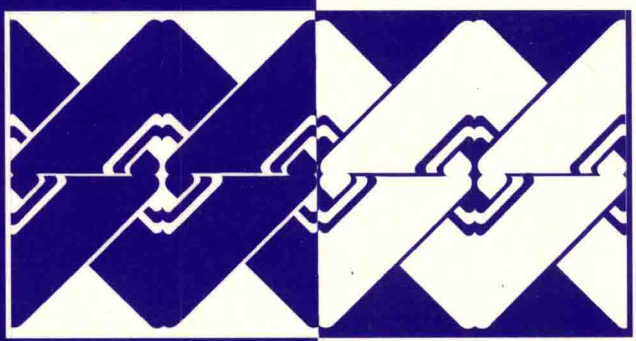
U.S.–Japan Technology Linkages in Biotechnology



Challenges for the 1990s

NATIONAL RESEARCH COUNCIL

U.S.-Japan Technology Linkages In Biotechnology: Challenges for the 1990s

Committee on Japan
Office of Japan Affairs

Office of International Affairs
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Since 1985 the National Academy of Sciences and the National Academy of Engineering have engaged in a series of high-level discussions on advanced technology and the international environment with a counterpart group of Japanese scientists, engineers, and industrialists. One outcome of these discussions was a deepened understanding of the importance of promoting a more balanced two-way flow of people and information between the research and development systems in the two countries. Another result was a broader recognition of the need to address the science and technology policy issues increasingly central to a changing U.S.-Japan relationship. In 1987 the National Research Council, the operating arm of both the National Academy of Sciences and the National Academy of Engineering, authorized first-year funding for a new Office of Japan Affairs (OJA). This newest program element of the Office of International Affairs was formally established in the spring of 1988.

The primary objectives of OJA are to provide a resource to the Academy complex and the broader U.S. science and engineering communities for information on Japanese science and technology, to promote better working relationships between the technical communities in the two countries by developing a process of deepened dialogue on issues of mutual concern, and to address policy issues surrounding a changing U.S.-Japan science and technology relationship.

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Introduction

The prevailing view is that the United States is a world leader in biotechnology.[1] U.S. researchers excel in basic science, and U.S. industry has moved new ideas to the market by commercializing technology. In fiscal year 1990 alone, the federal government provided more than $3.5 billion in funding for biotechnology R&D and U.S. industry invested approximately $2 billion.[2] Approximately 50 to 75 biotechnology companies were formed

[1]See, for example, Office of Technology Assessment (OTA), *Biotechnology in a Global Economy* (Washington, D.C.: U.S. Government Printing Office, October 1991), p. 19, and *New Developments in Biotechnology* (Washington, D.C.: U.S. Government Printing Office, 1988), p. 3. In the OTA report, biotechnology is broadly defined to include any technique that uses living organisms (or parts of organisms) to make or modify products, to improve plants or animals, or to develop microorganisms for specific use. For general statements on the state of the U.S. biotechnology industry, see also Japanese Technology Evaluation Center (JTEC), "JTEC Panel Report on Biotechnology," June 1985; Ministry of International Trade and Industry (MITI), *Sangyo Gijutsu no Doko to Kadai* (Trends and Topics in Industrial Technology) (Tokyo: Tsushosangyosho, 1988); George B. Rathmann, "An Industry View of the Public Policy Issues in the Development of Biotechnology," in John R. Fowler III, ed., *Application of Biotechnology: Environmental and Policy Issues* (Boulder: Westview Press, 1987). See also Mark D. Dibner and R. Steven White, "Biotechnology in the United States and Japan: Who's First?" *Biopharm*, March 1989.

[2]The President's Council on Competitiveness, "Report on National Biotechnology Policy," p. 6. G. Steven Burrill and Kenneth B. Lee, Jr. estimate that in 1991, the federal government invested $3.7 billion and industry $3.2 billion in biotechnology-related R&D. See G. Steven Burrill and Kenneth B. Lee, Jr., *Biotech 92: Promise to Reality* (San Francisco, Ca.: Ernst & Young, 1991).

each year during the decade of the 1980s, over 1,000 in the last 20 years. The biotechnology and pharmaceutical industries have been rated as second only to the computer software and services sector in terms of total value creation among U.S. high-technology companies founded since 1965.[3]

Is this rosy view of U.S. preeminence—across the board from basic to applied biotechnology R&D, to commercialization and global market competitiveness—accurate and will it persist?[4] Another, perhaps better, way to pose the question is to ask whether the United States will remain competitive and reap a "fair share" of future profits from the significant investments made in biotechnology. These broad questions set the context for this report, which assesses technology linkages between the United States and Japan. The purpose of this study is not only to examine the scope and nature of technology linkages between the United States and Japan but also to consider the forces behind these linkages as well as the future impact on competitiveness for the organizations involved and for the United States as a country.

To summarize some of the major themes, the study suggests that there are a number of powerful forces driving an expansion of technological linkages of many types between the United States and Japan. We are moving toward a global economy, and the desires of large Japanese companies, both pharmaceutical companies and ones doing business in unrelated fields, to access technology developed in the United States and to compete globally are important contributing factors. Japanese firms see biotechnology as a way to use scarce resources to improve their productivity and international competitiveness. For nonpharmaceutical companies, biotechnology is a technological tool allowing diversification into new, higher value-added product areas. From the U.S. perspective, a driving force for small innovative biotechnology firms is the need for capital to fuel their R&D, thus stimulating relationships of various kinds with large capital-rich Japanese companies. Another stimulus is the desire of large U.S. pharmaceutical companies and biotechnology firms to access the Japanese market.

Increased cooperation between the United States and Japan is desirable and inevitable as biotechnology becomes part of an increasingly global economy and technology base. In this context of increasing cooperation, the question is whether the U.S. biotechnology industry will continue to compete effectively. To do so, it will be necessary to structure technology linkages with Japan to ensure that U.S. participants gain clear benefits.

This study documents a prevailing pattern of transfer of biotechnology developed in the United States to Japan during the past two decades. The analysis in this report suggests that the linkages formed so far serve as

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[3]See Arthur D. Little and HOLT Value Associates, "The Upside 100," *Upside*, December 1990, p. 25. Value creation was measured in a number of ways, including shareholder value, for each firm since its establishment.

[4]For a more sober view, see President's Council on Competitiveness, op. cit.

mechanisms primarily for technology transfer from the United States to Japan. Looking at past patterns, some wonder whether the technology has been sold too cheaply and whether U.S. firms can develop effective strategies for making technology linkages with Japan work to their advantage in the future.

There are new trends, such as the establishment of Japanese "offshore" R&D facilities in the United States and growing investments by Japan in basic research, that hold a potential for learning from Japan. Increasingly, Japanese companies are building ties to American universities through training, research grants, and endowed chairs. Japan's strength in areas such as bioprocessing technologies suggests potential areas for future technology transfer from Japan to U.S. biotechnology firms.

From the perspective of individual U.S. biotechnology firms or larger companies, it may be possible or even necessary to ensure corporate growth (and possibly survival) by linking up with Japanese companies in joint ventures or other agreements that give the Japanese partners rights to license and market technologies and products that were developed in the United States. Over time, however, the result may be to create a significant competitive challenge in both the U.S. market and global competition unless these alliances are developed such that the U.S. firms benefit through the development of improved manufacturing and marketing capabilities.

The implications for the United States as a country must also be considered. Researchers from around the world are drawn to the open and excellent biotechnology research laboratories of U.S. universities and research institutions—organizations financed with taxpayer funds. Being first in basic science, however, in no way ensures that U.S. companies will compete effectively at home and around the world. Japan, a country where the primary emphasis has been on technology commercialization, benefits greatly from access to fundamental research carried out in the United States. Given the considerable investments that the United States has made in supporting biotechnology R&D, it may be appropriate to consider new policy approaches that ensure that the United States maintains its lead in global competition. Government and industry in Japan have identified biotechnology as a key technology for future industrial growth and are working together to increase R&D investments in this field.[5] Should we do likewise?

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[5]Estimates of expenditures by the government of Japan for biotechnology-related R&D vary, for reasons that will be outlined in detail later. According to research by the NRC working group, in 1991 expenditures increased approximately 16 percent over the previous year to a total of 89.6 billion yen. According to estimates by the U.S. Department of State (unclassified cable of July 1990), Japanese public and private spending on rDNA totaled 57 billion yen, and total R&D on biotechnology-related work for all Japan Bioindustry Association (JBA) members totaled 276 billion yen. See *Heisei Yonnendo Kaku Shocho Baiteku Kanren Yosan Seifu Genan* (Japan Fiscal Year 1992 Biotech-Related Budged Proposal), in *Biosaiensu to Indasutori* (Bioscience and Industry), March 1992, pp. 277-285. See Table 2 for more detail.

This report was prepared by a working group of experts, as part of a project initiated by the National Research Council's Committee on Japan to examine technology linkages between Japan and the United States. Co-chaired by Hubert Schoemaker of Centocor and G. Steven Burrill of Ernst & Young, the working group was formed in the fall of 1990 and met a number of times in 1991 to deliberate and confer on the data collection process. A workshop on U.S.-Japan Technology Linkages in Biotechnology was convened in June 1991 to gain additional insights from other experts in the United States and Japan. The staff of the National Research Council's Office of Japan Affairs, which also serves as the staff for the Committee on Japan, assisted the working group in data collection, and analysis and compilation of results.

2

Technology Linkages—Definitions and Approaches to Analysis

Biotechnology is a research- and capital-intensive industry for which intellectual property rights protection and government regulation are critically important. The industry is growing rapidly, both domestically and internationally, and the context is rapidly changing.[6] Linkages between U.S. and foreign-based biotechnology companies also are expanding, but there is no consensus about the long-term impacts. Will Chugai's acquisition of a majority interest in Gen-Probe or Roche's acquisition of Genentech lead to the creation of potent competing firms, or will these linkages bring new strength to U.S. industry and the U.S. economy? Will Hitachi's investment in an R&D laboratory on a University of California campus bring benefits to both sides? Put another way, will biotechnology go the way of the semiconductor industry to face severe competition from Japanese companies that focus their efforts on commercialization of technology that originated here?

This report was compiled to assess the nature, scope, and impacts of technology linkages between the United States and Japan in biotechnology and to outline policy issues for government, industry, and universities. The major focus is on commercial biotechnology—the use of biotechnological tools to develop and manufacture products for the market. The line be-

[6]See, for reference, Burrill and Lee, *Biotech '92*, op. cit.; G. Steven Burrill and Kenneth B. Lee, Jr., *Biotech 91: A Changing Environment* (San Francisco, Ca.: Ernst & Young, 1990); and Biotechnology Information Division, North Carolina Biotechnology Center, *Biotechnology in the U.S. Pharmaceutical Industry* (Research Triangle Park, N.C.: NCBC, 1990).

tween basic research and commercial biotechnology is not hard and fast, however. Companies focusing their efforts on the commercialization of biotechnology are research intensive, carefully watching the work going on in basic research laboratories because new developments in science can become the basis for new products seemingly overnight. But bringing these products to market can take a number of years, particularly in the health care field. Erythropoietin (EPO), for example, generated $200 million in revenues for Amgen in its first full year of sales in 1990. Amgen carried out research to bring this product to the clinical trial stage for approximately 3 years, and it took another 3 years to complete clinical trials and obtain regulatory approval before going to market.[7] Because of the importance of fundamental research to firms seeking to commercialize biotechnology, the working group decided to include in its analysis linkages formed between Japanese firms and research laboratories at U.S. universities, national laboratories, and biotechnology centers that are likely to have an impact on market competition.

Biotechnology is a diverse activity comprised of many scientific disciplines. Indeed, some prefer not to call it an industry because developments in biotechnology research span many fields of science and affect a wide range of industries (see Figure 1). For the purposes of this report, the working group has defined biotechnology as any activity, product, or process that involves recombinant DNA and/or cell fusion technology. These technologies are currently applied to develop products for human health care, specialty chemicals and biosensors, and human and agricultural applications and to improve the generation of energy and protection of the environment. More than 100 large chemical, pharmaceutical, and agricultural companies use biological processes. Large pharmaceutical and agricultural firms are using biotechnological techniques to complement their established in-house research efforts. These large companies should be distinguished from the dedicated biotechnology firms (many of them small firms formed by some of our nation's premier researchers and entrepreneurs) that focus almost exclusively on the use of biotechnology to develop new products through biological processes. In terms of market segments, health care (including human diagnostics, vaccines, and therapeutics) is by far the largest.[8]

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[7]See Gary P. Pisano, "Joint Ventures and Collaboration in the Biotechnology Industry," David C. Mowery, ed., *International Collaborative Ventures in U.S. Manufacturing* (Washington, D.C.: American Enterprise Institute, 1988), p. 199 for an estimate that the development of a pharmaceutical product takes 5 to 10 years from the initiation of basic research to marketing of the product.

[8]There are more than 1,000 biotechnology companies in the United States, about 76 percent of them small companies with 1 to 50 employees. (See Burrill and Lee, *Biotech 91*, op. cit., pp. 15-16.) The *Biotechnology in Japan Yearbook 1990/91* states that there are more than 800 Japanese companies involved in biotechnology commercialization and estimates the 1990

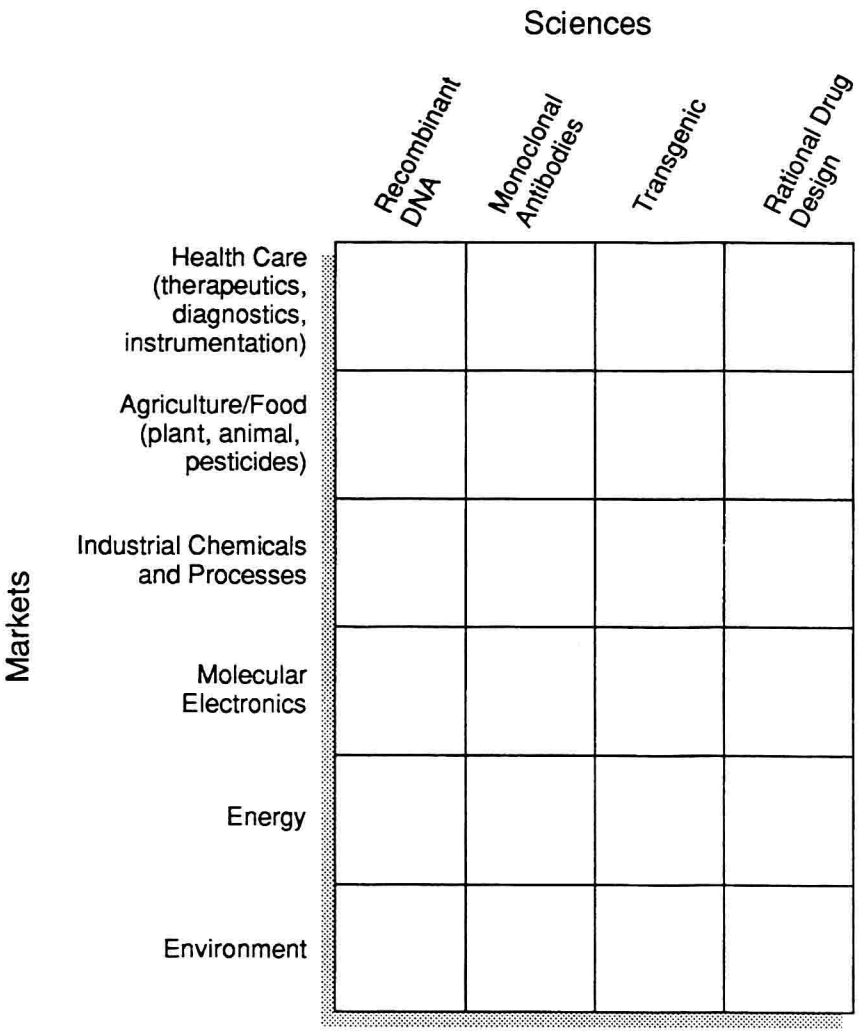

FIGURE 1 Matrix definition of biotechnology.

market in Japan for biotechnology-related products as more than 100 billion yen. Note that the Japanese count includes companies that are involved in biotechnology in some way; a large number of these companies have their primary business in some other area. See Mark D. Dibner and R.S. White, *Biotechnology Guide USA* (London: MacMillan, 1991), for a list of 742 biotechnology firms and 142 corporations involved in biotechnology in the United States.

Defining the term "technology linkages" is equally complex. Linkages include company-to-company activities such as marketing, sales, distribution and/or manufacturing, inward and outward licensing of technology, and various types of equity investments and R&D collaborations. As will be discussed in more detail in the following section, technology linkages between companies are the most prominent and most studied types—both domestically and internationally—but the degree of actual technology transfer involved varies greatly and must be evaluated on a case-by-case basis.

Other types of linkages relevant to a study of commercial biotechnology include relationships between companies and universities, national research laboratories, and biotechnology centers. In many instances these research laboratories are supported in part by taxpayer dollars. Companies establish ties with these organizations not only by endowing chairs and providing grants for facilities and research programs, but also by establishing links with individual professors through contract research and other mechanisms such as laboratory visits and training of employees. Conferences and specialized journals also offer mechanisms for learning about new developments in biotechnology R&D, as do patent registrations, cell line deposits, and related documents.

While the primary focus of attention has been on company-to-company linkages in biotechnology, consider the following hypothetical case as an example of how universities can be important mechanisms. A researcher from a U.S. university is invited to give a research seminar at another U.S. institution, unaware that the biotechnology program at the host institution is generously funded by a company based in Japan. Details from the presentation are quickly faxed to the firm's Tokyo headquarters, where they are used as the basis for filing patent applications by the Japanese company. In Japan, where the principle for patent rights is first to file rather than first to invent, the Japanese company stands a good chance of securing patent rights. Consider another example that illustrates the importance of scientific publication in one country to research around the globe. A young Japanese researcher, Masashi Yanagisawa, read about the work of Highsmith and his colleagues on cell membrane receptors for a family of peptides called endothelins. The young researcher persuaded his professor that this was a worthy topic for a Ph.D. dissertation, and a group of researchers at Tsukuba University began work that led to a breakthrough published in *Nature* in March 1988. Two independent groups in Japan continue path-breaking work in this area, while Japanese pharmaceutical companies race to find potential therapeutic agents.[9]

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[9]See John Vane, "Endothelins Come Home to Roost," *Nature*, vol. 348, December 20-27, 1990, p. 673.

Linkages provide opportunities not only for a transfer of technology and products but also for access to capital, market, and distribution channels; improved manufacturing capability; regulatory expertise; and research strengths. The creation or transfer of technology, whether consciously intended or an indirect result, is a prerequisite for a "technology linkage." One can study technology linkages by combing the trade press and other specialized publications for reports of specific interactions or deals between individual companies. This will provide a representative but not a complete accounting of either relationships among companies or the biotechnology-related in-house efforts of large pharmaceutical and other companies.[10] In many cases linkages between U.S. and Japanese organizations are complex and encompass a variety of mechanisms that evolve over time.

It is also important to underscore the ambiguity that arises in defining a "U.S." or a "foreign" firm. For years the standard approach has been to use equity ownership as the criterion for making the distinction. In practice, U.S. policy has been "national treatment" for foreign investors in the United States and the reduction of foreign barriers to investment overseas. Foreign investment has played a critical role in U.S. economic development, and U.S. multinational companies have grown through investments overseas, particularly in Europe where restrictions have been less extensive than those of Japan before the 1980s.

For the purposes of this study, the critical elements in distinguishing between foreign and domestic firms are the location of a firm's headquarters (or where most of its employees are working) and majority ownership by citizens of a country. This definition is practical but not entirely satisfactory from an analytical perspective. About one-fourth of U.S. biotechnology firms are publicly owned, but companies based in Japan and other countries are often privately owned, and the details of ownership and control are less accessible. Nor should U.S. ownership be equated with U.S. interests.[11] A "foreign" firm that operates manufacturing and R&D facilities in the United States may, under certain conditions, contribute more significantly to the U.S. economic and technology base than a "U.S." firm that moves its manufacturing and R&D overseas. Realities such as these complicate analysis of technology linkages and must be kept in mind.

To assess technology linkages between the United States and Japan in biotechnology, the working group developed a multidimensional matrix (see Figure 2). Linkage mechanisms, organizations involved, and industries make

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[10]Readers should note that the focus of this report is on the linkages *among* firms rather than the internal biotechnology-related efforts of larger firms. Readers interested in the internal activities of larger firms can consult other studies, such as OTA, *Biotechnology in a Global Economy*, op. cit.

[11]Robert Reich, "Who is Us?" *Harvard Business Review*, January-February, 1990, pp. 53-64.