Effect of mergers and acquisitions on drug discovery: perspective from a case study of a Japanese pharmaceutical company

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The pharmaceutical industry has experienced intermittent waves of mergers and acquisitions (M&As) since the 1980s and recently appeared to be in yet another wave. Previous studies indicated rather negative impacts of consolidation on research and development, suggesting that they do not necessarily lead to long-term reinforcement of research capabilities, although they may enrich the drug pipeline in the short term. However, recent studies have implied a positive side in terms of knowledge-base transfer. Further micro-organizational studies suggested that scientists learned new knowledge and approaches from partner scientists and improved their performance and innovation. These findings imply that measures for the scientist-level integration after M&As would reinforce fundamental research capabilities in the long term.

The pharmaceutical industry has experienced intermittent waves of mergers and acquisitions (M&As) since the late 1980s, and the industry appears to be in the midst of another wave in recent years (Figure 1(a)). The current wave is characterized by a gradual increase in high-value transactions (brown and yellow bars in Figure 1(b) and Figure 1(c)). This is partly because some middle-size pharmaceutical companies such as Bayer/Schering (2006) and Merck KGaA/Serono (2007) have tried to pursue global competitiveness through M&As. Another factor is a growing number of acquisitions of biotechs by large pharmaceutical companies, such as Amgen/Immunex (2002) and AstraZeneca/Medimmune (2007), as a result of the successful development of biotechs [1]. It is also noteworthy that small-size M&As constantly account for a major part of the deals (green and blue bars in Figure 1(b)). This is caused by many biotech start-ups combining together for growth toward integrated pharmaceutical companies [1]. In general, M&As seem to be functioning as an important measure for growth strategies in this industry.

Pharmaceutical executives have explained various rationales for M&As: enrichment of pipeline and products, acquisition of novel technologies, economy of scale in research and development (R&D) and in marketing, and expansion of corporate control [2]. Above all, a growing scarcity of pipeline and severe stagnancy in creating novel drugs, despite patent expiration of 35 blockbusters worth US$ 73 billion from 2002 to 2007 [3], has driven pharmaceutical executives to undertake M&As [4]. In practice, are their objectives achievable? The supplementation of pipeline in late-stage clinical development could possibly be achieved simply by legal completion of M&A deals, where collision of different corporate cultures and other formidable obstacles in the M&A process might be less significant. However, middle-term or long-term cooperation after M&A completion plays a key role in order to acquire drug candidates in early stages of development, programs of drug discovery, or basic technologies. For example, Merck & Co. acquired Sirna in 2006, in order to obtain the RNAi technology [5] and Johnson & Johnson acquired ALZA in 2001 for the Drug Delivery System (DDS) technology [6]. In these cases, substantial time and effort was required to achieve the objectives after M&A deals. Besides, regardless of their motivation, the long-term influence on R&D would vary with how inter-firm relationship is established. Subsequent to deal completion, most M&As involve integration of organization, personnel reduction, or other rationalization measures. The competitiveness of pharmaceutical companies largely depends upon scientists in R&D organizations,

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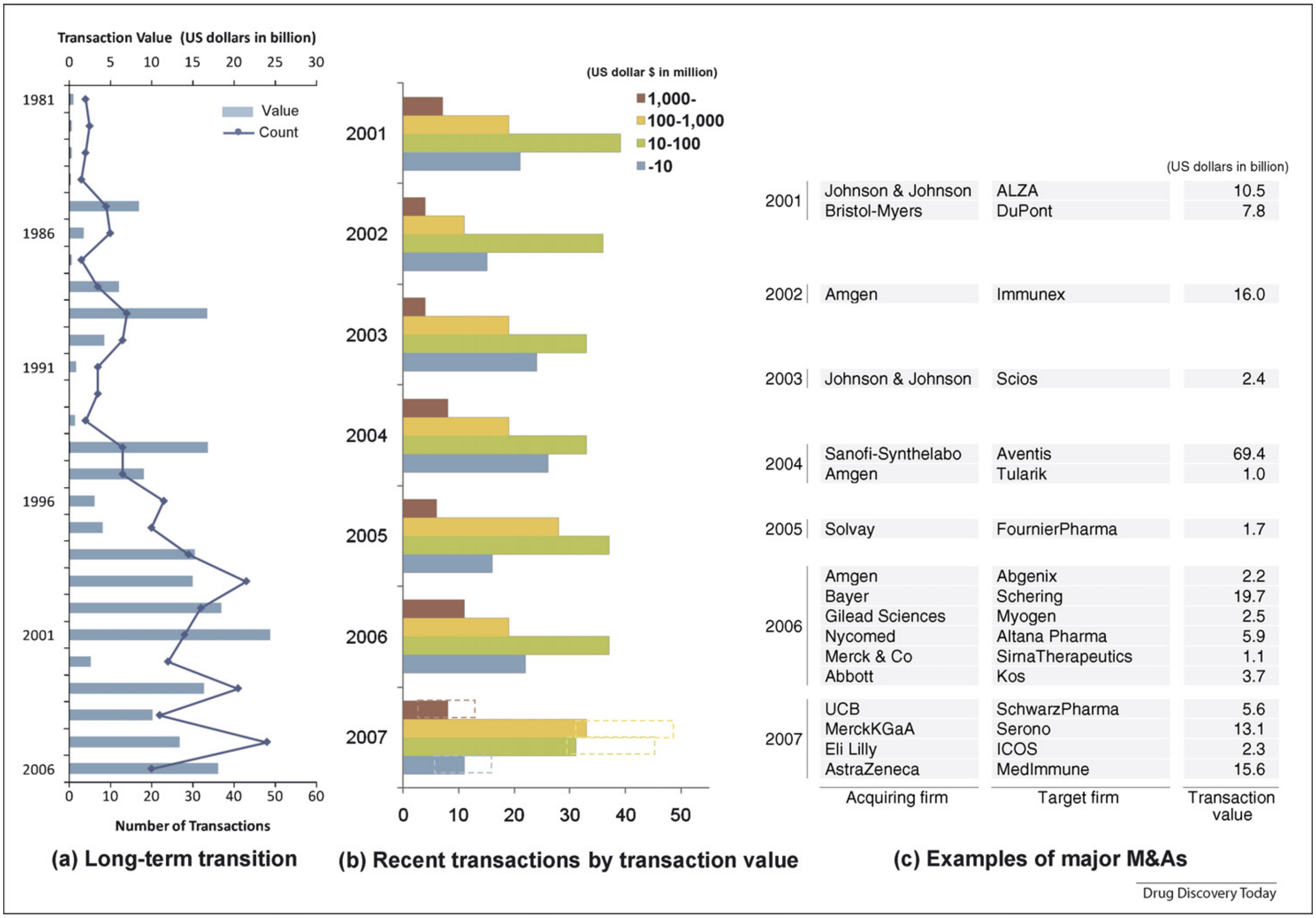

FIGURE 1

Transition of pharmaceutical M&As. **(a)** The long-term transition of M&As in pharmaceutical industry in the U.S. is shown. The data were collected from Mergerstat review (1981–2007) [41], where search criteria were that industry categorization was drug industry and the transaction value was disclosed. **(b and c)** The recent trend of M&As in pharmaceutical industry in the U.S. and Europe is shown. The data were obtained from M&A database 'Corpfin Wordwide.' Search criteria were that the acquirer's Standard Industrial Classification (SIC) code was 2834 and the transaction value was disclosed. The data for the year of 2007 are limited to January through August, so shadowed bars are also shown for the expected numbers.

as the industry is highly knowledge intensive. If the integration process discourages scientists and damages the R&D organization to the detriment of fundamental R&D capabilities, M&As cannot function as viable solutions for the industry-wide stagnancy in the discovery of novel molecules.

M&As impact on R&D activity has been studied in various industries [7–13]. The past decade has seen the emergence of some studies focusing on the pharmaceutical industry [1,2,4,14–18], although they have not reached a consensus. While a number of them indicated a rather negative effect [2,7–10,18], some suggested positive aspects in certain circumstances [11,15]. In order to disentangle these complicated explanations, the current article reviews previous studies and M&A cases from the macro-level and micro-level viewpoints and from the positive and negative sides. First, we mainly discuss shrinkage of internal R&D investment as a macro-level, or firm-level, negative effect. Second, various disincentives for individual scientists are argued as a micro-level, or personnel-level, negative effect. Third, complementarity of knowledge base is discussed as a macro-level positive factor. Last, we discuss the mechanism of knowledge-base transfer among scientists as a micro-level positive factor. In the last part, we refer to the results of our study on a Japanese pharmaceutical because previous research has not been well focused on this area. Finally, we summarize the above-mentioned viewpoints and suggest how M&As in the pharmaceutical industry could improve R&D and how they should be carried out, laying more emphasis on drug discovery for elucidating long-term impact.

Shrinkage of internal R&D

At the firm level, post-M&A performance could be reduced by various factors, such as the greater number of management levels and bureaucracy, geographical spread of facilities, and operational and organizational disruption [19]. Among these, decrease in R&D investment is noteworthy as a potential cause of declining R&D performance [7,9].

On completing M&As, management often tries to streamline their business by getting rid of redundancy, cutting off non-core businesses, and so on. R&D organizations are usually no exception: reduction of R&D expenditure, closure of research facilities, and layoffs of scientists in overlapping and non-prioritized therapeutic areas. In fact, previous mega-M&As often involved drastic reforms: 2000 scientists were made redundant by Pfizer/Pharmacia

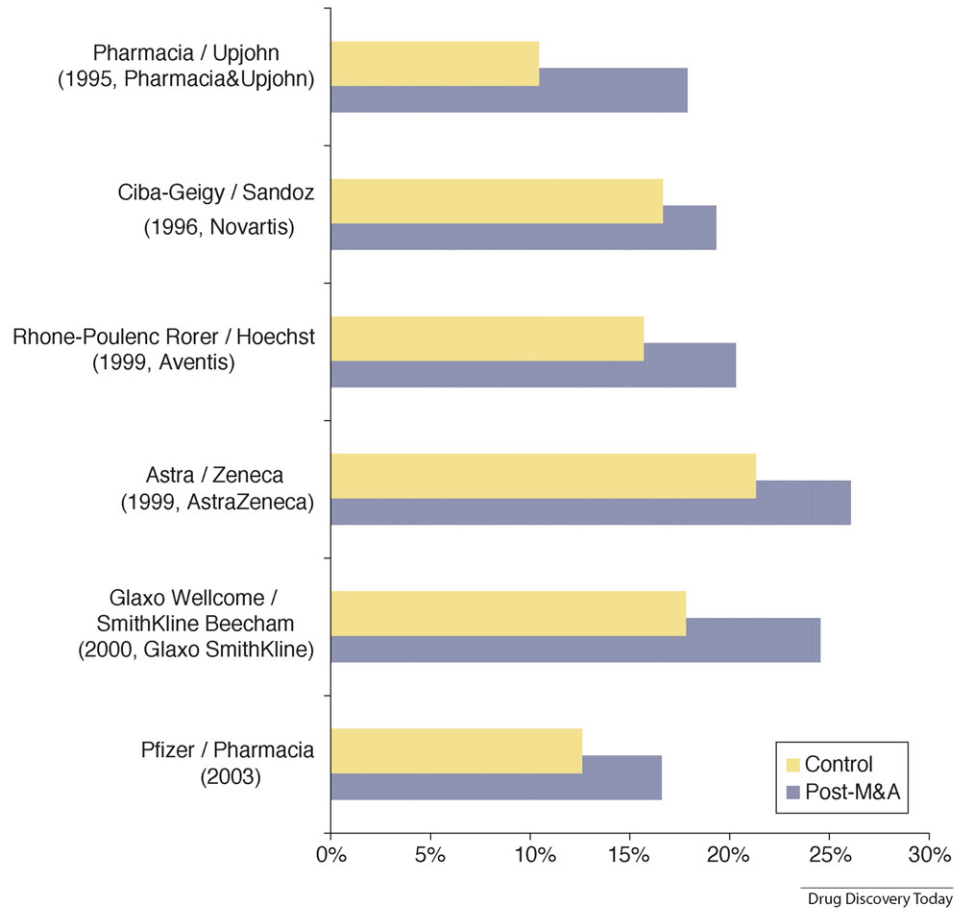

FIGURE 2

Turnover of scientists. Post-M&A scientist turnover is estimated for the six mega-M&A deals (blue bar). For comparison, turnover under ordinary conditions is also estimated for four years before each M&A (yellow bar). In every case, more scientists left the firms after M&As than the control. Turnover is estimated by the following procedure. Data of publications were collected from Web of Science. We supposed that a scientist left the firm when he or she published at least one scientific article in the year of or in the previous year of M&As but did not author anything from the same firm within three or four years after the M&As. Then turnover per year was calculated on the supposition of constant turnover during the time course.

(2003) [20]. In recent cases, Bayer/Schering (2006) had a plan to cut 1400 R&D staff by 2009 [21]. Eli Lilly, which acquired ICOS in 2007, has announced the layoffs of all 700 ICOS employees [22].

The above-mentioned downsizing is a temporary measure, taken during a few years after M&A completion. However, previous research has also reported that firms involved in M&As tend to reduce R&D inputs structurally, using multi-industry analysis based on finance and patent data [9]. When firms adopt M&As for supplementation of technologies, they also determine to re-direct their limited investment in internal R&D to the M&A activity. In the pharmaceutical industry, previous literature has reported that most large pharmaceutical firms increasingly rely on external sources for R&D [1], which might have resulted in reduction of investment in internal R&D activity [23].

In general, firms involved in M&As tend to tighten internal R&D input, when scientists are expected to work with more efficiency and mobility in leaner organizations. However, previous research indicated that R&D output declined simultaneously with decline of input [9]. Consequently, rationalization along with other factors sometimes leads to irrational outcome, bringing losses that are not outweighed by all the benefits of M&As.

Disincentives for scientists

Micro-level studies have also suggested various mechanisms of M&A demerits such as outflow of employees, anxieties and conflicts among employees, and collisions of different corporate cultures [24]. One of the simplest, and most serious, factors is the outflow of scientists. Figure 2 shows estimate of scientist turnover in several previous mega-M&As. Although some firms had relatively high scientist turnover before M&As, even higher turnover was observed in every case. This might cause outflow of invaluable knowledge assets and deterioration of R&D performance because not a small part of knowledge assets is embedded in each scientist [25]. Moreover, a previous study on M&As in R&D-intensive industries reported that approximately 50% of scientists with relatively higher achievement before M&As left the organization after M&As [10].

Although layoffs of scientists are not uncommon as a part of rationalization, management naturally expects superior scientists to remain with the firms. However, scientists frequently regard M&As as good opportunities to take redundancy compensation and move to other, more desirable, positions. Particularly, biotech start-ups have functioned as the destination for such scientists in recent years as a result of the successful development of biotechs [26]. Biotechs need talented and experienced scientists for their business expansion, and they are seeking the resource from large pharmaceutical companies [27].

On the contrary, how do M&As influence scientists who choose to remain, or have no choice but to stay on in the firm? The above-mentioned rationalization will lead to various influences on the laboratory environment. For instance, efficiency of R&D could decline because of breakdown of scientists' network and losses of intangible knowledge after scientist layoffs [18]. Pressure for reduction of daily expenses and orientation for short-term outcome might reduce R&D performance, as previous research has suggested those features of work environment impede scientists' creativity [28]. Furthermore, at least temporarily, the integration of organizations and operations possibly causes confusion, and labor that could otherwise be devoted to research activity is taken up in reorganizational activity [24]. These circumstances can easily demotivate scientists and lead to a deterioration in R&D output. An empirical study analyzed pharmaceutical scientists involved in M&As on the basis of patent data and showed the integration process hampered innovation produced by individual scientists [18]. As causes of this negative effect, they suggested that the scientists' network could be disrupted and that scientists could lose relative standing in laboratories when joined by superior scientists from partner firms. Furthermore, another study analyzed several acquisition cases of biotechs by pharmaceutical companies on the basis of interviews of management and scientists and indicated that forced integration of organizations could result in failure because of cultural disruption [17]. In fact, some cases preferred not to integrate in order to preserve autonomy or entrepreneurship, such as Roche/Genentech (1990) and Bayer/Chiron (1998).

Knowledge-based view of M&As

Contrary to the above-mentioned negative influences, recent studies, although in a minority, have implied positive effects of M&As [11–13,15]. Directing their attention to attributes of knowledge, they have examined how R&D output is improved by transferring and sharing knowledge base, such as scientific knowledge about disease, mechanism of organisms, and molecules, experimental technique, and skills and other knowledge.

One of the studies empirically showed that the number of phase 1 drug candidates increased when M&As were conducted by firms with a certain technological complementarity [15]. Another studies indicated that post-M&A innovation increased in technologically complementary firms, when innovation was measured by the number of patents [13]. This positive effect would be attributable to economy of scope for compound library, assay systems, and other technologies. For example, a compound library from one firm might be applied to an assay system developed by the other to create new lead compounds. Moreover, partner firms could revive and continue R&D projects that had gone out of main therapeutic areas or were not successful in original firms. These beneficial effects are consistent with what most pharmaceutical companies have insisted as rationales for M&As. Recent deals, such as Solvay/Fournier (2005) [29] and Merck KGaA/Serono (2007), have also claimed that complementary therapeutic areas would benefit their R&D activity [30]. However, previous literature also suggested that a certain level of common knowledge base is essential to take advantage of complementary technology of the other firms [11,13,15]. Thus, acquirers should not be too inexperienced in the field of target firms to utilize their knowledge base. In this respect, when firms with a single therapeutic area acquire other firms in other areas, which is sometimes the case for biotech start-ups expanding their business, they might need more efforts in making the most of targets' technologies.

From different viewpoints, some reports have referred to the relative size of knowledge base [11,13]. They showed that post-M&A innovation measured by the number of patents was improved when the acquirer's knowledge base was relatively larger than that of the target. More concretely, this finding indicates that acquisitions of small biotechs by pharmaceutical companies have good possibility of success, which is welcome news, given that such deals account for a certain amount of recent cases. On the contrary, the result also suggests that M&As between firms of equal size is likely to result in difficulty in integration of knowledge base, which should sound a note of warning for middle and large pharmaceutical companies seeking economies of scale.

Mechanism of knowledge-base transfer

It seems a reasonable explanation that M&As improve R&D output under the condition of a certain understanding of mutual technological fields. This raises the assumption that the post-M&A knowledge-base transfer is not an impersonal short-term transaction, but a middle-term or long-term transaction, requiring relationship development between scientists. Although micro-level research is inevitable to answer this question, previous research has seldom dealt with this issue. The authors' group is tackling this issue through a study on drug discovery scientists involved in M&As. For further discussion, we illustrate some results of our study. It deals with a Japanese pharmaceutical company, Astellas Pharmaceutical, which was formed as a result of a merger in 2005 (Box 1). We think that the Japanese pharmaceutical firm could be an appropriate sample for the purpose, because Japanese society has had a highly M&A-sensitive environment, and their M&A approach has been generally employee oriented [31]. The Japanese pharmaceutical industry had seldom experienced M&As until quite recently, and the job market of scientists had been so stagnant that post-M&A outflow of scientists was less intense. These features are atypical compared to the ordinary Western firms and could provide us with new perspectives.

Performance improvement by knowledge-base transfer

In our study, we employed survey and interview as the main data source (Box 1) and analyzed how knowledge was transferred among scientists and how their performance changed after the merger (Figure 3). First, we examined whether transfer of knowledge base contributed to research performance of drug discovery scientists. The result shows a positive relationship between knowledge-base acquisition and performance (1), suggesting that acquisition of knowledge base leads to research performance at individual scientist level. Our in-depth analyses also implied that knowledge in inexperienced field originating from the partner firm contributed to their research progress (Box 1).

At this point the question must be asked: did this knowledge-base acquisition require scientist interaction, or could it occur

BOX 1

Summary of a Case Study of Astellas Merger

Company background [38–40]

Astellas Pharmaceutical was formed as a result of a merger between Yamanouchi Pharmaceutical and Fujisawa Pharmaceutical in 2005. It is headquartered in Japan, achieved annual sales of JPN¥880 million, had 15 000 employees, and 1100 scientists in research division mainly in four Japanese sites (2006). Both pre-merger firms had been in strong position in Japan (third and fifth in the domestic sales share in 2003). They shared main research areas of diabetes, urology, and central nervous system, and besides, Yamanouchi had cardiovascular, gastrointestinal, and locomotorium, while Fujisawa had immunology, inflammation, and infectious diseases. They had approximately the same size of research assets including two main research sites in Japan

Merger process

On the merger, Astellas reorganized their R&D organization on the basis of therapeutic areas. Because the two pre-merger firms targeted partly different and partly the same therapeutic areas, some laboratories consisted of scientists well mixed from both firms and others mainly from either one firm. In both types of laboratories, scientists were sometimes assigned to projects consisting of members from both firms for better mutual understanding and synergy effects. Astellas basically aimed at soft landing of the merger process and avoided hasty downsizing, although early retirement system was offered before the merger and about 10% employees applied for it. Currently, Astellas plans to conduct further restructuring including R&D organizations, such as additional early retirement, employee transfer to subsidiaries, and integration of R&D facilities.

Comments from in-depth analyses

Management

"Drug discovery highly depends on research approaches of individual scientists. If they are in a closed world, their approaches would come to dead end. The collision of different cultures will develop our research approaches dialectically. Thus, we will merge research organizations in a flexible manner, regardless of pre-merger careers."

Scientist supervisor

"I prepared internal seminars and other places for face-to-face discussion to facilitate understanding of mutual knowledge. I also paid attention to the arrangement of laboratory desks to promote the inter-firm communication."

"I organized project members whose combination was likely to lead to synergy effects, considering personality and previous outputs of each scientist from both firms."

Scientist

"We could seldom learn in-depth know-how and implications from the previous alliances and co-researches. This merger gave us an opportunity not only to expand our knowledge but also to understand the reality of other approaches."

"I found substantial difference in the approaches between both firms, such as designing of chemical compounds. We have improved our research performance by making good use of both features."

Study design

Our study consists of the following three parts. First, we conducted face-to-face interviews with seven management members and six well-experienced scientists in manager rank. Second, we carried out a small-scale survey on 20 scientists from various departments and job ranks followed by e-mail-based questions and answers. Third, we conducted a large-scale survey on scientists. These respondents were selected as follows. Scientists were categorized into three types; supervisors who had responsibility for laboratory management (10%), leader scientists who played the principal role in designing, managing, and conducting individual research works (30%), and ordinary scientists who work under the control of leader scientists (60%). We focused on the leader scientists and requested their surveys. Furthermore, we also requested the supervisors to assess research outputs of the leader scientists. The valid response ratio for the leader scientists was 89% (193 valid responses).

without such human relationship? Varieties of measures could possibly facilitate the knowledge-base acquisition among scientists, such as mixture of scientists from both firms and supervisors' leadership. Furthermore, scientists' background such as age and academic career might affect. Thus, we analyzed the effects of various factors on the knowledge-base acquisition. Here, we observed a statistically significant positive relationship between the knowledge-base acquisition and scientist interaction (3). Because of their merger process (Box 1), the extent of interaction with partner scientists varied considerably from case to case. The result suggests that the knowledge base was transferred more efficiently with direct interactions among scientists. It also shows that knowledge base was efficiently transferred when scientists' supervisors facilitated communication between the two firms (4). Moreover, the knowledge-base acquisition was promoted by the laboratory climate that put importance on creative work and autonomy (5). Additionally, we analyzed a negative impact of the merger process, which indicated scientists failed to acquire knowledge base when they were stressed by the merger process (6). Thus, the scientists acquired knowledge base from the partner and improved on their performance, when the inter-firm interaction was encouraged by integration of laboratories, formation of combined project teams, and other channels facilitated by supervisors, and where they had creative climate in the workplace and the stress from the merger was sufficiently reduced. As mentioned above, scientists have often been laid off by acquiring firms. However, this result indicated that hasty downsizing might lose the opportunity to obtain invaluable knowledge assets from partner firms.

Diversification of research approach

The above discussion focused mainly on what is called knowledge or expertise. In other words, we argued that scientists could improve in performance when they learned scientific knowledge or experimental techniques from the partner. While this effect is basically important, we observed another beneficial phenomenon related to knowledge. In the following, we will discuss this noteworthy effect of M&As, namely, diversification of research approach.

Although 'approach' usually reminds us of drug discovery approach at strategic level such as target based and function based [32], we focused on research approach at the individual level. In this, we have included paradigms, viewpoints, routines, and principles regarding research activity [25,33]. They are usually

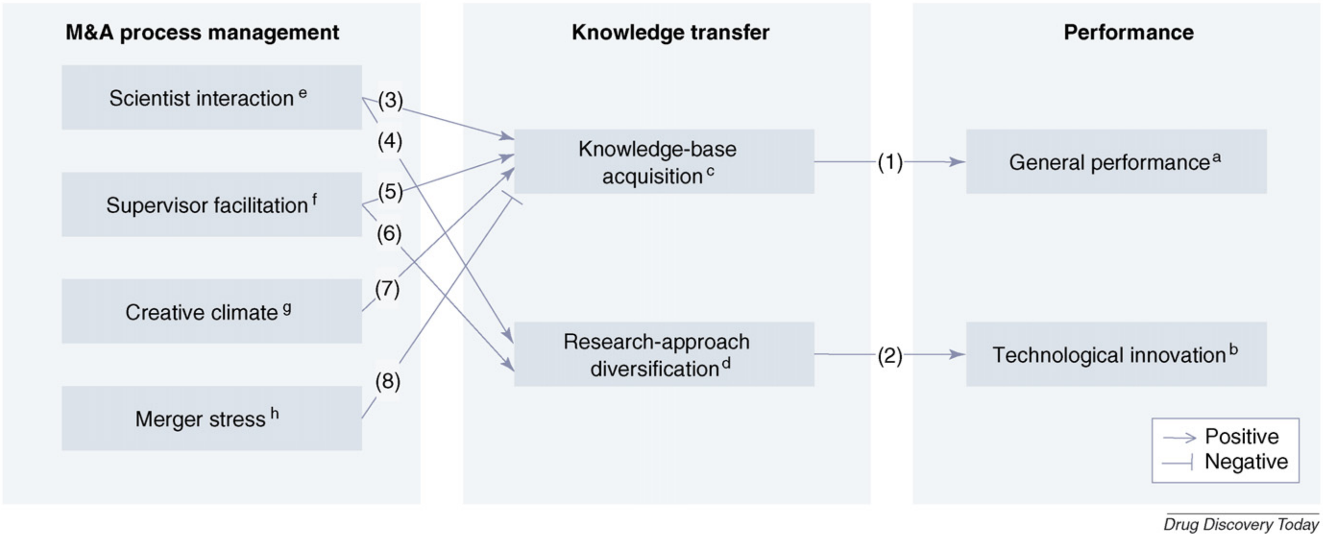

FIGURE 3

Effect of knowledge-base transfer. The result of structural equation modeling is shown. All indicated relationships are statistically significant ($P < 0.05$). Indicators for model fitting are χ^2 (22) = 131.09 ($P < 0.001$), GFI = 0.90, CFI = 0.69, and RMSEA = 0.16. For each variable, sources of data and examples of questionnaires are as follows: [a] supervisors assessed their subordinates in '*progress of projects*', '*technical quality*', '*value to the laboratory*', and '*overall performance*'; [b] supervisors assessed their subordinates in '*outputs which represented a major technological advance over existing technologies, or outputs which made prevailing technologies obsolete*'; [c] scientists assessed to what extent they acquired '*research data and knowledge peculiar to the partner firm*' (11 items); [d] scientists assessed to what extent they expanded '*viewpoints for interpreting the result and data of experiments*' (9 items); [e] we counted the number of scientists in the same laboratory or in the same projects from the partner firm; [f] scientist assessed their supervisors by '*my supervisor facilitated communication between both firms*' (2 items); [g] scientists answered '*new ideas or concepts are fostered in my laboratory*' (4 items); [h] scientists answered '*I feel insecure about my future career*' (4 items). We controlled scientists' pre-merger performance measured by published journals and scientists' tenure, which significantly associated with performance measures, although the illustrated relationship did not lose significance. Questionnaire items were measured by Likert-type scales, and most of them are based on previous studies. Details of questionnaire should be requested to the authors.

embodied in scientists' behaviors and thoughts: what type of research project is preferred, how theory is developed, what alternative is chosen when more than one experimental procedure is available, what countermeasure is taken when negative data are obtained, and so on. The interview results implied that scientists felt considerable difference in research approaches of the partner scientists (Box 1). Some scientists mentioned that they found the techniques and modes of work they had taken for granted before the merger were not necessarily common. In the pharmaceutical industry, the R&D process takes an extremely long time, which sometimes results in changelessness and persistence of their existing ways of work. In this respect, M&As could be ideal opportunities for scientists to review their approaches and to change their paradigms.

Thus, we examined how scientists were influenced by the different research approaches of the partner firm. We had expected that change in research approaches had the potential for fundamental improvement in research output because the approaches influence scientists' behaviors and thoughts on a high plane. Figure 3 demonstrates positive relationship between diversification of research approaches and technological innovation after the merger (2). It suggests that scientists with diversified research approaches came to create more innovative, fundamentally improved, technologies, such as novel drug candidate molecules, unique routes of chemical synthesis, original assay system, and useful research tools. Diversification of research approaches expanded options for action and decision-making in various situations, which might result in the improvement of the innovativeness.

Next, we examined how each scientist has diversified in their research approaches. First, we observed a positive effect caused by the interactions with partner scientists (7). This indicates that scientists have recognized different research approaches in partner scientists, reviewed their own approaches, and diversified them when they had enough interaction with partner scientists. Moreover, the result shows the importance of supervisors' facilitation for the scientist interaction (8). The in-depth analyses indicated that some supervisors prepared informal discussions, cross-firm seminars, and other opportunities for inter-firm interactions (Box 1), which proved to be effective for diversification of scientists' approaches.

Because the research approaches are usually built under the long-term influence from workplace surroundings, fresh approaches are difficult to absorb for scientists who have been in stable circumstances for a long time. In this regard, M&As could function as opportunities where different types of approaches are compulsorily blended, inducing variation of behaviors and thoughts of individual scientists. What is called knowledge or expertise can be acquired through co-research, a technical tie-up, or attending an academic meeting, even if M&A is not feasible. However, research approaches are difficult to transfer through such interaction because they are highly tacit and embedded more deeply in individual scientists. Therefore, the benefit of diversification of research approaches is regarded as a specific phenomenon for M&As.

Conclusion

Previous research has reported the rather negative impacts of M&As on pharmaceutical R&D activity. They indicated reduction of R&D input, disruption of scientists' network, and other inhibiting factors. On the contrary, some recent reports have taken up positive side of M&As, focusing on attributes of knowledge-intensive industries. They pointed out the beneficial effect of complementarity of knowledge base between firms. In general, M&As have both negative and positive impacts on R&D activity in a complex manner. However, most studies have used firm-level observations and depended on public information for the data source with a few exceptions [12,17,18]. This might have resulted in gauging aggregate superficial outcome and disturbed understanding of complicated phenomena. The future research should solve the limitation of research design and deconvolute these complicated effects. In this respect, micro-level and in-depth analyses could be helpful. One of the examples is the authors' study, which tries to elucidate the merger impacts by scientist-level in-depth observation. It indicated that scientist interaction promoted transfer of research approaches as well as knowledge base to improve research performance and technological innovation. These findings are noteworthy because the improvement in the capabilities embedded in individual scientists could benefit the research organizations over a long period of time.

In practice, could the beneficial effect due to scientist interaction be applicable to other M&A cases? It might appear that the Astellas case was peculiar in the employee-oriented culture and the weak pressure for rationalization. Although few cases have been studied from the viewpoints of the scientist interaction, we assume that some previous cases have enjoyed this merit and that it could be applicable to certain cases. For example, biotechs pursuing business expansion by M&As would be appropriate: in the case of Amgen/Immunex (2002), Amgen expanded their research campus in Seattle to consolidate former Immunex laboratories [34]. As the firms were in the growth stage, they had less pressure for rationalization, which might have facilitated their interaction. However, even though the firm has strong pressure toward downsizing, the effect of scientist interaction could be beneficial nevertheless. When Ciba-Geigy and Sandoz, both Switzerland based, merged into Novartis in 1996, 10% of R&D expenditure was reduced and 30% of clinical development projects were terminated [35]. However, the case was reported to be successful in the integration of organizations, possibly because of their similar corporate cultures. The difference in corporate culture is often indicated as a barrier for integration [17]: some previous acquisition cases of biotechs by pharmaceuticals preferred certain autonomy to full integration, such as Bayer/Chiron (1998) and Astrazeneca/Chembridge Antibody Technology (2006) in order to avoid the culture disruption. On the contrary, in the case of Sandoz/Genetic Therapy (1995), the acquirer chose to integrate the target firm. Thus, the extent of integration could depend upon corporate cultures and other circumstances. Besides, geographical issues may be significant; it might be impractical to integrate laboratories in distant locations. In cross-national M&As, for instance, their post-M&A interaction would depend on the ability to enter into international collaboration, which is another important issue in the R&D arena [36,37]. When research facilities of both firms are nearer to one another, they could integrate their organizations and, if necessary, downsize them simultaneously. In the cases of Myogen/Gilead (2006) and Biogen/Idec (2003), both U.S.-based biotechs established new research facilities after their M&As. The above-mentioned examples imply that the benefit of scientist interaction could be applicable to certain cases. Although each case must have each difficulty in the integration process, management should consider the integration of research organizations as a measure of long-term reinforcement of the research capabilities, whereby each scientist improves in fundamental capabilities by expanding knowledge and approaches.

Disclosure statement

Mr. Sotaro Shibayama had been a consultant before beginning this work, when Yamanouchi Pharmaceutical, a pre-merger firm of Astellas, was one of his clients. Mr. Kunihiro Tanikawa has had no relationship that might inappropriately influence the current work. Dr. Ryuhei Fujimoto is an employee of Astellas. The laboratory of Prof. Hiromichi Kimura has accepted cooperative researchers and received research fees from Astellas.

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