, covering community health, technology development, gastroenterology, respiratory diseases, metabolic disorders, infectious diseases, haematology, intractable diseases, clinical pharmacology, pathology, genetic diagnostics and therapeutics, plus an international clinical research centre with departments of epidemiology, medical ecology, and regenerative medicine.

The work of the PMDA, which oversees pharmaceutical research, development, and marketing, is described in the next section.

[29] IMCJ, "Message from the Director," http://www.imcj.go.jp/rese/top/edirector.html (as of April 14, 2008).

**MHLW Research Institutions: Science & Technology Budgets (2007)**

**National Institute of Infectious Diseases and National Institute of Biological Innovation receive over 75% of MHLW's budget for research institutions**




Source: Burrill and Company (2007), p. 9

MHLW is affiliated with several research institutions involved in health and medical sciences. As IAIs, they all receive funding from MHLW but retain substantial autonomy. The largest of these, the National Institute of Biomedical Innovation (¥11.6 billion in JFY 2007) (Burrill and Company, 2007), conducts basic research on pharmaceuticals and biological resources and promotes pharmaceutical research. It creates basic technologies used in pharmaceutical research; supplies, researches, and develops resources used for biological research; commissions and funds research; and disseminates results. In service of its goal of new drug development, it collaborates with private industry, universities, and other government agencies. The National Institute of Biomedical Innovation is physically located in the Northern Osaka Bio Cluster, which serves as a hub for Japanese pharmaceutical research companies, and is also the home of Osaka University and the National Cardiovascular Center. In the future, the National Institute of Biomedical Innovation envisions the importance of genomic, proteomic, and bioinformatic technologies, and expects to help to bring basic research from universities to private corporations.

The next largest research institute under MHLW is the National Institute of Infectious Diseases (NIID; ¥10.7 billion in JFY 2007, a 22.6 percent jump over the previous year) (Burrill and Company, 2007), which is aims to prevent and suppress disease by performing research, scientific reference services, surveillance, national control tests, international cooperation, and training. NIID has three departments of virology, and one department each for bacteriology, bacterial pathogenesis and infection control, parasitology, pathology, immunology, bioactive molecules, biochemistry and cell biology, medical entomology, veterinary science (and its connection to human health), and blood and biologics. Each of these departments contains at least three research laboratories. The laboratories of the first department of virology are currently studying arboviruses, neurovirology, herpes, rickets and chlamydia, and special pathogens, such as Ebola and hantaviruses.[30] NIID also has a Division of International Cooperation which, focusing on developing countries, runs a fellowship programme and administers aid for international research projects. NIID's local-level disease surveillance duties and national-level epidemiological activities are performed by its Infectious Disease Surveillance Center, established in 1997http://idsc.nih.go.jp/about/index-e.html.[31]

The National Institute of Health Sciences (¥3.55 billion in JFY 2007) (Burrill and Company, 2007), located in Tokyo, was established in 1874 and is Japan's oldest national research institute. It conducts research related to the evaluation of pharmaceuticals, drugs, and foods, ensuring their quality, efficacy, and safety.[32]

The National Institute of Public Health (¥2 billion in JFY 2007) (Burrill and Company, 2007), as its name implies, is Japan's lead agency for public-health research and training. Its departments cover public-health topics such as technology, statistics, policy, management, human resources, epidemiology, nursing, health promotion, social services, water supply, oral health, environmental health, building-related health, and education and training.

The National Institute of Health and Nutrition (NIHN; or the IAA of Health and Nutrition; ¥812 million in JFY 2007) (Burrill and Company, 2007) is a smaller agency, first known as the Nutrition Institute, and later as the National Nutrition Institute. As it now has IAA status, it is operationally flexible and its employees are no longer considered government workers. Much of NIHN's research is oriented towards gathering an evidence base to be used in the production of national dietary guidelines. Each year, NIHN conducts the National Health and Nutrition Survey. NIHN also conducts clinical trials to research the physiological effects of diet, nutrition, and exercise. Its clinical nutrition programme is currently examining how and why the Japanese people may be genetically more susceptible to diabetes than westerners. NIHN has plans to develop an international research network to promote international cooperation and host young researchers from around Asia (NIHN, 2007).

The National Institute of Health Services Management is a former agency within MHLW that conducted research on the "medical service system and medical economy as well as studies on hospital management including medical service management and education and training".[33] This agency, along with the Institute of Public Health, was a forerunner of the current National Institute of Public Health.

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[30] NIID, "Organization of NIID," http://www.nih.go.jp/niid/welcome/org-index-e.html (as of April 14, 2008).

[31] IDSC, "About IDSC," http://idsc.nih.go.jp/about/index-e.html (as of April 14, 2008).

[32] National Institute of Health Sciences Web site, http://www.nihs.go.jp/english/index.html (as of April 14, 2008).

[33] Ministry of Health, Labour and Welfare, "Facilities and Agencies/Regional Offices," http://www.mhlw.go.jp/english/org/policy/p42.html (as of April 14, 2008).

## METI's Research Activities

| Item | JFY 2006 (M¥) | JFY 2007 (M¥) |
|---|---|---|
| Basic biotechnology supporting acceleration of genomics-based drug development | 4,650 | 4,360 |
| Development of technologies to bridge basic and applied sciences | 0 | 1,900 |
| Development of biotechnology diagnostics to materilise personalised medicine | 650 | 400 |
| Development of new functional antibody production technologies | 1,200 | 1,190 |
| Molecular imaging equipment development project (F21) | 1,030 | 1,200 |
| Development of sugar chain function application technology | 1,190 | 1,190 |
| Research and development of next-generation DDS-type treatment systems for malignant tumours | 1,010 | 1,160 |
| Development of functional RNA analysis technology | 900 | 850 |
| Regenerative medicine evaluation R&D project | 650 | 830 |
| Intelligent surgical equipment R&D project | 700 | 700 |
| Genome information integration project | 540 | 520 |
| Care goods practical applications development project | 120 | 120 |
| Medical equipment development guideline project | 80 | 70 |
| Safety measures in biotechnology industry | 60 | 60 |
| Research on bioethical and other issues relating to commercialisation of biotechnology | 40 | 30 |
| Care goods information gathering, analysis, and supply | 30 | 30 |
| Standardisation and demonstration of local medical information integration system | 280 | 210 |
| Demonstration of interoperability of medical information systems | 300 | 150 |
| Contributions to biotechnology-related projects by the OECD's CSTP | 10 | 10 |

*"As its mission, METI will propel the Japanese economy by providing information and analytical insights, creating systems that support society and the economy, and enhancing Japan's technological foundations, so that companies, communities, individuals, non-profit organisations, and other players can exercise their capabilities to the fullest and maximise their potential."*

Source: Burrill and Company (2007); METI, http://www.meti.go.jp/english/other/METIintroduction/c10130bj.html

METI works to bring the fruits of basic scientific research from academia to industry. Naturally, some of its activities involve medicine and drugs. Nevertheless, the extent of METI's activities in health and medical research is slight compared to MHLW and MEXT. Of a ¥558.1 billion research budget in JFY 2006 (Shinohara, 2006b), only ¥15.2 billion was spent on health and medical research (Burrill and Company, 2007).

Most of METI's research is conducted in-house, without the use of grants (Shinohara, 2006b). One of its largest projects related to health and medicine supports the development of genomic-based drugs; ¥4.36 billion was spent for this purpose in 2007. This was carried out by METI's New Energy and Industry Technology Development Organization, which also received ¥1.9 billion for translational research and ¥1.19 billion to develop antibody pharmaceuticals (Burrill and Company, 2007). Other METI funds were spent on such activities as RNA analysis technology, molecular imaging equipment, cancer treatment, regenerative medicine, and the creation of development guidelines for medical equipment.

Beyond its efforts funding research, METI also works to foster a business environment that is conducive to R&D investments (OECD, 2005, p. 155).

## Kobe Foundation for Biomedical Research and Innovation

Foundation for Biomedical Research and Innovation

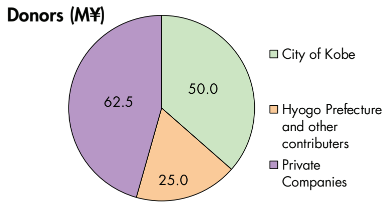
The Foundation (est. 1999) works in support of the Kobe MID Project.

Three main goals are:

- *Revitalising Kobe's economy by generating new industries, strengthening existing industries and creating jobs*
- *Improving citizen welfare by providing healthcare support and responding to the needs of Japan's ageing society*
- *Making a contribution to the international community by improving medical technology in other Asian countries*

The Foundation also supports the Institute of Biological Research and Innovation in Kobe and other institutes.

*Donors include*: Kobe City, Hyogo Prefecture, Hyogo Prefecture and Health Promotion Association, The Kobe Chamber of Commerce and Industry, Osaka Gas Co. Ltd, Oryx Corp., Olympus Optical Co. Ltd, Kawasaki Heavy Industries Ltd, Sankyo Co. Ltd, Nippon Steel Corp., Takeda Chemical Industries Ltd, Eli Lilly Japan K.K., Yamanouchi Pharmaceutical Co. Ltd




Source: Kobe Foundation for Biomedical Research and Innovation, http://www.ibri-kobe.org/english/outline_fbri.html

The Kobe Foundation for Biomedical Research and Innovation is an interesting collaboration between local government and private companies, and is an example of a locally driven effort to create an industrial cluster centred on biomedicine (other examples of this type of regional hub building can be found in Hokkaido, Kansai, Kanto, Kyushu, and Tokai) (Asia Pacific Trade Council, 2007). Created in 1998 in the wake of a devastating earthquake, the Foundation supports the Kobe Medical Industry Development (MID) Project, which is designed to revitalise and reinvent Kobe's economy as a medical industry hub. It is mainly funded by the City of Kobe, the Hyogo Prefecture, and private companies. Some of the business support received from Kobe Urban Promotion Service Company Ltd, ultimately comes from the central government's Japan Regional Development Corporation. Other central government funds have been received through MEXT's Intellectual Cluster Formation Project.[34]

The flagship of the MID Project is the Institute of Biomedical Research and Innovation, which conducts translational research in three fields:

- Medical equipment R&D,
- Support for clinical research into pharmaceuticals and other treatment tools,
- Clinical applications of regenerative medicine, the highest priority of the three.

[34] Kobe Medical Industry Development Project, "Creating an R&D Hub for Advanced Medical Technology with Medical Industry Businesses," http://www.city.kobe.jp/cityoffice/27/kigyo-yuchi/invest-kobe/e/project/iryo/index.html (as of April 14, 2008).

The Institute of Biomedical Research and Innovation works in cooperation with medical and healthcare companies, the RIKEN Center for Developmental Biology, universities, foreign and domestic research institutes, regional medical associations, and the Kobe City General Hospital. It is managed and funded by Foundation for Biomedical Research and Innovation.

Other centres created by Foundation for Biomedical Research and Innovation in Kobe include the following:

- Kobe Translational Research Informatics Center
- Kobe Business Support Center for Biomedical Research Activities
- Kobe Biotechnology Research and Human Resource Development Center/Kobe Incubation Center
- Kobe Medical Device Development Center (MedDeC)
- Kobe Healthcare Industry Development Center (HI-DeC)
- Molecular Imaging Research Program
- Kobe International Business Center
- Kobe KIMEC Center Building
- Kobe Incubation Office

The MID Project is aided by the nearby location of Kobe University, Kyoto University, and Osaka University. Kobe is now the home of over 100 companies engaged in biomedical research.

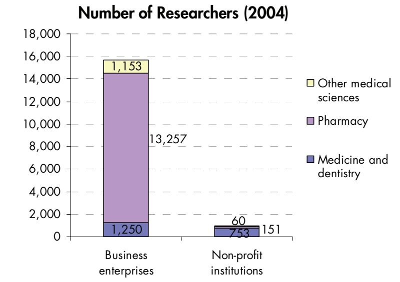
## Private Organisations

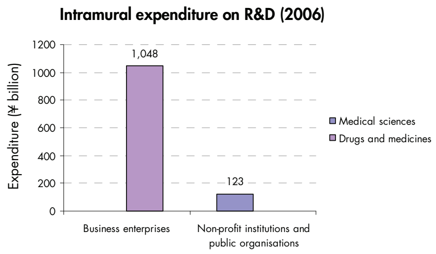
**Non-profit Organisations**
- Radiation Effects Research Foundation (RERF)
- Japan Epilepsy Research Foundation
- Japanese Foundation for Cancer Research (JFCR)
- Japan Heart Foundation

**For-profit Organisations**
- Pharmaceutical companies
- Medical device manufacturers

Non-profit and public organisations are dwarfed by businesses enterprises

Businesses have over four times as many researchers, and spend over eight times more on intramural research




Source: MIAC (2008)

Outside of government, non-profit organisations and corporations also play a part in health and medical research. However, their respective importance within the system could hardly be more different.

Compared to other sectors, the non-profit sector plays only a small part in Japan's health and medical research system. Some have speculated that the paucity of charity funding is due to the lack of extremes in wealth and poverty in the country (Imamura, 1993). Whereas 15,660 medical scientists worked in business enterprises, only 964 (<1 percent), worked in non-profit institutions, 3,801 worked in public organisations, and 90,889 worked in universities and colleges. Of those 964 workers in non-profit institutions, 753 (78.1 percent) worked in medicine and dentistry, whereas 151 (15.7 percent) worked in pharmaceuticals and 60 (6.2 percent) worked in other medical sciences.[35] As for intramural research budgets, non-profit institutions and public institutions together spent only ¥123 billion in 2006, while businesses and universities spent ¥1.05 trillion and ¥893 billion, respectively.

The Radiation Effects Research Foundation (RERF) is a private non-profit organisation of about 260 personnel devoted to researching the effects of radiation on people.[36] Although it is private, it operates under the jurisdiction of MHLW. It is particularly concerned with the after-effects of the atomic bombs that destroyed Hiroshima and Nagasaki. RERF's

[35] MEXT, "Statistics," http://www.mext.go.jp/english/statist/index.htm (as of April 14, 2008).

[36] Radiation Effects Research Foundation, "Objectives and History," http://www.rerf.jp/intro/establish/index_e.html; and "Organization," http://www.rerf.jp/intro/org/index_e.html (as of April 14, 2008).

long-term population studies have made it one of the world's premier centres for studying radiation and health (The National Academies, 2003). It also acts as a place of research cooperation between Japan and the Unites States, in fulfilment of an agreement between the two countries dating to the aftermath of World War II. Concordantly, RERF receives funding both from MHLW and from the U.S. Department of Energy: in JFY 2006, 47.9 percent of its ¥4.73 billion total income was contributed by the Japanese government, whereas another 29.6 percent came from the U.S. government (RERF, 2007). Additional funds came from loans and from its operational income. Governance is also shared between the Japan and the United States, as both its board of directors and its scientific council (which guides research activities) are filled by representatives from both countries. Within the realm of radiation effects, RERF's scope of research is fairly broad, and includes clinical studies, genetics, radiology and molecular epidemiology, radioisotopes, and statistics.[37]

The Japanese Foundation for Cancer Research (JFCR), a non-profit established in 1908, is the oldest cancer research institute in Japan.[38] It is involved in research in pathology, cell biology, biochemistry, carcinogenesis, genetic diagnosis, protein engineering, chemotherapy, molecular pharmacology, molecular biotherapy, genomics, gene therapy, and clinical research. JFCR not only conducts its own research, but also funds researchers at national universities and research institutions throughout Japan.[39] JFCR also has its own Cancer Institute Hospital and three research divisions: the Cancer Institute, the Cancer Chemotherapy Center, and a genome centre. Although JCFR does receive some funding from MEXT, it mainly depends on support from private sources.

The Japan Heart Foundation is a private organisation established in 1970 to research cardiovascular diseases. Its main activity involves the administration of scientific grants to sponsor young heart researchers throughout countries in the Association of Southeast Asian Nations. To participate, researchers must secure approval from their local heart foundations and home institutes. Grants are set at an upper limit of ¥800,000 per researcher, with no more than one researcher funded at a time in each country.[40]

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[37] Radiation Effects Research Foundation, "Objectives and History," http://www.rerf.jp/intro/establish/index_e.html (as of April 14, 2008).

[38] Japanese Foundation for Cancer Research, "Request for Donations," http://www.jfcr.or.jp/english/donation/index.html (as of April 14, 2008).

[39] Genome Center, "The Genome Center of the Japanese Foundation for Cancer Research," http://www.jfcr.or.jp/laboratory/english/gc/index.php (as of April 14, 2008).

[40] Japan Heart Foundation, "Japan Heart Foundation Procedures for Recommending Candidates for Supporting Grants for Training in Japan in the Field of Cardiovascular Diseases," http://www.jhf.or.jp/english/grants.html (as of April 14, 2008).

**Largest Japanese Pharmaceutical Companies, 2006**

| Revenue Rank (world) | Company | US$ millions | | | Employees |
|---|---|---|---|---|---|
| | | Healthcare Revenue | Healthcare R&D | Net income/ loss | |
| 18 | Takeda Pharmaceutical Co. | 10,284 | 1,620 | 2,870 | 15,000 |
| 22 | Astellas Pharma | 7,850 | 1,435 | 1,122 | 23,613 |
| 23 | Daiichi Sankyo | 7,158 | 1,459 | 671 | 20,100 |
| 25 | Eisai | 5,583 | 926 | 604 | 14,993 |
| 37 | Chugai Pharmaceutical Co. | 2,787 | 467 | 328 | 5,962 |
| 40 | Taisho Pharmaceutical Co. | 2,069 | 244 | 132 | 5,756 |
| 43 | Mitsubishi Pharma | 1,945 | 403 | 208 | 5,111 |
| 46 | Dainippon Sumitomo Pharma | 1,763 | 350 | 193 | 3,750 |
| 47 | Kyowa Hakko Kogyo | 1,698 | 268 | 108 | 2,895 |
| 48 | Shionogi & Co. | 1,640 | 320 | 159 | 2,868 |

Source: "Top 50 Pharmaceutical Companies," *MedAdNews*, September, 2007

Businesses, especially pharmaceutical companies, are much more active in the area of health and medical research than the non-profit sector. In 2006, 427 businesses were doing research in drugs and medicines, spending an average of 10 percent of their sales revenue on research (MIAC, 2008). At that point, 16.6 percent (21,791 of 131,581) of all health, medical, and pharmaceutical researchers in Japan worked for private businesses (up from 14.1 percent in 2004). The vast majority of private-sector health and medical researchers work in pharmaceutical companies, with only about 8 percent working in medicine and dentistry, and 7 percent working in other medical sciences.[41]

Pharmaceutical companies largely finance their own research activities. In 2006, they spent ¥1.27 trillion of their own money on research, while receiving an additional ¥36 billion from outside sources. Most of their research was done in-house, with only ¥248 billion being paid outside. This left about ¥1.05 trillion to be spent on intramural research expenditures. Because of the relatively high expenditures and relatively few number of researchers (compared to universities and non-profit organisations), researchers in private industry are richly funded. In 2006, researchers in businesses received an average of ¥48 million per person, compared to ¥25 million in non-profits and public organisations, and ¥9.6 million in universities and colleges (MIAC, 2008).

Medical device manufacturers are not as prominent as drug manufacturers in the area of research. The size of the medical device industry is only about one fifth the size of the drug industry, whereas its R&D expenditure ratio is half the size of the drug industry's (Sato, 2006). Due to a fear of forced compensation and reputational damage, most high-risk

[41] MEXT, "Statistics," http://www.mext.go.jp/english/statist/index.htm (as of April 14, 2008).

devices must be developed in foreign countries. However, foreign manufacturers are reluctant to conduct trials in Japan.

# Processes and Performance of the Japanese Health Research System

## Processes and Performance of the Japanese System

- CSTP sets government science and technology policy;
  SCJ advises government policy;
  ministries implement policy
- CSTP, the Ministry of Finance, and other ministries negotiate budgets; mixture of grant and block funding, with grant funding increasing
- Moneys flow from the central government down to researchers at independent research agencies and universities
- Universities and industry dominate health and medical research; public and non-profit institutes are relatively minor
- Concern about system's overall performance

The CSTP sits at the apex of the Japanese government's science and technology programme, formulating strategy and setting policy. Cabinet-level ministries involved in science and technology are responsible for designing plans for carrying out the policies set by the CSTP. Every five years, the CSTP creates a Science and Technology Basic Plan, which delineates policy, priorities, and plans. The 3rd Science and Technology Basic Plan, which began in April 2006, and will be operative through 2010, names life sciences as one of the top four priority areas, as did the 2nd Plan before it (CSTP, 2006). Each month, the Council convenes in the CSTP Conference to discuss policy, with the Minister for Science and Technology Policy presiding (CSTP, 2005). CSTP Conferences are supplemented by weekly steering meetings.

Assisting the CSTP in its tasks is the Science Council of Japan, an interest group for scientists under the jurisdiction of the Prime Minister.[42] It promotes public awareness about science, advises the Prime Minister on matters of policy, creates networks among scientists, and holds international conferences. It is known as "the voice of Japan's scientists". The Science Council of Japan has 210 elected members and 2000 associate members, who deliberate and decide on important issues concerning science, while

[42] Science Council of Japan, "About Us," http://www.scj.go.jp/en/scj/index.html (as of April 14, 2008).

working to coordinate Japan's scientific research efforts. It has three section meetings, one of which is concerned with life sciences. The Science Council of Japan regularly hosts international symposiums with topics that occasionally cover health and medicine.

Once high-level policy is established by the CSTP, ministries and agencies send budgets to the CSTP. The budgets name specific research programmes to which the CSTP gives priority ratings, based on each programme's scientific merit and importance. Programmes may receive a rating of S (excellent), A (very good), B (good), or C (to be reviewed) (Shinohara, 2007a). Nearly 400 science and technology projects were reviewed in this manner in JFY 2007, but the projects reviewed only cost ¥100 million or more in the case of new projects, or ¥1 billion or more in the case of continuing projects (Shinohara, 2007c, 2007d). Working closely with the CSTP, the Ministry of Finance then creates a science and technology budget based on the CSTP ratings. Budgets are set after final negotiations with the ministries and agencies (Burrill and Company, 2007). For nationally important R&D projects, CSTP assesses performance (OECD, 2005, p. 159).

Once research funds are received by the ministries, they are either offered up as competitive grants to directly fund researchers at IAIs or universities, or they are transferred to the IAIs. The IAIs then use the money to fund their own research or competitive grant programmes. In that way, some grants are provided directly by ministries and agencies, whereas others are first routed through organisations underneath (Shinohara, 2006a). The use of competitive grant funding has increased in recent years, in parallel with the process of agencification. Evaluations of R&D projects are done to improve their quality.

Outside of the universities, government's involvement in health and medical research is slight. Only 3.4 percent of researchers in health and medicine work in public or semi-public institutions. The government's sponsorship of corporate research (of all types) is also slight, as measured by the ratio of government-sourced R&D money to all R&D money used by industry. This figure stands at 1.4 percent in Japan, compared to 7.4 percent in Germany, 9.3 percent in the United States, 10.0 percent in France, and 11.9 percent in the United Kingdom (OECD, 2005).

Most research in Japan is performed by universities or private companies, with public research institutions playing a smaller, but significant role. Non-profit institutions perform (or fund) only a small fraction of health and medical research in Japan.

Japan cooperates internationally on two levels. With the developed world, it concentrates on collaborative research projects. With the developing world, it mainly assists in building research capacity in other Asian countries.

For reasons to be discussed later in this section, there is concern about the overall performance of the Japanese health and medical research system. Most of this concern involves the lack of a strong historical relationship between Japanese national universities and drug and device manufacturers, and the resulting lacklustre output in terms of new, marketable discoveries.

## Pharmaceutical Policy

- Pharmaceutical companies are major players in Japan's health and medical research system
- Industry is given tax breaks to encourage growth
- In the face of global competition, Japanese companies are undergoing a series of mergers
- Development process overseen by PMDA

As Japan is the world's second largest market for prescription and over-the-counter drugs, it is not surprising that drug companies are such a vital component of the Japanese health research system. These companies employ a large proportion of Japan's medical scientists, and spend an even larger proportion of the country's health and medical research funds. Most of their research is self-funded and conducted in-house, although they do collaborate with universities and research institutions. Even when compared to other sectors, Japanese pharmaceutical and biotechnology companies spend a large amount on R&D. Ten of the top eleven companies, as measured by the ratio of planned R&D funding to sales in 2006, were in pharmaceuticals or biotechnology. Six of these had a ratio greater than 10 (JST, 2007).

Tax breaks encourage R&D investments by the private sector. In 2003, a major tax reform was implemented that allows up to 20 percent of corporate tax to be deducted for R&D expenditures.

Recently, Japanese drug companies have begun a series of mergers. Japan's largest pharmaceutical company, Takeda Pharmaceutical Company Ltd, has acquired a privately owned UK drug company, Paradigm Therapeutics Ltd (Burrill and Company, 2007). A subsidiary of Eisai Company Ltd has acquired Morphotek, Inc. for $324 million. Early in 2007, Mitsubishi Pharma merged with Tanabe Seiyaku (Burrill and Company, 2007).

Throughout the drug development process, pharmaceutical companies work in cooperation with the PMDA, an IAA associated with MHLW. The PMDA was created in 2005 as part of an effort to make Japan's drug approval process more transparent, efficient, and harmonious with other developed nations.[43] Employees of PMDA, who are not considered civil servants, perform many services related to the development and use of pharmaceuticals in Japan. They oversee the process of drug and device development, approving reviews of products for quality, efficacy, and safety, provide guidance and advice to drug makers about going to clinical trials, ensure compliance with drug development guidelines, and audit manufacturers' facilities and quality control systems (PMDA, 2006). PMDA also collects information to monitor the safety of marketed drugs. PMDA even provides payments to certain patients, particularly sufferers of adverse drug reactions (PMDA, 2006).[44] PMDA's budget for JFY 2004–2008 stands at about ¥64 billion, with a large proportion coming from user fees (PMDA, 2005). In 2005, PMDA's services related to R&D promotion were transferred to the National Institute of Biomedical Innovation (PMDA, 2006).

After PMDA makes its scientific decision on drug and device safety and efficacy, MHLW makes its final regulatory decision on coverage (Uyama, 2005).

[43] ISPE, "February 2007—Japan's Pharmaceutical Affairs Law (PAL): Opportunities and Challenges," http://www.ispe.org/cs/root/regulatory_resources/regulatory_review_article_archives/february_2007_japans_pharmaceutical_affairs_law_pal_opportunities_and_challenges (as of April 14, 2008).

[44] PMDA, "Pharmaceutical and Medical Devices Agency—Objective," http://www.pmda.go.jp/english/about/objective.html (as of April 21, 2008).

## Academic–Industrial Disconnect

- Concern that biomedical innovations at universities are not sufficiently transformed into new products or economic growth
- Government has instituted reforms to combat this concern
- Cooperation between academia and industry is now encouraged

The historical disconnect between basic and applied health and medical sciences in Japan has led to concerns that the fruits of scientific research have not been sufficiently translated into economic strength. To counteract this deficiency, reforms have been made to increase cooperation between universities and industry.

In 1998, the Japanese government passed its version of the Bayh-Dole Act, which spurred innovation in the United States by giving intellectual property rights to publicly funded researchers at universities and in industry. The Japanese act, passed as a chapter of an industrial revitalisation law, allowed researchers at national universities and public research institutes to retain intellectual property rights, and allowed them to sell their innovations and expertise to the private market (Takenaka, 2005).

Private companies can now pay the central government to have National Universities perform research activities, and a system of tax breaks helps them do so. For joint research, the business must pay any direct costs plus ¥420,000 per joint researcher; for commissioned research, the business must pay direct costs plus indirect costs (equal to 30 percent of direct costs). The overall system of joint research activities between universities and private corporations dates back to 1983, but many important reforms to the system have been made since then. Private companies are even given discounted land rent prices to establish joint research facilities on university campuses, and joint research costs are given tax breaks. In JFY 2001, 21.2 percent of these joint research activities were related to life sciences.[45]

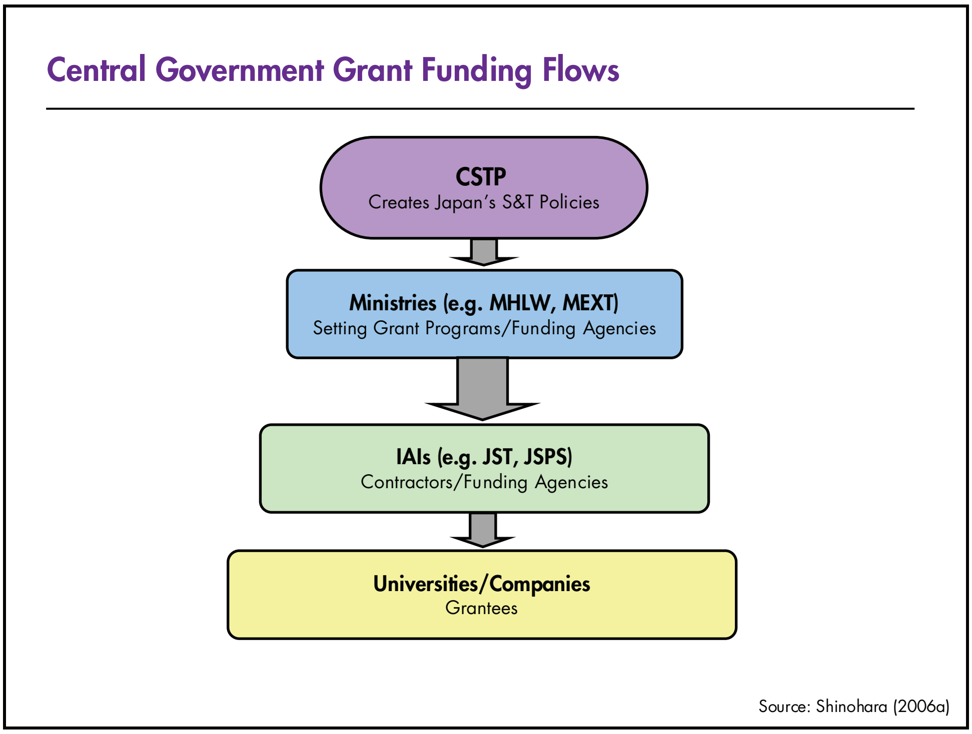
[45] MEXT, "Partnership Between Universities and Industry (2003 Edition)," http://www.mext.go.jp/english/org/science/07d/03061301.htm (as of April 14, 2008).

Besides simply engaging in joint research, university researchers may also be commissioned by a company, in which case the business must pay the central government ¥541,200.[46] Professors can even work concurrently as executives for businesses that use their research findings, and may go on leave to work for these businesses. Professors may also engage in technical consulting for businesses, and the businesses are now allowed to pay the professors "socially acceptable" fees.

Other efforts have also been made to allow companies to use patents held by professors or universities, and to help universities to profit accordingly. In 2004, another reform allowed private companies to own patents they developed even if the research was supported by government funds (Embassy of Canada in Japan, 2006). Since these reforms, entrepreneurial activity by academic researchers has increased.

Government has also attempted to increase cooperation between academia and industry by holding a number of Industry–Academic–Government Collaboration Summits (OECD, 2005, p. 147). By forcing face-to-face contact, these summits are designed to facilitate the development of cooperative networks. METI also encourages universities to set up patent application offices to help facilitate the transfer of technology to industry, and encourages businesses to work with government by permitting them to own the intellectual property that results from a government contract (OECD, 2005, p. 147).

[46] MEXT, "Partnership Between Universities and Industry (2003 Edition),"
http://www.mext.go.jp/english/org/science/07d/03061301.htm (as of April 14, 2007).




A good deal of health and medical R&D funding is given in the form of competitively selected grants, which are advertised annually or more frequently.[47] Many of these grants come from MHLW. In JFY 2008, some of the competitive grants funded by MHLW included the following (Shinohara, 2008):

- basic pharmaceutical research (¥5.20 billion),
- basic research for clinical application (¥4.96 billion),
- risk analyses of food and pharmaceuticals (¥1.75 billion),
- development of medical equipment (¥823 million),
- basic research in health medical areas (¥8.17 billion),
- AIDS, hepatitis, and recurring infectious diseases (¥6.01 billion),
- a comprehensive strategy for cancer (¥6.49 billion),
- cancer research support (¥1.80 billion),
- countermeasures for cardiovascular and habit-oriented diseases (¥6.59 billion),
- mental health science (¥1.86 billion),
- medical infrastructure in local areas (¥840 million), and
- development of nanomedicine equipment (¥1.94 million).

[47] Ministry of Finance, "Understanding the Japanese Budget—2004," http://www.mof.go.jp/english/budget/brief/2004/2004.htm (as of April 14, 2008).

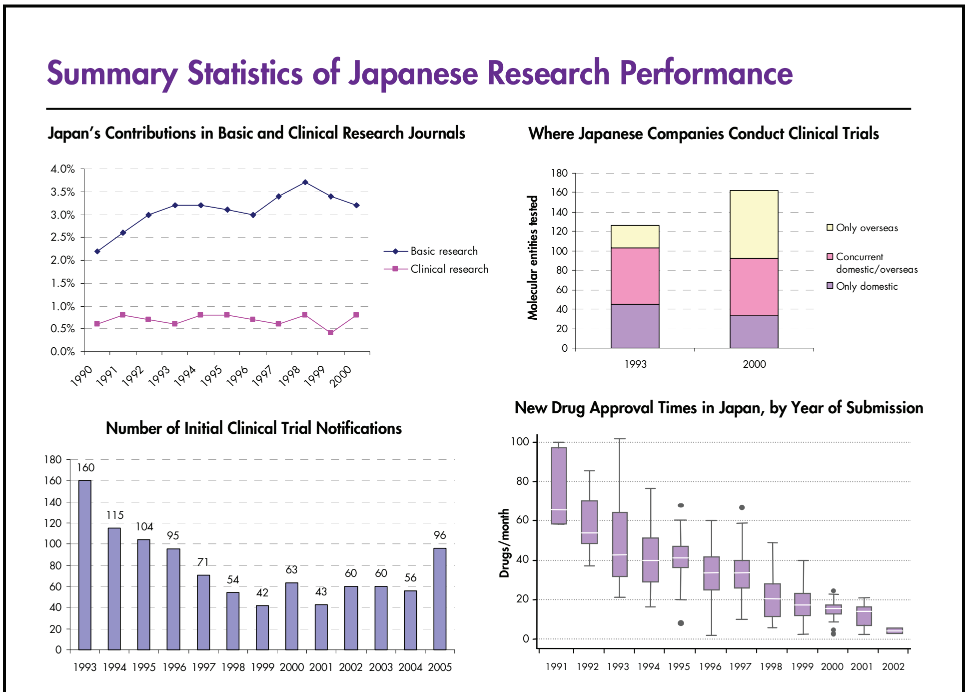
MHLW's grants for clinical studies sum to approximately ¥90 billion (OECD, 2005, p. 144). MEXT also funds many grants in health and medicine, through its competitive Grant-in-Aid for Scientific Research (¥193.2 billion for all scientific fields in JFY 2008) or through JST and JSPS.

Many of the organisations that distribute research grants are the IAIs associated with various ministries of the Japanese central government. Although they are somewhat operationally independent of their respective ministries, their funding still comes from the ministries, and the ministries are still responsible for creating the different grant programmes (Shinohara, 2006a). The ministries themselves also directly administer certain grants without assistance from IAIs.

The Japanese government has created a law mandating that government-funded R&D projects must be evaluated mid-course for validity and effectiveness (OECD, 2005, p. 148). Until the 2000s, grant administrators at the different ministries and agencies managed and reviewed their own grant programmes. However, since 2001, the CSTP has encouraged the uptake of a Program Officer System by funding agencies, whereby the Program Officers take control of selection of reviewers. JST supports the programme by holding Program Officers seminars for funding agencies. Japan's 3rd Science and Technology Basic Plan, which is currently in effect, has called for Program Officer Systems and improvements of existing ones, to achieve needed improvements in the competitive funding system. As of 2006, there were 400 Program Officers at funding agencies in Japan, mostly working part time (Shinohara, 2006a).

The Japanese government has placed an emphasis on developing regional research centres and hubs, where universities, businesses, and government come together around a certain topical area.[48] The 21st Century Centers of Excellence (COE) Program aimed to "cultivate a competitive academic environment among Japanese universities by giving targeted support to the creation of world-standard research and education bases," whereas the new Global COE Program "will continue the basic concept of the 21st Century COE Program with more focus on personnel fostering in an international context" (Shinohara, 2007a).

[48] Ministry of Finance, "Understanding the Japanese Budget—2004," http://www.mof.go.jp/english/budget/brief/2004/2004.htm (as of April 14, 2008).



Source: Fukui and Rahman (2002); Sato (2006); Takeuchi (2005); Hirota (2004); Miyajima (2006); Uden (2002); Office of Pharmaceutical Industry Research (2003)

The *World Competitiveness Yearbook of 2000* makes note of Japan's scientific prowess: Japan was first in the number of patent registrations, second in the number of patent acquirements overseas and in the number of people engaged in R&D, and third in private R&D spending per person and total R&D spending per person (International Institute for Management Development, 2000; OECD, 2005, p. 149).

Unfortunately, Japan has lagged behind other advanced nations in its contributions to health and medical research. Although Japan's overall strength in science and technology is impressive, life science has been one of the country's weaker fields of research (OECD, 2005). Japan has had only one Nobel price winner in biomedical science, Susumu Tonegawa, who attributes his success to leaving Japan (Imamura, 1993). One group of researchers found that among 20 developed nations, Japan had one of the lowest medical publication rates per capita (a fact that authors blame on a low level of English language ability).[49]

Although Japan's contribution to basic research journals places it fourth in the world ranking, its 14th place ranking in clinical research is less impressive (OECD, 2005). Japan trails other developed nations in conducting high quality clinical trials, especially randomised controlled trials (Rahman, Sekimoto, et al., 2001). Japan has a relatively strong tradition in immunology dating back to Shibasaburo Kitasato, yet this has not translated into enough clinical innovations and new forms of therapy (Riendl, 2004). High quality clinical trials, evidence, and research articles from Japan are lacking (Fukui, 2005;

[49] University of Alberta, Research Services Office, "English-speaking Researchers Dominate Top Medical Journals," Dec 15, 2004, http://www.rso.ualberta.ca/news.cfm?story=32492 (as of April 14, 2008).

Hirota, 2004; Hayashino, Rahman, and Fukui, 2003). As measured by the number of articles published in leading paediatric journals, Japan's contribution to clinical paediatrics research is smaller than other types of clinical research in Japan (Okamoto, Rahman, and Fukui, 2004).

Links between science and industry are low, as discussed earlier (OECD, 2005, p. 137). Japanese pharmaceutical companies face a declining market share at home and around the world, and they face particular hurdles (discussed below) to the conducting of domestic research. In recent years, Japan has had to depend mainly on imported drugs and medical devices (Imura, 2006).

Clinical trial costs, which are very high in Japan (Takeuchi, 2005), have been growing, and the number of clinical trials has been on a downward slope (Miyajima, 2006). Consequently, there is talk of a "drug lag", describing the delayed approval of drugs in Japan (Ebihara, 2007). Meanwhile, the speed of drug approval has been decreasing. It has been said that the high cost and slow speed of clinical trials, coupled with the fact that so many Japanese companies now conduct their clinical trials outside the country, has led to a "hollowing out" of clinical trials in Japan (Hirota, 2004; Takeuchi, 2005).

Much of the problem stems from insufficient capacity for clinical research, in terms of well-trained researchers and evidence reviewers, facilities, and funds (Lagakos, 2006). In addition, it is felt that drug approval should be streamlined so that that the review process can become faster and less costly.

Inadequate human resources are frequently mentioned as a hindrance on Japanese health and medical research. According to the Dean and Professor of Internal Medicine at Keio University School of Medicine, the development of human resources is urgently needed if Japan is to be able to conduct world-class clinical studies (Ikeda, 2006). Stephen Lagakos of the Harvard School of Public Health (Cambridge, MA, United States) believes that to build Japanese research capacity, more well-trained clinical researchers are needed in academia, industry, and government (Lagakos, 2006). He also mentions a lack of sufficient drug reviewers (Lagakos, 2006). Japan's PMDA has only about 10 percent as many drug reviewers as the U.S. Food and Drug Administration (295 compared to 2,395 in 2005) (Asaka, 2006; Uyama, 2005). Japanese physicians are also very busy, and with their high workload and few support staff, they usually do not have a great deal of time to conduct high quality clinical research on the side (Yanagawa et al., 2006; Low, 2001). This problem is compounded by the nature of the Japanese health insurance system, which makes no distinction between physicians and physician-scientists (both have the same clinical workload) (Imamura, 1993). Some have commented that a higher physician-to-patient ratio is a prerequisite to building up Japan's research abilities (Ebihara, 2007). In addition, the current system lacks incentives for researchers (and patients) to engage and participate in research (Hirota, 2004).

With regard to human resources, quality is as much of a concern as quantity. Training and education must be improved to create qualified specialists for high-quality clinical trials and regulatory reviews (Takahashi, 2005; Fukui and Rahman, 2002). Particular areas of training weaknesses in the Japanese system include clinical epidemiology (Fukui, 2005) and research methods (Rahman, Saito, and Fukui, 2005; Hayashino, Rahman, and Fukui, 2003). Weak, unsophisticated study designs such as case studies are common (Imamura, 1993; Fukui 2005; Rahman, Saito, and Fukui, 2005; Fukui, Rahman, Sekimoto, et al., 2002). There seems to be a reluctance to perform randomised controlled trials, which may partly be caused by ethical concerns on the part of physicians (Imamura, 1993).

A poor clinical trial infrastructure (Hirota, 2004; Rahman, Saito, and Fukui, 2005) and a lack of good sites and facilities is another factor holding back the Japanese system. It has been suggested that separate facilities for clinical trials might give clinical researchers time away from patients to conduct clinical research (Fukui and Rahman, 2002). Specifically, the creation of clinical research divisions in academic hospitals (complete with biostatisticians and clinical epidemiologists) (Hayashino, Rahman, and Fukui, 2003) and outpatient clinics exclusively for clinical trials (Yanagawa et al., 2006) are mentioned as solutions to Japan's lacklustre performance.

Of course, more money would help the Japanese system, and calls have been made for greater grant funding of patient-oriented and clinical research (Fukui and Rahman, 2002; Hayashino, Rahman, and Fukui, 2003; Rahman, Saito, and Fukui, 2005). Government R&D budgets in health are low in Japan when compared to the OECD average, representing just 0.03 percent of GDP in 2004, compared to 0.2 percent in the United States and over 0.1 percent in the United Kingdom (OECD, 2003b, p. 126).

Cultural factors have also shared part of the blame for Japan's limited contribution to medical research, such as a lack of sufficient English language skills among Japanese scientists, and preferences for conformity that inhibit risk taking and competition (Tokumasu, 2006; Rahman, Saito, and Fukui, 2005). There is a general unwillingness of patients to take part in clinical trials (Yanagawa et al., 2006). Suggested reasons for this phenomenon include a lack of trust of physicians (Imamura, 1993), and negative views of clinical trials stemming from use of placebos, double blinds, and randomisation (Asai et al., 2004). Also, open debate is rare in Japanese society, and physicians are reluctant to send critical comments about journal articles.

Other factors that have been blamed for inhibiting innovation in the medical field include poor public management, drug price controls (Tokumasu, 2006), and insufficient collaboration with foreign researchers.

# Outlook

## Outlook

- Ageing society will put new pressures on the research system, but also new incentives
- "Agencification" will increase competitive stance of universities and research institutes, but process needs to be monitored to ensure success
- Competitive grant funding expected to increase as formula-based automatic funding decreases
- Cooperation between business and academia expected to increase
- Growing emphasis on translational research
- Difficulties for pharmaceutical industry will continue in near future
- Development clusters are becoming popular
- Government has shown commitment to spending growth in health and medical research
- Difficulties may continue until resources and capacity increase
- Recently, some encouraging signs of success

Although Japan's global contributions to health, medical, and pharmaceutical research have been underwhelming, there are some reasons for cautious optimism about the future.

One of the biggest challenges Japan faces is its rapidly ageing society. As this process continues to unfold, the physician shortage it faces will be exacerbated. New pressures will be placed on physicians to spend time with patients—and less time conducting clinical research (Ebihara, 2007). However, societal ageing may create the additional political will needed to invest in the research system. Calls for increased clinical research capacity may yield funding increases, but this is by no means certain, given Japan's budgetary constraints and deficit concerns. As for the private sector, inasmuch as demand pulls innovation, the ageing of Japanese society will encourage greater investments in research (OECD, 2005).

Another looming problem that concerns some observers is that young Japanese people are disinterested in science generally. Long-term declines have been witnessed in the number of students enrolling in science and engineering programmes, and in the number expressing interest in scientific research (OECD, 2003a). One survey placed Japan 39th out of 55 countries ranked by the percentage of young people interested in science and technology (International Institute for Management Development, 2000). If Japan is to gain ground in health and medical research, it will need to encourage its youth to join the effort. Fortunately, MEXT is expanding competitive funding opportunities for young researchers (OECD, 2003a), helping to ensure a sufficient pool of researchers in the future.

The agencification of universities is expected to increase their sensitivity to the needs of industry and the nation, while making them more adaptive and competitive (OECD, 2005, p. 143). Professors are now able to more easily switch between private sector and academic activities, and cooperation between the two sectors is expected to increase. In 2004, MEXT began cutting operational funds to universities at a rate of about 1 percent per year. These cuts are set to continue through 2011, making universities more dependent on government and outside grants, and hopefully, more competitive as institutions (Shinohara, 2007b). There is also talk about moving from a system of formula-based operational funding to performance-based funding (as measured by the quality of research and education), which would add further to the developing culture of competition. So far, the rise in competitive funding has helped offset the decline in automatic funding. In an encouraging sign, universities have also started looking towards industry for funds and cooperative opportunities, and in the current environment one can expect collaborative research efforts between academia and industry to increase.

However, agencification of universities and research institutes may prove to have its drawbacks. Principle-agent theory from economics suggests that the new agencies may have different incentives from central government, and monitoring their performance may prove to be difficult and costly (OECD, 2005, p. 165). These concerns speak to the need for well-designed contracts between ministries and independent agencies.

The continued globalisation of clinical research will also impact the Japanese system (Shinohara, 2007b). The practice of Japanese drug manufacturers conducting trials abroad will likely continue until the domestic review process substantially improves; for the time being, most pharmaceutical companies expect Japanese drug trials to increase their trend towards internationalisation (Sekine, 2006). Globalisation may encourage further consolidation among Japanese pharmaceutical companies, as they work to amass the resources needed to compete against large foreign businesses. Nevertheless, Japan's share of the pharmaceutical market may continue to shrink in the near future. On the bright side, the future holds potential for global collaboration on drug review, saving both time and money for Japan and other nations (Uyama, 2005).

Japan has recognised that this is an area of weakness in their research portfolio, and is working to improve the situation. Successes such as the Northern Osaka Bio Cluster and the Kobe MID Project may lead to increased use of industrial cluster programmes (OECD, 2005, pp. 151, 159). Despite Japan's concern about its large public debt and its aggressive attitude towards budgetary discipline, spending for health and medical research continues to increase. This underscores the importance of the area to government planners, and is an encouraging sign for Japan's future research success. Not only have grant moneys increased for research institutes and universities, but the number of PMDA reviewers has been increasing and is likely to increase further (Asaka, 2006).

Government investments to develop researchers with English language capabilities may pay off in the form of a larger Japanese presence in top medical journals. An increase in funds for translational research is expected to continue, in order to parlay Japan's relative strength in basic research into innovative new treatments.

There are encouraging signs on the horizon. Recently, use of randomised controlled trials, case-control studies, and sophisticated statistical methods has been on an upward trend

(Hayashino, Rahman, and Fukui, 2003). The rising cost of clinical trials has finally levelled off. The number of clinical trial notifications also seems to be rebounding, having declined through the 1990s.

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