Autarkic Drug Discovery in Japanese Pharmaceutical Companies: Insights into National Differences in Industrial Innovation

Robert Kneller
Professor, Research Center for Advanced Science and Technology (RCAST),
University of Tokyo [1]

Abstract: Structured interviews with eight leading Japanese pharmaceutical companies and industry data show that drug discovery in the Japanese companies occurs predominantly in-house. In contrast, European and US pharmaceutical companies rely more on alliances with university based start-ups and other biotechnology companies for drug discovery. Personnel policies in the Japanese companies are still geared to on-the-job training for lifetime employment and the accumulation of company-specific tacit knowledge. Despite government policies that discouraged innovative drug development, Japanese companies are discovering innovative drugs at rates comparable to those of overseas rivals of comparable size. However, in view of the explosion of new biomedical knowledge, autarkic innovation may no longer be compatible with global competitiveness. Autarkic innovation may be a characteristic of most Japanese technology-based manufacturers. Thus, the competitive advantage of Japanese companies may be greatest in industries where innovation does not rely upon inputs from universities and independent companies.

Key words: alliances, collaboration, culture, drug development, Japan, licensing, pharmaceuticals, research management, start-ups

[1] Correspondence to: Robert Kneller, 4-6-1 Meguro-ku, Komaba, Tokyo 153-8904, Japan. Tel: 81-3-5452-5271. Fax: 81-3-5452-5376. Email: kneller@ip.rcast.u-tokyo.ac.jp.

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Biosketch: Robert Kneller (J.D. Harvard Law School 1980, M.D. Mayo Medical School 1984, M.P.H. Johns Hopkins 1986) worked in cancer research and technology transfer for nine years at the U.S. National Institutes of Health (NIH) before becoming in 1998 Professor in the Department of Intellectual Property of the University of Tokyo's Research Center for Advanced Science and Technology. His research compares university-industry cooperation in Japan, the US and other countries—particularly with respect to biomedical technologies, the ownership and transfer of intellectual property rights, and the role of start-up companies.

1.0 Introduction

1.1 Framing of research question

This paper begins with the simple question, "Where do Japanese pharmaceutical companies obtain the key ideas and technologies that lead to the discovery of new drugs?"[1] However, the likely answer, that they tend to rely more on in house research than their European and US counterparts, raises intriguing questions about early stage innovation[2] within the companies, as well as differences between the systems early stage innovation in Japan, the US and European countries.

European and US pharmaceutical companies rely upon universities and biotechnology companies, many of which are university start-ups,[3] to provide them

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[1] "Drug discovery" henceforth refers to: "lead or target identification," "lead or target validation" and "lead optimization." (Here "lead" refers to the actual prototype drug itself, and "target" refers to the initial binding target of a drug, often a cell surface or nuclear membrane receptor.) In other words, drug discovery" refers to the drug development process up to the point of proof of concept, but not including testing aimed primarily at confirming safety and efficacy. In particular, it does not include clinical testing in humans. Regulatory authorities such as the US Food and Drug Administration (FDA) and the Japanese Ministry of Health, Labor and Welfare (MHLW) mandate tests in laboratory animals and then humans to confirm safety and efficacy. Although clues how to improve drugs can arise at any stage of the development process, most innovative research occurs during the early stages, while later development stages (particularly later stage clinical trials) are intended to be confirmatory. Since the topic of this paper is early stage innovation, it focuses on drug discovery and the early stages of the development process.

[2] Henceforth the terms "early stage innovation" and "early innovation" refer to the discovery of new products and processes, and their early stage refinement. It includes many types of applied research as well as basic research aimed at facilitating such discovery or the assimilation of outside discoveries.

[3] Henceforth, the term "biotechnology company" is used in a broad sense to include not only a company involved in the manufacture of therapeutic, naturally occurring proteins by recombinant genetic engineering (the narrow definition of biotechnology), but also to other biomedical companies aiming either at discovery of new drugs or at new technologies to assist drug discovery, and which are typically new (less than 20 years old) and were originally formed to develop or exploit a particular science-based technology. Often such technologies originate in universities or are discovered by scientists who have recently left an academic laboratory. Such biotechnology companies are henceforth referred to as bio-startups. Pharmaceutical companies are distinguished from biotechnology companies by having been in existence longer, being focused on drug commercialization (including clinical trials and often marketing) as well as drug discovery, traditionally being focused on developing small molecule drugs (rather than the larger naturally occurring proteins that have been the typical focus of biotechnology companies), and traditionally placing more emphasis on screening large libraries of compounds to discover drug candidates rather than on the exploitation of new technologies to discover new drugs. For descriptions of how the distinction between pharmaceutical and biotechnology companies has begun to blur, see Galambos and Sturchio (1998) and van Brunt (2002). The analysis of this article depends not upon an increasingly

with new drug candidates and drug discovery technologies.

Several lines of evidence support this assertion. One is Cockburn and Henderson's 1997 study of the development history of the 21 drugs launched between 1965 and 1992 that had the "highest therapeutic impact" worldwide. They found that the key enabling discovery for all but 5 of these 21 drugs came from publicly funded research, mainly in European and US universities. The likelihood that the key enabling discovery originated in a public laboratory was even greater in the case of the drugs discovered by "modern" methods that required in depth understanding of biological processes (rational drug design) or screens targeted at specific biological functions, as opposed to drugs discovered by random screening methods. Of course, simply because the key enabling discovery occurred in a university does not mean that the pharmaceutical company did not contribute a significant amount of innovative research in its own laboratories. Nevertheless, the Cockburn-Henderson study shows that universities, and by extension start-ups that develop university inventions, are important in the pharmaceutical innovation process, as is interchange between university and company scientists.

As universities have become more entrepreneurial and the number of bio-startups has grown, it is likely that pharmaceutical companies will in-license more developed drug candidates and drug discovery technologies from start-ups formed to develop university discoveries. In the past, pharmaceutical companies may have had no option other than to absorb such discoveries directly via academic publications, consultations, hiring of university researchers or formal licenses.

A second line of evidence is that medicines sponsored or owned by biotechnology companies constitute the majority of drugs in clinical trials to support a marketing application to the US Food and Drug Administration (FDA) - at least in the fields of cancer, heart and circulatory diseases and infectious diseases. In contrast, drugs sponsored or owned by major pharmaceutical companies account for a distinct minority of new drugs in each of these therapeutic areas (see Table 1).

[insert Table 1 approximately here]

Indeed, the contribution of biotechnology companies may be even higher, because drugs that may have been discovered by biotechnology companies but then sold at an early stage to major pharmaceutical companies often would be classified as being sponsored by the pharmaceutical companies.

12 of the 40 new medicines (30%) approved by the FDA in 1999 were owned by biotechnology companies. Equivalent percentages for 1998 and 1997 are 36% and 24%, respectively (van Brunt, 2000).[4]

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artificial distinction between "biotechnology" and "pharmaceutical" companies, but rather between established companies with significant downstream drug development (i.e., clinical trial and marketing) capabilities and small new companies focusing on drug discovery research.

[4] Of the 40 new medicines approved by the FDA in 1999, five, all produced by biotechnology

A third line of evidence consists of industry data showing the extent of alliances between pharmaceutical and biotechnology companies. Alliance revenues of biotechnology companies have been increasingly steadily. In 1999, these amounted to 1.9 billion USD. That year, Pharmacia reported that alliances accounted for 21 percent of its entire R&D budget, up from 4 percent in 1995, and the CEO of Lilly similarly indicating that about 20 percent of Lilly's R&D budget is for outside collaborations (van Brunt, 2000). Since most alliances occur before a drug has entered clinical trials, while total R&D expenditures by pharmaceutical companies include substantial amounts for clinical trials as well as post clinical development, these percentages may underestimate the extent to which pharmaceutical companies rely upon biotechnology companies for early stage drug discovery. Data from Aventis (2001) suggest that 40-45% of drugs under development in major pharmaceutical companies involve an in-licensed drug candidate.

From the standpoint of pharmaceutical companies, reliance upon biotechnology companies to develop early stage drug leads to the point of proof-of-concept or "target validation" is an appealing strategy. Any drug candidate faces daunting obstacles even beyond the proof of concept stage. It must be shown to work in live animals. Then it must be shown to be safe and effective in first small, then large-scale human trials. Each development stage is more expensive than the previous, and the chance of failure at each stage is high. So pharmaceutical companies welcome the ability of universities and biotechnology companies to reduce the uncertainty associated with early stage drug development. They help bridge the development gap between potentially promising but highly uncertain basic biological discoveries and the desire of pharmaceutical companies for evidence that particular drug candidates will work safely, before the pharmaceutical companies invest in the expensive trials leading to regulatory approval and then commit resources to marketing.

Whether biotechnology companies are actually more effective at discovering new drugs and new drug discovery technologies and developing these to the proof-of-concept stage appears still to be an open question. Galambos and Sturchio (1998) as well as Zucker and Darby (1997) have shown that some pharmaceutical companies have learned to use technologies pioneered by biotechnology companies in their in-house laboratories. However, they do not shed much light on whether pharmaceutical companies are better at discovering new drugs than biotechnology companies, and my own discussions with persons

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companies, were variations of proteins, antibodies or other naturally occurring substances produced by the human body (i.e., "biologics" or "biotechnology medicines" according to the classical, narrow definition). The remaining 35 approved medicines were small molecule drugs (new chemical entities or "NCEs"). But seven of these had been licensed by biotechnology companies to pharmaceutical companies, that had assumed primary responsibility for obtaining FDA approval.

associated with pharmaceutical companies paint a more negative picture.[5]

The answer to the question in *italics* has profound implications for the future of Japanese pharmaceutical companies, because there are few biotechnology companies in Japan[6] and because there are significant barriers to university-industry technology transfer (Kneller 1999 & 2003). But its implications may be even more far reaching, depending upon whether start-up companies are also more innovative in other industries. To the extent they are, this may suggest a reason for the relative competitiveness of particular US and Japanese industries.

Are Japanese pharmaceutical companies indeed discovering most of their drugs on their own? Are their drugs innovative? If so, does this mean there is an effective Japanese alternative to the US innovation model? Will Japanese companies be able to survive using their traditional means of drug discovery as a wealth of complex, disbursed biological information becomes available? Finally, are the conclusions pertaining to the pharmaceutical industry generalizable to other high technology industries? These were the questions that motivated the beginning of this study three years ago.

1.2 Historical context

The above issues are complicated by a long history of government policies that have discouraged innovative drug discovery. Before the mid-1970s, the Japanese pharmaceutical industry was strongly protected against foreign competition. Patent protection was not available on the core chemical constituents of drugs. Incentives to copy foreign drugs were high and incentives to invent innovative drugs were low. Japan's national health insurance system reimbursed consumers the

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[5] These discussions suggest that pharmaceutical researchers often are frustrated by bureaucratic management and, conversely, researchers in some companies spend too much effort pursuing basic research interests. The most positive assessment I have heard of in-house corporate research came from the CEO of a newly formed US company with only about 40 PhD level researchers (i.e., smaller than many biotechnology companies). This person asserted that access to technologies and information from an array of biotechnology companies and university laboratories is not critical to drug development. Rather what matters most are skilled in-house researchers who can work in teams, well-chosen and clearly defined research goals, and advice from a strong advisory board of 3-6 outside scientists. Although these are anecdotal observations, they go to the heart of the issue of the ideal environment for drug discovery and they deserve systematic investigation.

[6] The total number of Japanese biotechnology companies in all fields including agriculture, energy, and foodstuffs and related sales and service, and with less than 300 employees (even less in the case of sales and service companies) was about 340 at the end of 2002. Over 70 % of these companies were formed after 1998. Of the 340, about 90 have a biomedical focus. Their average number of employees is 10. (JBA 2003) Most have academic ties. Four have had IPOs, three of which were in 2001 or later. Although the number of Japanese biotechnology companies is increasing, it is still less than the approximately 500 in each the UK and Germany and the 1500 in the US and their average size is relatively small (Ernst & Young 2000a&b).

cost of drugs and the reimbursement price allowed prescribing physicians, wholesalers and the manufacturers to reap healthy margins from pharmaceutical sales.. However, beginning in the late 1980s, financial pressures caused the government to periodically cut reimbursement prices and thereby squeeze the pharmaceutical companies' profit margins. The Ministry of Health and Welfare (MHW) still approved new drugs that offered little or no improvement over existing drugs. It also gave only marginally higher reimbursement prices for new innovative drugs. So financial incentives still favored development of derivative drugs that were cheaper to develop but often offered little improvement over existing drugs. Also it was still difficult for foreign companies to gain approval to market drugs in Japan. So Japanese pharmaceutical companies tended to focus on the domestic market, which was relatively free from foreign competition and where they could receive satisfactory profits for minimal research effort. The government price reimbursement system and lack of foreign competition also restrained merger pressures and kept companies small. (Thomas, 2001; Kimura, 1993)

By 2000, however, all this had changed. With international guidelines in effect to standardize regulatory approval procedures, it is easier for foreign drugs to be approved for sale in the Japanese market. Foreign companies are expanding marketing of their own drugs in Japan. Most representatives of foreign pharmaceutical companies believe the approval system is no longer biased against foreign drugs, although some believe that marketing requests by foreign companies still generally take longer to approve. The harmonization guidelines also require informed consent before patients can join clinical trials. Since Japanese patients are not used to the concept of informed consent or its procedures, carrying out the clinical trials in Japan has become difficult, particularly so in the case of cancer drugs. MHW and its successor, the Ministry of Health, Labor and Welfare (MHLW), began to withhold approval from new drugs that did not offer clear advantages over existing drugs, thus squeezing out copycat drugs. Government reimbursement rates were further cut. Pharmaceutical companies realized that they had to be more innovative and to reap more overseas sales in order to obtain profit margins that would allow them to remain internationally competitive. Table 2 provides summary statistics for the eight largest Japanese pharmaceutical companies in terms of world wide pharmaceutical sales.

[Insert Table 2 approximately here.]

Row 2 of this table indicates that overseas sales account for a significantly higher share of profits than domestic sales for half the companies, and row 3 indicates that R&D expenditures as a percentage of pharmaceutical sales are now in the same range as the weighted world-wide average of 12.6 percent (weighted by each company's sales) or even the unweighted average of 16.5% (HSBC 2000).

However, the legacy of the previous policies is that Japanese companies are small by international standards, to some extent they still focus on imitating

breakthroughs made overseas, and their small overseas sales forces put them at a severe marketing disadvantage with respect to their larger European and US competitors. Thus, this study's finding that the current pipeline drugs of the largest Japanese companies do not seem markedly less innovative than those of European and US companies, is even more remarkable. It suggests that an autarkic strategy of early stage innovation can succeed, even in pharmaceuticals - at least in the Japanese social context and at least up until recently.

1.3 Related research

Several other lines of research are germane to the issue of cooperation between Japanese pharmaceutical companies and outside organizations. Most notable is a study by Odagiri (2001) of the R&D boundaries of Japanese pharmaceutical companies. Rather than inquiring into sources of drug discovery leads, Odagiri focused on motives for pharmaceutical companies engaging in external research collaborations. Using publicly available data, including a complete compilation of reports from Japan's leading financial newspaper on alliances involving Japan's ten largest pharmaceutical companies, Odagiri obtained numerical data on the types of research alliances between 1989 and 2001 involving these companies. He also obtained data on joint patent applications. Odagiri concluded that external R&D collaborations were driven by technology rather than economic motives. In other words, the pattern of alliances was best explained by companies trying to access technologies in which they were inferior, rather than outsourcing those R&D activities that could be more economically conducted by outside organizations.

Odagiri's conclusion recalls a major body of literature dealing with the internationalization of R&D by Japanese, European and US multinational corporations (MNCs). One consistent conclusion of these studies is that Japanese pharmaceutical companies establish overseas laboratories in order to gain access to leading edge technologies and to establish links to human capital in key centers of foreign research [Florida, 1996; Kuemmerle, 1999; Odagiri, 1996; Pearce, 1999]. More generally, Grandstrand (1999) found that R&D intensive large Japanese corporations relied on collaborations with US universities more than any other method, except in house R&D, to increase their technological capabilities. Grandstrand's survey found that "technology scanning" (including monitoring and intelligence) was the third most important method to increase technological capabilities, while collaboration with Japanese universities was fourth. However, Grandstrand did not include pharmaceutical companies in his survey. Like the studies mentioned earlier in this paragraph, he found that the driving force behind internationalization of Japanese R&D was the need for access to foreign technology and scientific expertise, not to respond better to the needs of foreign markets.

Analyses by Pechter (2001) and Hess (2001) of numbers and percentages of English language scientific papers by an industry author with at least one university co-author show that both these metrics are equivalent for papers authored by Japanese and non-Japanese industry scientists. Pechter (2001), Hess (2001)

and Hicks (1993) found that Japanese industry scientists are more likely to co-author with Japanese university scientists than with foreign university scientists. These bibliometric findings may appear to contrast with Granstrand's conclusion that research links between Japanese companies and US universities are more important than links with Japanese universities. But Grandstrand asked companies directly about what types of interactions were most important for technology development.

This suggests that co-authorship may not be a good proxy for collaboration that contributes substantially to technology development. This possibility is supported by Murray's (2002) analysis of the cooperative research networks involving scientists who made breakthrough discoveries related to tissue engineering to repair damaged cartilage. She found that the most important interactions were not captured by bibliometric analyses. Instead they depend upon personal networks, participation in conferences, service on corporation advisory boards and other forms of consultation, formation of start-up companies, licensing of inventions, and sponsored research agreements – information about which she obtained primarily through interviews.

I also relied on interviews to explore the most significant collaborative relationships for drug discovery by major Japanese pharmaceutical companies. But by focusing on the "pipeline drugs"[7] of each company and the collaborations that lead to their development, I was able to supplement the interviews with substantial written information from various sources. Both types of information complemented each other. The interviews allowed me to probe the history of individual drugs and to confirm their origins. The written data on pipeline drugs helped to focus the interviews and to confirm some of the interview data.

2.0 Methods

2.1 Selection of companies

I chose the eight largest Japanese pharmaceutical companies in terms of revenue from world-wide pharmaceutical sales: Takeda, Sankyo, Yamanouchi, Dai-ichi, Eisai, Shionogi, Fujisawa, and Chugai (listed in descending order [JPMA 2002]). (Table 2 shows a slightly different rank order based upon 1998 sales).

2.2 Lists and categorization of pipeline drugs

I made a composite list of each company's pipeline drugs current as of 2001, based upon lists in investment advisory reports prepared by analysts in the Tokyo offices of UBS Warburg and HSBC as well as the companies' own internet sites. These lists

[7] Hereinafter the definition of "pipeline drugs" is "drugs in human clinical trials, drugs that are about to enter human trials (i.e., for which animal studies are complete) and drugs that have completed human trials but are still awaiting marketing approval in either Japan, Europe or the US."

classified each drug according to its development stage.[8] To the extent the source lists varied, it was mainly with respect to drugs in phase 1 or 2 clinical trials. I removed a drug if (a) there was evidence its development has been halted or (b) it had already been approved worldwide but was in clinical trials to obtain official certification for a different dose or delivery method or a slightly new indication. (Morphine and vancomycin fall into this latter category.)

The source lists also indicated which drugs were developed in house and which were in-licensed from other companies. In the latter case, the licensor was identified.[9]

Following the interviews (see section 2.4), I classified each drug according to whether it was:

1. a drug that originated in the company and is likely to be first to market in its therapeutic and mode-of-action class;
2. a drug that originated in the company and is likely to be 2nd or 3rd to market in its class, or is currently the 1st or 2nd global sales leader in its class after a recent launch;
3. a new use of a current drug that originated in the company and, when initially launched, was 1st or 2nd in its class;
4. a drug that originated in the company but meets none of the above criteria, i.e., a derivative drug (note that some derivative drugs incorporate significant improvements over earlier drugs in their class);
5. a drug that was in-licensed by the company prior to completion of clinical trials in any of the world's major markets (often the licensor is a smaller company seeking the resources of a larger company to complete clinical trials);
6. a drug that was in-licensed by the company after clinical trials had been completed in at least one of the world's major markets (in most such cases, the Japanese company obtained rights to sell and sometimes manufacture a

[8] These stages are as follows: "Pre-phase 1" => completed animal testing and about to begin human trials in at least one major market (i.e., Europe, Japan or the US). "Phase 1" => the earliest stage of human trials, involving 15-100 patients or healthy volunteers (depending upon type of disease and drug) to determine a safe dose and assess how the body handles the drug. "Phase 2" => human trials involving 30-500 patients or healthy volunteers to assess effectiveness and risk of side effects. "Phase 3" => human trials involving hundreds or thousands of patients to confirm effectiveness and safety. Most phase 3 studies include a "control" group of patients who receive standard therapy so that the effectiveness of the new drug can be compared with that of existing drugs. "Pending approval" => clinical trials completed in at least one major market and the results are now under review by drug regulatory authorities. "Approved" => approved in at least one major market.

[9] This appears to be a unique practice of Japanese companies indicating a degree of openness I did not find for any major European or US pharmaceutical company. Many US and European pharmaceutical companies do not make publicly available comprehensive lists of their pipeline drugs – even lists that do not show which drugs were in-licensed.

foreign drug in a limited geographic area, usually Japan but sometimes also other Asian countries);
7. a diagnostic agent, nutritional supplement, or new drug delivery system; and
8. a compound I could not classify according to any of the above categories.

This classification relied on various sources and my own medical knowledge. I excluded from further analysis products in category 7 and two drugs that ultimately remained in category 8.[10] Classification of the remaining drugs between in-house originating (categories 1-4) and in-licensed (categories 5-6) drugs relied upon the UBS Warburg and HSBC investment reports and interview data.

Classification of in-house originating drugs according to degree of innovativeness relied partly on the UBS Warburg and HSBC reports. However, for almost all these drugs, I searched the internet for scientific reports that would clarify the nature of the drug and its mode of action, and whether competing drugs with similar modes of action have been developed or are under development. I searched not only under the name of the drug, but also under its mode of action and sometimes the names of competing drugs.[11]

As for in-licensed drugs (categories 5-6), I relied on the UBS Warburg and HSBC reports as well as internet-available reports by the licensees and licensors to determine the stage at which each drug was in-licensed,. The latter reports also helped determine the status of the licensor. For example, Fujisawa licensed abciximab, a monoclonal antibody to prevent restenosis of cardiac arteries following balloon angioplasty, from Centocor, which is now a subsidiary of Johnson & Johnson (J&J). Information under Centocor's home page revealed that abciximab was marketed in the US in 1994, two years before the license to Fujisawa - thus enabling me to assign the drug to row 6 rather than 5. This information also revealed that Centorcor was still an independent biotechnology company at the time of the license – the merger with J&J not occurring until 1999.

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[10] These two drugs are listed under footnote (b) in Table 3. Queries to the companies enabled me ultimately to classify two other drugs.

[11] Here are several examples of how I classified pipeline drugs: I classified Chugai's ED71 for osteoporosis as a derivative drug, because there are other analogs of Vitamin D3 for the same purpose and this use of Vitamin D3 has been long known. Chugai's maxacalcitol to treat psoriasis is also a Vitamin D3 analog. But this use of Vitamin D3 is more recent, there appear to be only two other Vitamin D3 analogs for this purpose, calcipotriol and tacalcitol, and maxacalcitol appears to be superior to both. Therefore I classified maxacalcitol as a 2nd or 3rd in class drug (row 2). Another "close call" is another Chugai drug, GM611, used to increase bowel motility in, for example, Parkinson's disease patients. GM611 is a derivative of erythromycin, a common antibiotic that has long been known to increase gastro-intestinal (GI) motility. However, there appear to be no derivatives of erythromycin on the market to increase GI motility, and GM611 is probably the best of the erythromycin derivatives currently under development to treat low GI motility disorders (Salat 1999, Tack 2001). Therefore, I also classified GM611 as a 2nd or 3rd in class drug.

I sent each company a list of its pipeline drugs allocated among categories 1-8, requesting that they confirm my classification. Seven of the eight responded. As a result, I reclassified about 10% of the responding companies' drugs, but this did not affect my main findings. Most of these changes involved reclassifying row 6 as row 5 drugs.

For the purpose of comparison, I had originally hoped to analyze the pipeline drugs of Schering-Plough (S-P), Bayer and Abbott (see section 2.3), but I found a complete list of pipeline drugs only for S-P.[12] These I classified in the same manner as the Japanese drugs. The S-P list did not indicate which drugs were in-licensed, so I had to find this information from other sources. Because I did not interview S-P personnel, outside input may also have played a role in the discovery of some S-P's drugs listed in rows 1-4..

The number of drugs in each category for each of the Japanese companies is shown in Table 3. Because of the confidentiality promise I made at the beginning of the interviews (see section 2.4) and the fact that publishing this table with the names of the drugs in each cell may reflect negatively on some companies, only the total number of drugs in each cell is shown. Moreover, I have identified the eight companies by randomly assigned letter codes. I can send interested readers an alphabetical list of all the pipeline drugs I classified according to this scheme so that they can repeat the classification.[13] The names of the S-P drugs assigned to each category appear in a note following Table 3 as an example of how I classified and annotated the drugs for each company.

2.3 Use of the rDNA alliance data base

I was kindly granted time limited access to the proprietary online database "rDNA,"[14] which captures most cooperative research or development agreements, licensing agreements, and marketing agreements that are disclosed in press releases or in filings before the US Securities and Exchange Commission. Therefore most contractual agreements involving a US pharmaceutical or a US biotechnology company are captured by this data base. Sometimes a full text of the contract is available on line, sometimes just a summary or press release, and occasionally only the existence of an agreement is noted. The database only captures a few cooperative agreements involving universities. It captures some, but probably not all agreements involving only Japanese companies. This may also be true of agreements involving only European companies. Although when I examined the alliances involving Bayer, I found that the database included many alliances

[12] Available at www.sch-plough.com/documents. Non-official lists for all three companies are available at http://newmedicines.org/meds/development, however the lists at this URL for Bayer and Abbott are much shorter than those for S-P and probably are not complete.

[13] As noted in note 9, readers can also obtain lists of pipeline drugs for each company from the internet and use these as the basis for making their own classification.

[14] Password accessible via www.rdna.com.

involving only European companies. Therefore, the database provides a useful mechanism to compare the extent to which pharmaceutical companies are engaged in drug discovery research collaborations with start-up companies, as well as in-licensing of drugs in pre-clinical or clinical development.

I scanned all the rDNA materials on research and license contracts concluded in 1997 or later involving the Japanese pharmaceutical companies. The most numerous and useful materials were press releases issued by the alliance partner, usually a US biotechnology company. I classified the alliances according to whether they were:

(a) to gain access to early stage drug leads (prior to pre-clinical testing in animals to prepare for human trials) or drug discovery technologies (e.g., screening techniques and genome and protein data bases),
(b) to in-license drugs that were already in or about to begin clinical trials; and
(c) for other purposes (e.g., development of diagnostics or non-prescription or non-human drugs, out-licensing of drug candidates, cancellation of licensing agreements, or dispute settlements).

Ignoring alliances in category (c), I then summed the number of alliances separately for categories (a) and (b) for each company and recorded these values in the two rows of Table 4. Because of the confidentiality promise I made at the beginning of the interviews (see section 2.4) and the fact that identifying the companies in this table may reflect negatively on some companies, I have identified the eight companies by randomly assigned letter codes that are different from those used for Table 3.

For purposes of comparison, I selected three non-Japanese companies, S-P, Bayer and Abbott, that are roughly equivalent in terms of world-wide pharmaceutical sales to the eight Japanese companies. I performed the same analysis for these companies and also recorded the totals in Table 4. In fact, these companies are at the high end of the Japanese range. S-P has larger sales than Takeda, the largest Japanese company, Bayer's sales are between those of Takeda and Sankyo, while Abbott's sales are between those of Sankyo and Yamanouchi (HSBC, 2000). However, I wanted comparison companies that have a global presence and whose focus is primarily pharmaceuticals as opposed to chemicals or foodstuffs. Also I wanted at least one US and one European company, and I did not want companies that have recently undergone a major merger. With all these criteria, the number of possible comparison companies was limited. I felt S-P, Bayer and Abbott met these criteria best.

2.4 Interviews with the pharmaceutical companies

I conducted interviews with each of the target companies between April 2000 and May 2002. Using a variety of contacts, I identified research planning, business development and intellectual property (IP) managers, or lead scientists in each company. These persons were usually contacted initially by email and sent a short questionnaire with open ended questions addressing the following issues:

- sources of drug discovery and drug optimization leads,
- research collaborations with outside entities,
- the nature of these collaborations (type of collaborator,[15] type of collaborative agreement[16] and how the exchange of information occurred[17])
- recruitment patterns/policies,[18] and
- whether any drugs indicated as discovered in-house in the list of pipeline drugs had outside input to identify or optimize the drug.[19]

In addition, I knew in advance whether each company had overseas research laboratories (not laboratories devoted to manufacturing or clinical trials) and I asked about drug candidates coming out of such laboratories and the home office's impressions about such laboratories.

I promised not to report information in a manner that would identify the company or person that provided the information. Nevertheless, it was sometimes difficult to obtain interviews. In one company, two offices rejected interview requests citing concerns about revealing sensitive information. Finally, a third office agreed to a visit. Openness among interviewees was variable. Typically three company officials were at the table. On two occasions, however, the only respondent was a single senior company scientist, although these turned out to be among the most informative discussions. Sometimes I was alone and sometimes with an English graduate student, a Japanese research associate, or a Japanese colleague who had introduced me to company officials. Usually the interviews were in English, but in some cases they were mainly in Japanese. I do not believe the language of the interview directly affected the quality of responses. I was able to make my questions understood and to understand the responses – either on my own or with the help of colleagues or additional probing. All interviews occurred in the company laboratories or central offices, although one interview continued over into

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[15] E.g., university, government laboratory, consortium, biotechnology, or other pharmaceutical company, (differentiating between foreign or domestic for each category).

[16] E.g., donation to professor's laboratory, contractual cooperative research agreement, dispatching of corporate researchers to outside laboratories, license agreement, consultation, or service on advisory board. Whenever possible, I obtained numerical data as to the number of various types of relationships.

[17] In particular, I asked questions to confirm or refute the hypothesis that Japanese companies prefer to receive *codified* knowledge from outside organizations, rather than to develop long-term scientist-scientist relationships that would allow them to continuously tap into the *tacit* knowledge of independent outside collaborators.

[18] Including numerical breakdowns of new hires by MS vs. PhD qualifications, and when available, numeric breakdowns by field of specialization and gender. Separately I also asked for numbers of researchers dispatched to various types of institutions and their backgrounds.

[19] During the interviews, I sometimes went through the list drug by drug. More often, I had several key or representative drugs in mind and in the course of the interview asked about the development history of these and related drugs.

dinner. Sometimes I asked follow-up questions by email and usually received meaningful replies.

I summarized responses for each of the eight companies in a large table (not shown) under the following categories (row headings):

1. sources of leads for pipeline drugs;
2. collaborations with universities (domestic or foreign) and the form of these collaborations (type of contract and how information exchange occurs) including all available numeric data;
3. collaborations with foreign biotechnology companies, the form of these collaborations and the reasons for alliances with biotechnology companies;
4. importance of and access to bioinformatics technologies;
5. technical needs and focus of the company;
6. collaborations with and outlook towards Japanese biotechnology companies;
7. cooperation with government consortia or laboratories;
8. recruitment practices, including all available numeric data;
9. dispatching of researchers to universities, government consortia or foreign companies;
10. organizational and management issues; and
11. overseas laboratories and spin-off companies.

On the basis of the information under item 1, I estimated a relative rank (1-5) score for each company's recent propensity to seek outside drug development leads rather than to rely entirely on in-house research. On the basis of the information under item 2, I estimated a comparative rank score for each company's (a) extent and depth of cooperation with Japanese universities and (b) extent and depth of cooperation with foreign universities. Similarly on the basis of the information under items 3, 11, 7 and 6, I estimated a relative rank score for each company's extent and depth of cooperation with foreign biotechnology companies, foreign stand-alone research laboratories, Japanese government laboratories and consortia, and Japanese biotechnology companies. These relative rank estimates are summarized in Table 5, where the eight companies are assigned by randomly assigned letter codes that are different from those used for Tables 3 or 4.

2.5 Interviews with Japanese biotechnology companies

Over the past two years, I conducted interviews with about 15 Japanese biotechnology companies and several venture capital funds focused on biomedical start-ups. This is a major component of my research on university-industry cooperation and technology transfer in Japan and the results are the subject of an article now in preparation.

I asked each biotechnology company to describe (and if possible, identify) its ties with other companies, including research-oriented ties. In addition, I asked about their business plans as well as sources of capital, research manpower, managers, IP and customers/markets.

2.6 Interviews with university researchers

During my five years as a professor in a science and engineering research center in a major Japanese national university, I have had many conversations and interviews with university faculty and students related to cooperation with industry. Relevant data from these contacts are included in this paper.

3.0 Findings and analyses

3.1 Sources of leads for pipeline drugs

Table 3, row 8 shows that the percentages of in-licensed drugs for the Japanese companies range from 22% to 43 % (median = 36.5%). These percentages are low compared to those cited in section 1.1 as well as the 53% value for Schering-Plough.

Even more striking is the fact that most of the licensors to the Japanese companies are major foreign pharmaceutical companies, 25 of 48 in-licensed drugs (52%), with the remainder being Japanese companies (13 of 48 or 27%) and foreign biotechnology companies (9 or 21%) (Table 3, row 9). In contrast, section 1.1 indicates that the largest source of in-licensed pipeline drugs for European and US pharmaceutical companies are biotechnology companies. Such companies are the origin of 7 of S-P's 9 in-licensed pipeline drugs, while a Canadian university (Laval) and a UK charity (Cancer Research Campaign) were the other sources.

The Japanese licensors of drugs in rows 5-6 are chemical, foodstuffs or smaller pharmaceutical companies, including Ajinomoto (foodstuffs), Dai Nippon Pharmaceuticals, Kyoto Pharmaceuticals, Meiji Milk, Nissan Chemical, Toray Chemical, and Toyama Chemical. All of the 13 in-licenses from these companies appear to be for drugs that are in early stage clinical development (row 5). In contrast, 16 of the 25 in-licenses from foreign pharmaceutical companies appear to be for drugs that had already received market approval in either the US or Europe (row 6), as were two or the ten drugs in-licensed from foreign biotechnology companies. In contrast, S-P in-licensed all of its drugs prior to completion of clinical trials.

[Insert Table 3 approximately here.]

This analysis suggests that Japanese companies tend to participate in a cooperative drug development/commercialization process primarily in the final international marketing stage by licensing already developed foreign drugs for sale in the Japanese market, sometimes in exchange for out-licensing their own drugs for sale in foreign markets. This allows them to expand their product lines and sales in Japan. Foreign companies out-license their drugs to Japanese companies because this allows them to reap royalties from sales in Japan, without the need to build strong sales forces and while relying on their Japanese partners to obtain regulatory approval. In other words, for Japanese companies, partnering and licensing is mainly a mechanism to divide up geographic markets and to

accommodate regulatory and marketing challenges, rather than to integrate their companies into a global network addressing the earlier, more scientifically challenging stages of drug development.

The principal exceptions are licenses from Japanese chemical and foodstuff companies and small Japanese pharmaceutical companies. These companies are playing a role similar to that played by foreign biotechnology companies. Yet these drugs represent only 10 percent of the Japanese pipeline drugs.

The rDNA data base indicates that even the "in-house" drugs of foreign pharmaceutical companies draw more upon alliances with outside organizations than those of the Japanese companies. Row 1 of Table 4 shows that the Japanese companies enter into fewer alliances with biotechnology companies to in-license drug discovery technologies or early stage drug targets and drug candidates. The mean number of such drug discovery alliances for the eight companies is 5 (range: 1 to 11) while S-P, Bayer and Abbott have 25, 32 and 24, respectively.[20] As for later stage alliances to acquire "validated" candidate drugs (i.e., those ready for pre-clinical or human trials) the eight Japanese companies together had 10 (range: 0 to 3), while S-P, Bayer and Abbott had 12, 9 and 34, respectively (Table 4, row 2).[21]

[Insert Table 4 approximately here.]

But the rDNA data base captures only formal alliances, and primarily those with biotechnology companies. What about informal interactions, particularly those involving university researchers? The interviews suggest that even in this respect, Japanese pharmaceutical companies are pursuing an autarkic drug discovery strategy. Only one company (U in Table 5) reported significant reliance on outside organizations for help in discovering or improving its in-house pipeline drugs (those listed in rows 1-4 of Table 3). This company indicated that important leads for about 40 percent of its in-house-originating pipeline drugs (lines 1 – 4 in Table 3) came from outside sources, specifically Japanese and foreign universities. Company T acknowledged that two of its in house drugs (about 15%) were inspired by outside sources, one a Japanese university professor and another a foreign

[20] These technologies vary widely. Some of the licenses were for access to proprietary genetic or protein data bases, such as Incyte's. Some involved the licensor searching for drug candidates in particular therapeutic areas. Still others involved combinatorial chemistry, animal models for disease, and other drug discovery technologies.

[21] There is only a partial overlap between the later stage in-licensing data from the rDNA data base and the list of pipeline drugs in clinical trials (rows 5 & 6 of Table 3). Some of the compounds that are the subject of the licenses tallied in row 2 of Table 4 have not entered clinical trials. Some may be in phase 1 trials. (The lists of pipeline drugs sometimes do not include some drugs in early stage clinical trials.)

biotechnology company. Company S said a university professor and some of his associates were temporarily recruited to lead development of one of its pipeline drugs. Companies R and W each credited a university professor with the ideas that lead to the development or refinement one of one of their currently marketed in-house drugs. In the case of Company R, this input came from a foreign scientist. Company X hinted that outside input contributed to some of its pipeline drugs. Company Q acknowledged a foreign source in helping it to develop a new high throughput screening system, and also credited cooperation with a multinational pharmaceutical company in helping it elucidate basic biology issues that may be helpful in drug development. These interview findings are summarized in row 1 of Table 5.[22]

[Insert Table 5 approximately here.]

In summary, the interview responses suggest that, with the exception of Company U, the vast majority of the drugs designated as originating in house (Table 3, rows 1-4) actually were conceived of in-house as were any major improvements. As a whole, outside organizations contributed to the discovery of only 8 of 85 pipeline drugs designated as originating in house (9.4%).[23]

I do not know equivalent percentages for European and US companies. However, the data in Table 4 suggest that US and European companies in-license more early-stage drug candidates from biotechnology companies than their Japanese counterparts.

Thus a picture emerges of Japanese companies not as symbiotically integrated into a drug development network as their European and US counterparts - a chain that begins with university and biomedical start-up research and ends with late stage clinical trials and marketing by the pharmaceutical companies. Aside from fully developed drugs in-licensed from foreign pharmaceutical companies, Japanese pharmaceutical companies tend to develop most of their drugs in-house. The

[22] Company U scores highest because nearly 40% of its pipeline drugs were discovered with input from universities. All the other companies were scored 2 reflecting outside input into just one or two of their pipeline drugs, except I scored Company V 1 because it reported that none of its pipeline of drugs relied upon outside input for discovery.

[23] While searching for information on the pipeline drugs in Table 3, only one contradiction of the interview data arose. This concerned a drug which apparently was discovered in a company's foreign laboratory, although the interview subjects did not mention this. Sometimes, publicly information that I discovered confirmed the interview responses. For example, internet searches revealed a particular Japanese professor was working on a particularly therapy. This turned out to be the same professor that Company T named as aiding its drug discovery effort in this area. This provides some assurance that if early stage academic input into a particular drug was substantial, (a) I would have found out about this during my investigations and (b) the company would have revealed this input to me.

major exception to this pattern is in-licensing drugs still in clinical trials from smaller Japanese pharmaceutical companies and Japanese chemical and foodstuff companies. But this supplies a small proportion of pipeline drugs.

3.2 Innovativeness of pipeline drugs

Nevertheless, Japanese pharmaceutical companies are producing innovative drugs - despite their reputation for developing variations of drugs pioneered by foreign companies (Thomas, 2001; Kimura, 1993) – in Japanese, the so-called "zoro-shin" or "follow-on drug" strategy. Drugs that imitate a line of earlier drugs (row 4, Table 2) account for less than half of the in-house originating drugs (rows 1-4 combined) of the all the surveyed companies, except Companies F, G and H (see row 10, Table 3). It is true that drugs that are 2nd or 3rd to market (those in row 2) might also be developed using the *zoro-shin* strategy. So a stricter "innovativeness" ratio for in-house R&D is the number of first-in-class drugs (those in row 1) as a percentage of all new in-house-originating pipeline drugs (the sum of rows 1, 2 and 4). But even using this ratio (row 11, Table 11), over half of the in-house-originating pipeline drugs of Companies A, C and D would be classified as original. Schering-Plough (S-P) would meet both of these originality tests, but unlike the Japanese companies, its in-house-originating drugs account for less than half its pipeline. S-P's number of innovative drugs (row 1) is respectable by Japanese standards, but by no means extra-ordinarily high, especially considering that S-P is larger than any of the Japanese companies. Nor are S-P's innovative drugs markedly further advanced in development (and therefore less likely to fail) than those of the Japanese companies.[24]

Taking into account currently marketed as well as pipeline drugs, Japanese companies as a whole are global leaders in cholesterol, diabetes, Alzheimer's disease, infectious diseases and dermatitis medications. Sankyo's in-house researchers discovered mevastatin, the first of the statins, which are now the leading class of drugs to control high cholesterol. Although mevastatin was never marketed, information about it significantly helped Merck to launch lovastatin, the first of the marketed statins, in 1987. Sankyo launched the world's second commercial statin, prevastatin, two years later, which continues to have world wide sales of over 2 billion USD. Shionogi's recently FDA-approved rosuvastatin (Crestor®), albeit a derivative drug out-licensed to Astra Zeneca, may produce better cholesterol control than any other approved statin. Pitavastatin, in-licensed by Sankyo from Nissan Chemical and Kowa Pharmaceuticals, and now in advanced

[24] Of the 28 Japanese drugs in row 1 (i.e., first-in-class, non-derivative drugs), 3 (11%) are pre-phase 1, 5 (18%) are in phase 1 trials, 16 (57%) in phase 2, 1 (4%) in phase 3, 1 (4%) pending approval and 2 (7%) approved in one major market. Of Schering-Plough's four row-1 drugs, 2 are in phase 1 trials, 1 is in phase 2, and 1 is pending approval. Of the 13 Japanese drugs in row 2 (i.e., close follow-on drugs), 2 (15%) are in phase 1, 8 (62%) phase 2, 2 (15%) phase 3 and 1 (8%) approved in one major market. Schering-Plough has one row 2 drug and it is in phase 2 trials.

clinical trials, may control cholesterol even better than rosuvastatin. Sankyo pioneered the first of the thiazolidine-diones /glitazones, the current mainstay drug therapy for adult onset diabetes, with troglitazone (Resulin®). Troglitazone has been withdrawn because of safety concerns. However, Takeda's pioglitazone (Actos®) is now vying with Glaxo's rosiglitazone (Avandia®) for market leadership among diabetes drugs. Four years ago, Eisai launched donepezil (Aricept®), the first β−amylase inhibitor and currently the best approved drug to treat Alzheimer's disease. Donepezil was created entirely by an in-house researcher team, whose dynamic head scientist was warned repeatedly that the project would fail.
Dai-ichi's levofloxacin vies with Bayer's ciprofloxacin (famous following the 2001 anthrax attacks in the US) for sales leadership among the oral quinolone antibiotics. Less than two years ago, Fujisawa launched topical tacrolimus (Protopic®) derived from its leading immunosuppresant, Prograf®. Protopic is the first new drug in decades to treat eczema and other forms of dermatitis (Brody, 2001).

Although my interviews included only a small number of company scientists involved in drug development, they have included persons familiar with the development of several successful innovative drugs. These interviews suggest that innovative drug development often depends upon a single insightful, dynamic and sometimes iconoclastic lead scientist who mobilizes a team of in-house researchers to pursue many years of groundbreaking, risky research. The research methods usually involve traditional science-based pharmaceutical chemistry – in other words, understanding of the targeted biological process and a combination of screening and chemical modeling to create a small molecule that has the intended medical effect. The overall corporate research organization seems to have little bearing on the chance for innovative drug discovery. In other words, the successes seem not to have occurred within particularly innovative or efficient corporate research structures or as a result of cues from illustrious advisory boards. The coming to the fore, almost as if by chance, of a lead scientist with the right insights and personality seems to be the crucial element. However, the following factors can also be important:

(a) a bottom up system of project selection that gives promising, innovative proposals, even by junior researchers, a chance to gain the support of senior research managers,
(b) superiors who give the team leader the resources (sometimes grudgingly) to pursue his vision and
(c) the system of semi-flexible personnel rotations within companies that enables capable researchers from various disciplines to migrate to the innovative scientist's research team. (See Reger (1999) for an insightful review of personnel rotation and socialization within Japanese multinationals.)

These, however, are preliminary conclusions, which need to be verified.

The above discussion is not to argue that Japanese companies are more innovative than their European and US counterparts. Rather it suggests that the in-house research teams of Japanese companies can and do produce innovative

drugs, and they are probably not significantly less productive or innovative than their overseas counterparts of similar size.

3.3 Outside contributions not necessarily reflected in specific pipeline drugs (listed in approximate order of importance for accessing new technologies)

3.3.1 Cooperation with foreign biotechnology companies

The majority of the eight pharmaceutical companies said that foreign (mainly US) biotechnology companies are their most important access to important new biomedical technologies. Thus, the relatively low number of alliances with biotechnology companies shown in Table 4 may indicate a problem in accessing new biomedical discoveries.

The following interview responses illustrate some of the varied perspectives on dealing with foreign biotechnology companies: One company described a productive collaboration with a US biotechnology company that has already resulted in one drug now in clinical trials. Transpacific video conferences occur monthly between US and Japanese scientists. Another company, while acknowledging the importance of biotechnology companies as a source of new technologies, said that because of geographic and cultural barriers, the best biotechnology companies are already saturated with alliances with US and European companies, leaving only second rank biotechnology companies to work with Japanese companies. The company representative described how one US biotechnology company charged an "exorbitant" price for a one-time data report that was of little value. A scientist from still another company told how his company was developing in house capabilities in a particular sophisticated platform technology, even though he felt that foreign biotechnology companies could offer higher quality technology at a lower price. This scientist, a specialist in this technology, said it was difficult to convince senior management of the merits of engaging in alliances to access such capabilities.

Row 2 in Table 5 gives a comparative score for each company's extent and depth of cooperation with foreign biotechnology companies based upon the interview responses.[25] The correspondence is reasonably good between these scores and the alliance counts in Table 4 from the rDNA data base.

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[25] I scored Company T 5 because it stressed it was trying to establish more links with US biotechnology (biotech) companies, one pipeline drug has already emerged from these collaborations, and it had developed good working relationships that involve ongoing sharing of tacit knowledge. I assigned 4 to Q and X because both said they relied on foreign biotechs for their main sources of new technologies, they currently have alliances with 5-10 biotechs, and are experimenting with new financial mechanisms to support research in biotechs. I scored R, V and W 3 because, although they said biotechs are their most important sources for new technology, they either were not specific about alliances, expressed dissatisfaction with alliances or indicated that the number of alliances are relatively small. U suggested it had only a few alliances and I scored it 2. S indicated it probably had just one alliance.

3.3.2 Japanese universities

The studies cited above by Odagiri (2001), Grandstrand (1999), Hicks (1993) and Pechter (2001) show a long tradition of university-industry collaboration in Japan, as does a review of this subject by Odagiri (1999). My interview responses also indicate a significant number of collaborations. Six in-house pipeline drugs were discovered with substantial inputs from Japanese university researchers. No other type of outside organization directly contributed to the discovery of so many in-house pipeline drugs. (Foreign universities and other non-profit research institutes contributed to the discovery of two drugs, and a foreign biotechnology company and a branch foreign laboratory contributed to the discovery of one each.) However, four of the six drugs discovered with university assistance belong to one company, which is clearly an outlier in terms its reliance on collaborations with universities to discovery pipeline drugs. The other seven companies appear to seek cutting edge discoveries mainly from foreign universities and biotechnology companies, and to pursue drug discovery mainly on their own. The vast majority of collaborations with Japanese universities are aimed at monitoring university research and preserving access to promising graduates. Research partnerships in which university and company researchers share a specific common goal, or collaborations in which a company relies upon university researchers to pursue independently research of particular value to the company are rare. However, some professors suggest that small pharmaceutical companies turn more frequently to university researchers for help in discovering drugs.

For the eight surveyed companies, the majority of collaborations occur underare so-called “Donation” support to individual professors. Four and possibly five of the eight companies indicated they are giving Donations to over 100 professors annually. Government guidelines limit annual donations to less than 5 million yen (~$40,000). Also they cannot be linked to a specific research project or to a promise that the company will receive intellectual property rights to any resulting discoveries. Along with one-time honoraria payments ostensibly for lectures or written reports, Donations were the only means to reimburse university professors for consultation activities - prior to reforms in 2000 that officially permitted compensated consulting and advisory board membership by national university faculty. (Kneller, 2003)

Formal mechanisms of research collaboration are limited to so-called “Commissioned” or “Joint Research” contracts. Six of the eight companies indicated they supported at least 50 Commissioned or Joint Research projects annually in Japanese universities. There is no monetary limit on the amount of funding via such contracts, but as in the case of Donations, paying salaries or living expenses for university researchers has been problematic. In other words, mobilizing university researchers for projects of value to the pharmaceutical companies is problematic, although the situation has improved since 2001 (Kneller, 2003).

Several companies said they used Commissioned or Joint Research contracts

to obtain specific information from universities, whereas the networks created by Donations are valuable for keeping abreast of advancing research frontiers. When pressed further on this point, several companies said that project-specific sponsored researcher is mainly valuable for target validation, for example, showing that a particular cell-surface receptor actually is linked to a disease. If this is indeed the prevalent practice, then a typical cooperative project leaves the university laboratory little opportunity to exercise initiative or creativity.

The companies reported no licenses from universities. But this is not surprising in view of the standard practice among university inventors to attribute (often mis-attribute) inventions to funding sources that permit the inventors to retain ownership (Kneller, 2003).

Row 3 in Table 5 gives a comparative score for each company's extent and depth of cooperation with Japanese universities.[26] Company U is unique in its reliance on university research. Company U also has a relatively large number of innovative drugs (row 1, Table 3) a majority of which were discovered with input from universities. This suggests that collaboration with university researchers may give research teams in pharmaceutical companies an advantage in terms of being able to produce innovative pipeline drugs.

3.3.3 Foreign universities

Five of the pharmaceutical companies said they had formal consulting agreements with foreign university professors aimed at drug discovery. Four said they had major sponsored research agreements with foreign universities. One of these, begun about ten years ago, involved funding most of the costs of a laboratory in a major US academic medical center devoted to a particular disease interest of the company. After a long and sometimes frustrating learning process, the collaboration has improved, meetings between company and university scientists occur regularly, and the company believes some likely drug candidates are

[26] Company U scored 5 because its in-house pipeline has benefited from collaborative research with universities. It also has about 100 Donation and Commissioned/Joint Research (C/J) collaborative research projects with Japanese universities. Companies R and T scored 4 because each emphasized the importance of university consultants and estimated that it had over 200 recent Donation and C/J projects with Japanese universities. T said it had 200-300 informal university consultants (many involved in Donation or C/J projects) and about 5 full time consultants (some retired), while R said it budgeted about $10 M annually for Donation projects and "several" million for C/J projects. In addition R said it relies on its advisory board for target identification. I scored Companies Q and W one point lower because they did not have as many Donation and C/J collaborative projects (approximately 100). Company Q specifically stressed the importance of Donations for networking with academics. Both had 5-10 formal consultation agreements with Japanese academics. Companies V and X reported somewhat lower numbers of collaborative agreements and consultative relationships. Company S specifically denied having a large academic network.

emerging from this collaboration. Other companies are expanding collaborations with foreign universities and some have formed drug discovery advisory boards consisting largely of foreign university professors. In general, most companies believe that expanding interactions with foreign universities is important for future drug discovery. Row 4 in Table 5 gives a comparative score for each company's extent and depth of cooperation with foreign universities.[27]

3.3.4 Government laboratories and consortia

Company U said it had obtained drug discovery leads from national laboratories. Three other companies acknowledged significant participation in government-organized research consortia, for example consortia focused on the development of new drug delivery mechanisms, genomics, and computer assisted drug design.[28] The most frequently cited benefits were contact with companies in other industries, for example Hitachi. The most frequently cited concerns were (1) that their own technologies would leak to rivals and (2) government pressure to commit resources to the consortia. Row 5 in Table 5 gives a comparative score for the extent and depth of each company's involvement with government research institutes and consortia.[29]

3.3.5 Branch foreign laboratories

Three of the companies have a total of five stand-alone research laboratories in the US and/or the UK focusing on drug discovery and related basic research. All but one of these laboratories is located close to a major university medical center. One of the pipeline drugs in Table 3 emerged from one of these laboratories. Nevertheless, the interview responses suggested that these laboratories usually do not provide good windows on research in the adjacent universities, even though they often recruit young researchers from the ranks of recent Ph.D. graduates. In other words, the experience of these laboratories seems to suggest that citing a laboratory close to a well known university medical research center and recruiting

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[27] The scores are based on the above-mentioned experience with a US university, the number of reported sponsored research agreements with foreign universities, the number of consultation agreements, the existence of a formal advisory board composed of foreign academic scientists, the existence of pipeline drugs discovered with help from foreign universities, and links between foreign branch laboratories and nearby universities. More specific information cannot be given for confidentiality reasons.

[28] Some of these consortia, for example Helix which is focused on genomics, have their own laboratories. More often, however, consortium research is conducted in the laboratories of participating members.

[29] I scored Company U 4 for the reason stated in the text. I assigned the same score to V because it obtained important drug delivery technology from a consortium. I scored Q and X each 3 because each said participation in some consortia had been helpful. I scored the remaining companies 1 because they indicated either they did not participate or participation was not beneficial.

graduates from the university does not necessarily allow the company to tap into ongoing university advances. Some other form of interaction is necessary. Row 6 in Table 5 gives a comparative score for the benefit each company attributes to its foreign laboratories.

3.3.6 Japanese biotechnology companies

None of the eight pharmaceutical companies said that collaborations with Japanese biotechnology companies were an important source of technology, and the majority suggested that Japanese biotechnology companies have little technology of significant value to them. But some respondents said that some biotechnology companies are developing technologies that probably are of value, but it is often difficult to convince senior managers to cooperate with these companies. To balance this negative picture, one of the eight pharmaceutical companies recently provided contract research support to a university start-up during its first years of operation when it had no other major outside support. This company recently had a successful initial public offering (IPO) and has a medical therapy in human clinical trials.[30] Table 4, row 7 gives a comparative score for each company's willingness to consider Japanese biotechnology companies as potential sources for valuable technologies.

3.3.7 Human resources

Lifetime employment is still the norm in all the pharmaceutical companies, despite signs of breakdown in other industries. The small number of researchers hired in mid-career (30s or 40s) are usually Japanese scientists who have completed post-doctoral training or have spent some time in a tenure-track faculty position in a US, UK, Canadian or Australian university. Also, among newly hired young researchers, MS level graduates still predominate, ranging from 70% to 90% among the eight companies. It was common to hear respondents say that Japanese PhD level training is of little value to the company because it is too specialized, and it does not enhance the career of the holder. However, one respondent, an accomplished scientist who himself earned only a bachelor's degree, acknowledged that in some fields Ph.D. training is valuable and more Ph.D. graduates should be recruited. Only one company said it was taking affirmative steps to retain female researchers who are starting families.

Most companies dispatched fewer than ten researchers per year to Japanese universities, often to do research for a PhD degree, and about five post-doctoral level researchers per year to foreign universities. These numbers represent a significant long-term investment in human resources as well as an opportunity to bring back to the corporate laboratories valuable outside knowledge. Whether this knowledge is regarded as important to drug discovery is unclear, however.

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[30] However, this alliance mainly involves research funding in exchange for Japanese distribution rights for any medicines to emerge. It probably has not involved significant research cooperation.

All companies acknowledged they needed more expertise in bioinformatics. However only two had been able to hire experts in this field. The responses revealed that a branch of a major Japanese electronics company is positioning itself to offer bioinformatics expertise to pharmaceutical companies on a contract basis, as well as developing instruments related to bioinformatics. In other words, it is filling a role filled by biotechnology companies in the U.S.

4.0 Discussion

4.1 Why autarky?

These findings show that, although Japanese companies do have important collaborations with outside organizations, they rely more on their own in-house research to discover new drugs than do their US and European counterparts There are various, interrelated reasons for this autarkic system of early stage innovation, some of which affect the supply of and others the demand for outside inputs.

One obvious supply factor is the dearth of Japanese biotechnology companies (see note 6). In addition, Japanese biotechnology companies face problems obtaining managers; researchers; and proactive, informed private financing that are more severe than for biotechnology companies in the US and UK (Kneller, forthcoming).

Supply side factors also make Japanese universities less appealing sources of drug discovery leads than US and UK universities. Section 3.3.2 mentions some of the reasons, analyzed in detail in Kneller (2003). They include:

- difficulties mobilizing university researchers for research relevant to drug discovery,
- a tendency for young university researchers to follow the research leads of senior faculty patrons, and for these patrons to rely on large government research grants allocated without sufficiently objective and informed peer review,
- autarky in university laboratories,
- low numbers of university researchers with Ph.D. level training interested in drug discovery research,
- inability of companies to obtain clear, transferable intellectual property rights to discoveries they fund in universities,
- until recently, barriers to university researchers consulting for companies and forming start-up companies, and
- inability of universities to champion the development of early stage biomedical discoveries that might lead to drug discovery.

But “demand” factors are also important. As noted in the 3.3.6 above, the pharmaceutical companies have a generally disparaging outlook on Japanese biotechnology companies. Even if these companies have valuable technologies, senior management may be reluctant to approve substantial collaborations.

Comments about Japanese university research are also generally disparaging, and the vast majority of collaborations with universities seem to be aimed at research scanning, recruitment, and narrowly defined confirmatory projects.
In the case of overseas universities and biotechnology companies, the general impression from the interviews is that such collaborations are often difficult, but the companies feel they have no choice but to pursue them. There may be a tendency for the Japanese companies to seek mainly codified research results from foreign partners rather than to exchange, on an ongoing basis, tacit as well as codified knowledge. Further research is needed on how information is exchanged in collaborations involving Japanese, European and US companies. Finally, it appears that none of the Japanese companies have initiated the sort of grant and fellowship training programs that Pfizer, SmithKline Beecham, and perhaps other companies use to establish long-term relationships with young university researchers – linkages that these companies value even if the grantees never work in pharmaceutical companies (see Lam, 2002; Leigh, 2000).

In the case of overseas collaborations, Japanese managers and researchers face linguistic challenges much greater than those faced by, for example, continental Europeans cooperating with US biotechnology companies and universities. Therefore, the assertion by some interviewees that Japanese companies are inherently disadvantaged in developing overseas collaborations, may be largely true.

But linguistic differences cannot explain the apparent reluctance of the pharmaceutical companies to engage Japanese organizations in substantive collaborations. Two other possible factors are the system of lifetime employment and the related practice of hiring researchers with no more than MS-level university training.

The system of lifetime employment and the attendant lack of labor mobility creates incentives to keep in-house researchers productively employed and diminishes incentives to outsource early stage drug discovery research. Several companies volunteered this as a reason they tend to rely more on in-house research than their US and UK counterparts, who are more likely to outsource research to reduce costs. This desire to preserve their in-house research teams and to keep them productively busy may be a factor behind a tendency for these companies to seek codified knowledge from outside organizations, codified knowledge that can be imported into in-house laboratories where it becomes part of the pool of internal tacit knowledge. Several companies said that this wealth of tacit knowledge was the main benefit of the system of lifetime employment.

The hiring of MS degree researchers reinforces the practice of lifetime employment. Because their advanced training occurs in-house and is focused towards the specific needs of their companies, and because their mentors and patrons are also in-house, researchers are socialized to the environments within their companies and it is difficult to move to outside jobs. At the same time, however, it may be more difficult for them to work collaboratively with outside

researchers and to evaluate outside research results.

Cultural factors may underlie the system of lifetime employment and the general tendency towards autarkic innovation. Nakane (1970) described the hierarchical organization of Japanese organizations, including the primacy of vertically-structured relationships and the discouragement of unsanctioned horizontal relationships – especially those extending outside of one's group. Yamagishi (1998) found that Japanese are more reluctant than Americans to form relationships requiring trust with persons outside their group. Coleman (1999) notes that career advancement is dependent upon maintaining close relations with and following the lead of one's superiors. But Doi's work (1971) suggests that, far from being simply confining and burdensome, close hierarchical relationships create reciprocal mutual obligations that can provide stability and mutual benefit within an organization. This is not to suggest that autarkic practices in Japanese industries are culturally determined. Rather such cultural observations may provide a partial explanation why autarkic patterns of innovation have emerged; even while ongoing changes in pharmaceutical companies, biotechnology start-ups, and Japanese society as a whole, show that cultural factors are neither immutable nor singularly determining.

4.2 Reasons for concern and optimism

Sections 1.2 and 3.2 suggest that, despite severe disincentives to innovative drug discovery created by past Japanese government policies, in-house research teams in the Japanese companies are producing globally competitive drugs at rates that are comparable with overseas companies of similar size. However, this does not necessarily imply that the drug discovery industry as a whole is as innovative in Japan as in the US. As noted in Table 1, the majority of current pipeline drugs are being sponsored by (mainly US) biotechnology companies. If these drugs are added to the pipeline drugs of US pharmaceutical companies, the number would probably be significantly larger than the number of pipeline drugs of all Japanese companies combined.[31] It is not clear whether this apparent dominance among pipeline drugs of drugs from US biotechnology companies will be reflected in their future dominance on world markets.

In any event, most of the eight companies seem determined to transform themselves into globally competitive companies. *Can they do so if their drug discovery systems remain autarkic?* The following are reasons for concern:

1. The explosion of biological and bioinformatics information and technologies relevant to drug discovery is beyond the scope of any company, no matter how

[31] Unfortunately, coverage in the PhRMA New Medicines in Development Surveys is not complete for Japanese drugs. However, even using a generous multiplier to adjust upward the number of Japanese drugs still would leave Japanese sponsors with a lower number of pipeline drugs relative to US sponsors than would be expected from the relative ratio of these two countries' pharmaceutical markets (the ratio of these two markets is roughly 1:3, Japan:US (HBSC 2000a&b)).

large, to evaluate, assimilate and use effectively. Some division of labor is necessary. The strength of the US-style innovation system appears to lie partly in the large number of independent but networked actors (universities, biotechnology companies, pharmaceutical companies and their individual researchers and managers) that continuously interact with each other, and partly as a result of this interaction, generate new ideas. This type of interactive environment composed of multiple independent actors does not exist in Japanese pharmaceutical research.

2. The innovative ability of in-house research teams composed of MS graduates is probably limited – despite substantial in-house training and access to corporate tacit knowledge. Ten years ago, I took part in a fact-finding visit by a number of US protein scientists to major Japanese protein laboratories, including the Protein Engineering Research Institute near Osaka (PERI). PERI was a MITI organized consortia to which some university faculty were seconded along with researchers from pharmaceutical and chemical companies. A common refrain of the university scientists at PERI was that industry scientists, although comparable in technical skills to university researchers, could not compare in terms of fundamental understanding of research problems and creativity (Protein Engineering in Japan (1992)). Furthermore, some of my interviewees described situations where their companies were not able to evaluate properly the research of other organizations or even, on occasion, the results of their own research.[32] Not having many researchers who can understand the significance of new biological information may be a serious disadvantage.
3. Because of changes in Japanese society, companies may no longer be able to expect a near total commitment of time and loyalty from their employees - assuming that this actually played a role in the past successes of their in-house research.

But even if Japanese pharmaceutical companies want to become less autarkic, their near term options are limited due to the small number of Japanese biotechnology companies, the barriers to close cooperation with universities and the low number of Japanese Ph.D. graduates interested in working in industry. As a near term solution to these challenges, most of the pharmaceutical companies are trying to increase alliances with overseas biotechnology companies and, to a lesser extent, overseas universities. But, maximizing benefits from such alliances will require scientists and managers who can overcome linguistic and cultural barriers – a requirement that has proved difficult in the past (Westney, 1999; Reger, 1999).

Nevertheless, this study suggests that some of the eight companies have been reasonably successful in developing alliances with universities and overseas

[32] One company licensed global marketing rights (except for Japan) to one of its promising new drugs to an overseas pharmaceutical company, not knowing how effective this drug was. If it had known, it probably would have made sense for the company to market the drug itself.

biotechnology companies. Furthermore, since my interviews, the number of Japanese biotechnology companies has continued to grow. Some of these new companies have reported success forming alliances with pharmaceutical companies. Also the pharmaceutical companies seem to be changing their perspective, with various newspaper reports and personal communications suggesting they are placing more importance on collaborations with Japanese biotechnology companies and universities. These alliances may help some of these companies to maintain a stream of innovative pipeline drugs, and thus to remain globally competitive in terms of drug discovery. Some may come to resemble established US biotechnology companies more than typical large multinational pharmaceutical companies.[33]

4.3 Economy-wide implications

Early stage innovation in other industries may also occur autarkicly. Two years ago, I conducted a study of university-industry cooperation in information technology (IT). I found only one example of an IT-oriented university start-up and only one university center actively cooperating with industry in this area (Kneller, 2000). More recently, a Stanford University engineer and I found that foreign magnetic resonance imaging (MRI) manufacturers are more likely than their Japanese competitors to seek collaborations with Japanese universities and to empower university researchers to make substantive changes in software design (Nayak and Kneller, forthcoming). Research in other industries is necessary to confirm this hypothesis that autarkic innovation is a widespread characteristic of Japanese industry.

Does the experience of the eight Japanese pharmaceutical companies suggest that companies in other industries can be globally competitive while innovating autarkicly? The answer is not yet clear. But the fact that Japanese pharmaceutical companies seem to be shifting away from autarky, cautions against this being a successful strategy, and least in biomedical industries.

It may be that Japanese companies have done well in industries suitable for autarkic innovation, but recently they have been at a disadvantage in industries where innovation occurs most effectively through interaction with universities and other companies. For example, in the 1970s and 1980s, large Japanese manufacturing companies made great technical (especially process engineering) strides in industries such as automobiles and electronics where innovation could occur effectively in-house. Innovative inputs from universities or other companies - other than open publications and examination of competitors' products – were either not available or not necessary. In such industries, an autarkic style of innovation

[33] The recent purchase by Roche of a majority ownership interest in Chugai is an example of such a transition. Chugai is now paired with Genentech as one of Roche's two principal subsidiary companies. Roche acquired both for their drug discovery capabilities. Roche is assuming responsibility for clinical development and marketing of many of these companies' drugs. However, most Japanese pharmaceutical companies want to remain independent.

relying on accumulated in-house tacit knowledge and small research teams networked by close-knit hierarchical relationships was an advantage. However in the 1990s, rapid commercially important technical advances seemed to occur most in industries such as biomedicine and IT. These are industries that currently seem to lend themselves well to early stage innovation in small companies and universities.

Further studies into what types of environments are most conducive to early stage innovation in various industries and countries are sorely needed. For example, what is the relative importance of the following factors in various countries:

- small organizational size,
- venture-capital backed management,
- academic colleagues motivated by strong business incentives, and
- close interpersonal work relationships?

Such studies will shed light on whether the extended malaise of the Japanese economy is due partly to a system of autarkic innovation within established companies, and on ways all countries might improve early stage innovation in their industries.

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Table 1: New Drugs in Clinical Trials by Type of Sponsor and Therapeutic Field

Therapeutic Field	*Major Pharma*	*Biotechnology & Small Pharma*[1]	*Other*[2]	*Total*
Cancer[3]	68 (20%)	216.5 (62%)	62 (18%)	346.5
Heart Disease & Stroke[4]	55 (45%)	68 (55%)	--	123
Infectious Diseases[5]	54 (21.5%)	193.5 (77.1%)	3.5 (1.4%)	251

Notes:

[1]Small pharmaceutical companies such as Roberts Pharmaceuticals account for only a few of the drugs that appear in this column

[2] Most of these drugs are sponsored by the National Cancer Institute (NCI) of the NIH. The remainder are sponsored by the US Army or non-profit organizations such as the Robert Wood Johnson Foundation.

[3] Source: 1999 Survey: New Medicines in Development for Cancer, PhRMA.

[4] Source: 2001 Survey: New Medicines in Development for Heart Disease and Stroke, PhRMA.

[5] Source: 2002 Survey: New Medicines in Development for Infectious Diseases, PhRMA.

Methodology: In case a drug was sponsored by only one type of organization (large pharmaceutical company, small pharmaceutical company, biotechnology company, NCI, or other non-profit) I assigned the value "1" to that type of organization. In case a drug was sponsored by more than one type of organization, I assigned 1/2 to each type of organization. The principal exception was that, if dual or triple sponsors included a large pharmaceutical company and a biotechnology company, I assigned 1 to the biotechnology company and 0 to the large pharmaceutical company on the assumption that the drug was discovered by the biotechnology company and then licensed to the pharmaceutical company. Then I summed scores over all drugs according to type of sponsoring company, and thereby calculated percentage estimates of the origins of these drugs.

Table 2: Summary Statistics for the Eight Japanese Companies

	Sankyo	Takeda	Shionogi	Yamanouchi	Dai-ichi	Eisai	Fujisawa	Chugai
1. Global 1998 pharm sales ($B) (rank)	4.7 (18)	4.3 (19)	2.6 (26)	2.5 (28)	2.2 (30)	2.2 (31)	2.0 (33)	1.5 (35)
2. % 1999 sales overseas (% profits) ‡	22% (35%)	21% (70%)	10% (6%)	41%Δ (35%)	15% (31%)	24% (18%)	30% (60%)	12% (10%)
3. R&D as % of est. FY2000 pharma sales	13.5	12.1	13.3	11.8	15.6	15.6	16.9	20.5

Source: UBS Warburg, HSBC and individual companies.

‡ Sales percentages do not include royalties from out-licensed drugs (e.g. Shionogi's rosuvastatin licensed to Astra Zeneca).

Δ Includes revenues from US health foods subsidiary, Shaklee.

Table 3 - Pipeline Drugs Classified According to Whether In-Licensed or Originating In-House, with the In-house-Originating Drugs Subclassifed by Innovativeness

(Rows 1-6 list number of drugs[a] as of 2000)

	A	B	C	D	E	F	G	H	Mean for Japan cos.	S-P
1. New, not derivative of existing drug	5	6	5	3	3	3	2	1	3.5	4
2. Second or third in class in terms of launch time, or first or second in class in terms of global sales	3	3	0	2	1[1]	1	3	0	1.6	1
3. New indication for a previously approved first or second in class drug	4	0	0	2	1	0	0	1	1.0	1
4. Derivative of existing drug (fourth, fifth, etc. in class)	1	6	3	0	4 [1]	8 [3]	5 [3]	9	4.5	2
5. In-licensed before clinical trials completed in any major market	7	4	4	0	3	5	4	3	3.8	9
6. In-licensed for marketing (after clinical trials complete in at least one major market.)	3	1	0	2	2	2	3	5	2.2	0
7. Total number of pipeline drugs: (∑ rows 1-6)[b]	23	20	12	9	14	19	17	19	16.6 (total 133)	17
8. Rows 5+6 (as percentage of row 7)	10 (43)	5 (20)	4 (33)	2 (22)	5 (36)	7 (37)	7 (41)	8 (42)	6.0 (total 48) (36%)	9 (53%)
9. Row 8 by source: foreign pharma, Japan company, foreign biotech	6-2-2	1-4-0	0-4-0	1-0-1	3-1-1	4-0-3	4-0-3	6-2-0	Totals only: 25-13-10	--
10. Innovativeness ratio (∑ rows 1-3 / ∑ rows 1-4)	0.92	0.60	0.62	1.00	0.56	0.33	0.50	0.18	0.58	.75
11. Stricter innovativeness ratio (row 1/ (rows 1+2+4))	056	0.40	0.62	0.60	0.38	0.25	0.20	0.10	0.36	.57

UBS Warburg, HSBC and individual companies (for pipeline drug lists); UBS Warburg and HSBC, company interviews, and my research using various sources (basis for classification). The following classification of S-P's drugs illustrates how I classified the drugs of each company among rows 1-6. Row 1: ezetimibe(P), IL-10(2), SCH-C(1), SCH58261(1). Row 2: lonafarnib(2). Row 3: Clarinex®. Row 4: mometasone(P), posaconazole(3). Row 5: infliximab [Centocor], eptifibatide [CorMillenium], peg-intron [Enzon/Biogen], marimastat [British Biotech], melacine [RIBI], doxil [ALZA], temozolomide [Cancer Res Campaign], PDE4 inhibitor [CellTech], SCH57050 [Laval U]. Row 6: none. (For rows 1,2&4, ( ) indicate the most advanced clinical trial stage, while (P) indicates approval pending in a major market. For row 5, the organization in [ ] is the licensor of the drug.)

[a] Numbers in [ ] indicate drugs that are being developed for the Japanese market only.

[b] Excludes diagnostic compounds and drug delivery formulations as well as the following drugs that I could not classify: TAK427 and TAK428 by Takeda

Table 4: Alliances Between Pharmaceutical and Biotechnology Companies (contracts made 1997 – 2001):

	I	J	K	L	M	N	O	P	Schering-Plough	Bayer	Abbott
# alliances to acquire drug discovery technologies or identify drug targets	5	4	4	4	11	6	1	6	25	32*	24*
# alliances to acquire drug targets ready for pre-clinical or clinical trials	0	2	1	1	3	2	0	1	12	9*	34*
1999 global pharmaceutical sales ($M)	Range: 6000 – 1900								7700	5300	3900

- Diagnositic related alliances (~12 for Bayer and ~24 for Abbott) not included.
- Source: www.rdna.com

Table 5: Interview Findings on
Cooperation with Outside Organizations for Drug Discovery
(Organizations in rows 2-7 are listed in approximate order of importance for accessing new technologies. Within each row, scores are relative rank indices on a 1-5 scale*)

	Q	R	S	T	U	V	W	X
1. Drugs whose key discovery originated outside co.	2	2	2	2	5	1	2	2
2. Foreign biotechnology companies**	4	3	1	5	2	3	3	4
3. Japanese universities	3	4	1	4	5	2	3	2
4. Foreign universities	4	4	1	3	3	4	2	2
5. Japanese government labs or consortia	3	1	1	2	4	4	1	3
6. Stand alone foreign research labs**	3	1	1	1	1	1	3	2
7. Japanese biotechnology companies	2	2	1	2	1	3	2	1

Source: row 1: all data sources; rows 2-7: primarily interviews

* See notes above for explanation of individual scores.

** excluding a DNA diagnostics company was wholly owned by one of the companies until a recent merger