

RESEARCH PAPER

The importance of drug target selection capability for new drug innovation: definition, fostering process, and interaction with organizational management

Ryo Okuyama and Masaharu Tsujimoto

Department of Innovation Science, School of Environment and Society, Tokyo Institute of Technology, Tokyo 108-0023, Japan

ABSTRACT

The productivity of new drug discovery has not changed for decades, although the information on physiological functions and molecules, which are the sources for new drug discovery, has markedly increased. Furthermore, technologies for lead compound acquisition and compound optimization for creating drug candidates have greatly progressed. One possible reason for this low productivity is that it is still difficult for drug discovery researchers to correctly evaluate and select physiological mechanisms that could be drug targets. Nevertheless, there are very few studies on drug target selection capability, specifically on researchers' capability to determine whether modulating the function of a newly discovered physiological mechanism would be a suitable therapeutic option for a certain disease. How is this capability developed? In this study, we propose that the long-term experience of researchers in investigating disease causes and existing drug action mechanisms contributes to enhancing their insights into druggable physiological mechanisms, based on the comparative analysis of cases that were focused on the same physiological mechanism, where one was successfully developed as an innovative new drug while the other failed. We also discuss managerial practices to strengthen capability.

Introduction

New drug discovery and development processes have an extremely high attrition rate, and the success rate from the discovery research stage to market approval is reported to be only 0.1% (Bioscience Innovation and Growth Team, 2004). Moreover, R&D efficiency in new drug discovery and development has not improved in the last 50 years (Munos, 2009, Scannell *et al.*, 2012). The number of US Food and Drug Administration (FDA)-approved drugs per year has flatlined (Munos, 2009), while approval of new drugs per R&D expenditure has declined because of increased R&D investment by pharmaceutical companies (Scannell *et al.*, 2012). Because the R&D process of new drug discovery and development includes research (the phase that identifies new drug candidates) and clinical development (the phase that tests drug candidates in humans), it might be thought that the attrition rate at the clinical development phase has increased. However, the probability of drug candidates successfully completing clinical trials from phase 1 to new drug approval has remained constant for the last 50 years (DiMasi *et al.*, 2010; Smierana *et al.*, 2016). This observation means that the efficiency of the research phase has not improved either. This phenomenon is an apparent paradox because information on physiological functions and molecules which could be a source of

new drug discovery has increased markedly because of biotechnological progress and because technology for lead compound acquisition and optimization for obtaining drug candidates has improved (Varmus, 2010; Munos, 2016).

A possible reason for the lack of improvement in new drug R&D efficiency, despite the progress in basic biology and drug discovery technologies, is the persistent difficulty drug discovery researchers face in determining whether modulating a physiological mechanism could be a novel therapeutic option for a certain disease. Before the 1970s, drug discovery researchers identified new drugs mostly by directly treating animals/cells with compounds and by observing the effects (the phenotype-based approach). Subsequently, increased information on physiological mechanisms enabled drug discovery researchers to identify new drugs by determining certain physiological mechanisms/molecules to be drug targets and identifying compounds that modulate the function of the target mechanisms/molecules (the target-based approach). However, it has been reported that the target-based approach did not increase (or even reduce) the efficiency of new drug discovery (Swinney and Anthony, 2011; Gittelman, 2016). This observation suggests that the efficiency of selecting correct drug target mechanisms by drug discovery researchers has not improved, although the information on physiological mechanisms has increased.

Over the last two decades, approaches have been developed for seeking novel drug targets by identifying genes/proteins that are differentially expressed between normal and disease tissues using newly developed omics technology and by identifying disease-sensitive genes in genome-wide association studies (GWAS) (Stranger *et al.*, 2011; Galizzi *et al.*, 2013). However, there have been very few successful cases where the targeted mechanisms of new drugs that reached the market were identified (Folkersen *et al.*, 2015; Nagano and Higashisaka, 2016). Therefore, the effectiveness of such approaches has been questioned. Taken together, these observations suggest that drug discovery efficiency has not improved because of the lack of improvement in drug discovery researchers' capability to evaluate the suitability of physiological mechanisms as drug targets, despite the large increase in physiological information.

Conversely, strengthening researchers' capability to evaluate whether modulating the function of certain physiological mechanisms/molecules by drugs could be a relevant therapeutic option for a certain disease would increase the extremely low success rate of new drug discovery, and provide competitive advantage for drug discovery researchers in the pharmaceutical industry. AstraZeneca's analysis of its internal projects also identifies that selecting the right drug targets in the early discovery phase is an important success factor for drug discovery projects (Cook *et al.*, 2014).

Therefore, the research question of this study is how such drug target selection capability is fostered. Once novel physiological mechanisms applicable to new drug discovery are identified, some researchers successfully evaluate the drug target potential of the mechanisms, which leads to drug discovery. However, others fail to evaluate correctly whether the mechanisms apply to drug discovery. Therefore, there must be a difference in the drug target selection capability of drug discovery researchers. If the factors determining the difference in capability could be identified, pharmaceutical companies could improve the low success rate of drug discovery processes and gain a competitive advantage in new drug discovery by implementing management practices to strengthen these factors.

This study focuses on an extremely important issue in drug discovery research management. Nevertheless, this point has not been sufficiently addressed in previous studies. Previous studies report that drug discovery research is not manageable because of its extremely high uncertainty (Kuwashima, 2006; Nagaoka, 2016). Reports indicate that it is important for corporate researchers to increase the collaboration with academic researchers, who mainly conduct basic biomedical research to elucidate physiological mechanisms (Cockburn and Henderson, 1998; Furukawa and Goto, 2006). In addition, there is consensus that it is important for corporate researchers to strengthen their absorptive capacity by conducting basic research of their own similar to that of academic researchers (Fabrizio, 2009; Toole, 2012). Pharmaceutical companies have been actively collaborating with researchers in academia and have increased their investment in basic research, but this has not

improved drug discovery research efficiency. Thus, drug discovery efficiency does not increase without appropriate selection of ‘druggable’ physiological mechanisms, although drug discovery researchers can become familiar with newly discovered physiological mechanisms through increased connection with academic researchers and strengthened absorptive capacity.

Previous studies on absorptive capacity have debated the capability of transforming and exploiting external knowledge for product innovation (Zahra and George, 2002). These studies focused mainly on organizational capability (Apriliyanti and Alon, 2017). Individual champion-like researchers play a key role in product development, such as drug discovery (Kuwashima, 2006), but how the capability of transforming basic science into product innovation is formed at an individual level has not been sufficiently studied. Nor has how the capability affects the competitive advantage of product development through interaction with organizational management been explained. This study discusses the factors that foster the capability of drug discovery researchers to determine correctly whether a novel physiological mechanism is applicable to drug discovery. How the individual capability and organizational management interact and affect the competitive product development of companies will also be addressed.

Case analysis is appropriate for seeking factors and processes that have not yet been fully identified. Here we focus on the individual-level capability of drug discovery researchers and discuss the processes that foster the drug target selection capability of researchers by comparing two drug discovery cases. Both cases focus on the same physiological mechanism. One successfully identified the mechanism as a drug target for a certain disease, while the other failed to do so. We also analyse organizational management affecting the drug target selection capability of individual researchers and discuss research management strategies that pharmaceutical companies should implement to strengthen the factors that foster capability.

Theoretical background and literature review

How the drug target is selected

Once novel physiological mechanisms/molecules are identified using basic biomedical research, these mechanisms could be the source of new drug discovery. Cockburn and Henderson (1996) demonstrate that key scientific discoveries that enabled the discovery of new drugs were made by academic researchers and the scientific discoveries were subsequently applied to new drug creation by corporate researchers in new drug discovery. In the case of captopril, an inhibitor of the angiotensin-converting enzyme (ACE), academic researchers discovered ACE. Because ACE is the enzyme that converts angiotensinogen into angiotensin, which raises blood pressure, the blockade of the ACE function was expected to reduce blood pressure. Corporate researchers who focused on this notion created captopril and developed it as an antihypertensive drug. In this manner, if the modulation of the function of a newly discovered physiological mechanism/molecule is expected to ameliorate certain disease symptoms, the physiological mechanism/molecule is selected as a drug target, which drug discovery researchers pursue. This is the typical strategy of drug target selection.

However, the low success rate of drug discovery indicates that the selection of physiological mechanisms/molecules as drug targets using simple predictions based on the function of the physiological mechanisms/molecules does not provide suitable drug targets efficiently. As described in the introduction, the target-based drug discovery approach that focused on specific physiological mechanisms uncovered by biotechnology was no more efficient than the old-fashioned phenotype-based drug screening for drug discovery. The recently developed omics technology, which enables researchers to select differentially expressed genes and proteins between normal and diseased tissues, has produced only a few examples of successful identification of drug targets (Varmus, 2010, Nagano and Higashisaka, 2016). Among the many criticisms of the methodology of omics technology is the lack of clarity on whether the differential expression levels actually cause the diseases or are just reflections of the disease status, and whether the expression level of genes, proteins, and

metabolites always changes, and, therefore, this parameter at a single time point is not relevant or reproducible (Plymoth and Hainaut, 2011; Savino *et al.*, 2012; Yan *et al.*, 2015).

GWAS, which determines disease-associated genes from single nucleotide polymorphisms (SNPs), was also expected to increase identification of drug targets, but this approach has produced very few drug targets (Folkersen *et al.*, 2015). GWAS simply identifies the correlation between disease etiology and SNPs. Therefore, the relevance of the genes as therapeutic targets is still unknown, and the contribution of each of the identified genes to the disease etiology may be low (Nadeau and Dudley, 2011; van der Sijde *et al.*, 2014). Accordingly, the considerable progress made in basic biomedical research and technology evolution over the decades has not sufficiently contributed to the improvement of drug target selection capability.

Importance of drug target selection in drug discovery competitiveness

New drug discovery processes have an extremely high failure rate (Bioscience Innovation and Growth Team, 2004). Only a few corporate drug discovery researchers succeed in correctly selecting applicable basic research findings and producing novel drugs, whereas others lose the same drug discovery opportunities without appropriately evaluating the application potential of scientific discoveries. Furthermore, many drug discovery researchers select basic research findings that are ultimately unsuitable as new drug targets. Basic biomedical research, mainly conducted in academia, is the source of information on new physiological mechanisms that apply to drug discovery. The research outcomes are published in most cases and so are available to drug discovery researchers. Nevertheless, some researchers succeed in transforming certain scientific discoveries into new drugs while others fail. Therefore, it is fair to consider that there is a difference in some capabilities of drug discovery researchers.

Actually, the importance of drug target selection has been highlighted in the analysis of drug projects in pharmaceutical companies. AstraZeneca analysed the success factors of their projects and determined that selecting the right drug target in the early discovery phase is crucial in determining the fate of drug discovery and development projects (Cook *et al.*, 2014). In their follow-up analysis, Morgan *et al.* (2018) report that ‘A selective high-quality molecule will never become a medicine if the target it modulates is not the “right target.”’

Researchers’ ability to select an appropriate drug target

Despite the importance of drug target selection for the competitiveness of new drug discovery, little has been said about factors that affect this capability. This is partly because the literature says that basic medical research has inherent application potential (Rosenberg and Nelson, 1994; Stokes, 1997). Comroe and Dripps (1976) emphasize that a considerable amount of biomedical research has an application focus to resolve clinical issues, as well as aspects that pursue fundamental understanding of biological, chemical, and physiological mechanisms. Stokes (1997) refers to use-inspired basic research that offers both significances, in that these studies extend the frontiers of understanding, which can be linked to applications. The study opined that basic research that falls into this category is in the Pasteur quadrant. Pasteur was a researcher who pursued a basic understanding of microbiology while also aiming to prevent the decay of foods and beverages. Pasteur-type researchers who succeed in achieving both basic and applied studies have significantly contributed to product development achieved through collaboration between the industry and academia (Fabrizio and Di Minin, 2008; Baba *et al.*, 2009). Therefore, it is widely accepted that biomedical research not only has features of basic science, but also has application potential. Thus, the research findings are automatically applied to drug discovery if they have such potential. However, as described above, the dramatic increase in biomedical information and technological advancement, such as omics and GWAS, have made little contribution to increasing the capability of drug target evaluation. Therefore, it is obvious that the discovery of new physiological mechanisms is not automatically translated into drug application.

Some reports highlight the importance of increased connection to academic researchers in drug discovery because basic academic research is the main source of potential drug targets (Cockburn and Henderson, 1998; Tralau-Stewart *et al.*, 2009). Therefore, the importance of a strong tie with academic researchers who mainly conduct basic research has repeatedly been emphasized (Cockburn and Henderson, 1998; Furukawa and Goto, 2006). In terms of the success of biotech companies, collaboration with high-performing ‘star’ researchers in basic research is important (Zucker *et al.*, 2002). In addition, there is a strong connection between the publication of cutting-edge research papers and technological development (Powell *et al.*, 1996). In contrast, other scholars have reported that the citation rate of related papers and patents shows a negative correlation, and important scientific discoveries do not produce innovations with major impact (Gittelman and Kogut, 2003). Moreover, star researchers do not have a positive effect on the number and citation rates of patents (Hess and Rothaermel, 2011). These studies imply that a capability, which differs from that of basic research, is required to connect basic research findings to drug applications. Previous studies have not sufficiently discussed what this capability is, and how it is formed and affected by organizational management.

To utilize basic research findings for product development, corporate researchers should perform their own basic research and strengthen their ‘absorptive capacity’ to understand outside basic research outcomes (Cohen and Levinthal, 1990). The importance of absorptive capacity has often been cited in drug discovery (Fabrizio, 2009; Toole, 2012). These studies focus on the capacity to research basic science, which corresponds to potential absorptive capacity that acquires and assimilates external new knowledge (Zahra and George, 2002). On the other hand, some absorptive capacity studies argue about the concept of ‘realized absorptive capacity’, the ability that transforms and exploits the acquired external knowledge for product innovation (Zahra and George, 2002). These absorptive capacity studies have mainly focused on organizational capacity, such as intra- and inter-organizational learning and knowledge transfer, and dynamic capability (Apriliyanti and Alon, 2017).

The individual capability of a champion researcher plays a key role in drug discovery (Kuwashima, 2006). It is an individual researcher’s idea to evaluate and select drug targets from physiological mechanisms discovered in academic biomedical research. Once a drug target is selected, a small drug discovery research team is formed, which is normally led by the researcher who proposed the drug target. Such a research champion plays a key role in drug discovery projects (Kuwashima, 2006; Nagaoka, 2016; Okuyama, 2017). In addition, the probability of success is extremely low for drug discovery and development projects, and only a handful of new drugs support a corporation’s business performance. Thus, increasing the number of projects that produce marketed drugs is essential for a corporation’s growth. Management research that focuses on individual drug discovery researchers and research teams is consequently more important than research focusing on the entire organization. For this reason, previous studies that focus mainly on organizational capacity are insufficient. Gittelman and Kogut (2003) suggest that a ‘bridging scientist’ is needed to close the gap between science and innovation in the biotechnology industry, based on the observation that citations are negatively correlated to patents and papers. However, their studies and those of others do not address the issues of what kind of capability is required for the bridging scientists, how the capability of such individual researchers is formed, and how capability building and organizational management interact, which are the central research questions of our study.

Our research aims to address how the ability of drug discovery researchers to transform basic science knowledge into drug applications is formed. Furthermore, we focus on how such capability provides a competitive advantage to individual drug discovery researchers. For corporate researchers who work for companies, the development of the capability of individual researchers is associated with organizational management. Therefore, our study also addresses how each drug discovery researcher and organizational manager interacts, and how this affects product innovation. A few studies have focused on the ability of individuals to transform external knowledge into product innovation in the context of absorptive capacity. Gittelman and Kogut (2003) suggest that a

‘bridging scientist’ who crosses the gap between science and innovation is important, but the paper does not mention anything about the research capability requirements of bridging scientists. We believe that our study will contribute to filling this gap in the literature.

Clarification of the drug discovery research phase

The selection of physiological mechanisms is the initial step in drug discovery research. Once a certain physiological mechanism/molecule is selected as a drug target for a certain disease, applied research (including acquisition of lead compounds that modulate the function of the selected drug target mechanism and compound optimization to create clinical candidates) is conducted. To avoid confusion, this study focuses on the drug target selection step, which is the initial step in drug discovery research, and does not include the subsequent applied research phase. Significant technological advancements have been made in lead compound acquisition and optimization for decades. The high-throughput screening system allows lead compounds to be identified by the random screening of millions of compounds (Hertzberg and Pope, 2000). Compound optimization technologies, such as absorption, distribution, metabolism, and excretion (ADME) prediction (Kirchmair *et al.* 2015), safety assessment (Holmes *et al.*, 2015), and protein crystallography (Erlanson *et al.*, 2016), have made great progress. Antibody medicines have become popular, and new drug modalities, including nucleotides and cells, have emerged in addition to the conventional small-molecule drugs. Therefore, the options to modulate the function of targeted physiological mechanisms/molecules have increased (Dimitrov and Marks, 2009). This means that the correct identification of drug target mechanisms would enhance the efficiency of drug candidate creation. Nevertheless, currently, the overall efficiency of drug discovery has not improved because of the persistently poor ability of drug target selection. This study focuses on the drug target selection step, which is prior to the compound acquisition and optimization steps. There is no doubt that much discussion is still needed to address the technological and managerial issues in the compound acquisition and optimization steps; even so, our focus in this study is the drug target selection step, which is a bottleneck of the drug discovery process.

Research framework

This study aims to identify the factors that formulate drug target selection capability from a detailed analysis of drug discovery research processes that focus on newly discovered physiological mechanisms. We also discuss how individual capability and organizational management have interacted and affected the innovation of a company in the cases analysed. A case study is suitable for seeking factors that have not been fully explored (Edmondson and McManus, 2007). The purpose of this study is not theory testing, but theory development. That is, we propose a hypothesis for the mechanism of the formation of drug target selection capability in an individual drug discovery researcher. Furthermore, our hypothesis encompasses how the formed capability affects the success or failure of drug discovery projects and a company’s innovation by interacting with the organization’s managers. If the purpose of the research is to develop theory, theoretical case sampling is appropriate (Eisenhardt and Graebner, 2007).

Case selection

We selected interleukin-6 (IL-6) related drug discovery research for the case examples. IL-6 was identified in 1986 as a novel protein that shows a variety of physiological functions such as B-cell differentiation and platelet-increasing actions. Immediately after IL-6 was identified, researchers at Chugai Pharmaceuticals and Company A attempted to apply the IL-6 mechanism to drug discovery. Researchers at Chugai Pharmaceuticals correctly predicted that the inhibition of IL-6 signalling could be used in autoimmune disease therapy and succeeded in developing a new drug. Researchers

at Company A focused on the platelet increasing action of IL-6 and attempted to develop it as a therapeutic drug for thrombocytopenia. However, the development attempts of Company A failed because of insufficient efficacy and safety in clinical trials.

The reasons for selecting these particular cases for analysis are as follows.

First, our study focuses on the individual researchers' capability, which enabled them to evaluate whether the modulation of a certain physiological mechanism/molecule could be applied to a specific disease after the acquisition of information about the physiological mechanism/molecule. Therefore, the comparative analysis of the thinking process of the researchers involved in the selection of drug targets in drug discovery cases aimed at translating the same basic research result, which was IL-6 in our study, into drug applications is an appropriate approach. In both case examples, details of the research processes, including related past research, were identified to analyse the process by which drug target selection capability was being formed.

Second, the capability that transforms and exploits external knowledge into product innovation has been studied mainly at the organizational level, and little in the context of the relationship between individuals and organization. However, in a product development such as drug discovery, an individual research champion plays a key role in the R&D process. Therefore, analysing the individual capability formation and its interaction with the organization are important. In the IL-6-related drug discovery cases, details of the thinking process of research leaders were identified at an individual level and, therefore, these cases are appropriate to analyse the effects of individual capability on product innovation. In addition, these cases involve corporate researchers at pharmaceutical companies so we could analyse how the drug target selection capability of individual researchers was affected by organizational research management.

Third, it is rare to identify concurrently cases that aim to translate the same physiological mechanisms into different disease applications. In addition, it is hard to track the detailed research and thinking processes of individual corporate researchers, especially in failed drug discovery cases. In this study, the authors' long experience and accumulated knowledge of industrial drug discovery research and personal relations with drug discovery researchers allowed the identification of these rare examples and the gathering of detailed information of both successful and failed drug discovery cases.

Data source

This study focuses on the drug target selection capability that enables an individual drug discovery researcher to evaluate whether a certain physiological mechanism/molecule could be applied to drug discovery. In addition, it aims to identify the processes that foster development of the capability. It was necessary to clarify the detailed research and thinking process of the researchers who evaluated the drug application potential of the IL-6 mechanism. Specifically, we clarified what modulated the researchers' analysis of how the IL-6 mechanism could be applied to specific diseases, and their considerations in arriving at the decision. In addition, the background process used to reach the consideration of the IL-6 mechanism application needs to be clarified. Therefore, the long-term research background of the researchers before they were involved in IL-6 research had to be traced. We interviewed the main researchers involved in IL-6-related drug discovery research cases and identified the details of their research and thinking processes. To analyse the processes that foster capability, we conducted open-ended interviews and encouraged the interviewees to speak freely.

In the case of Chugai Pharmaceuticals, we had two two-hour interviews with Ohsugi, who played a key role in the research project. We asked Ohsugi to describe his long-term research history from when he joined Chugai Pharmaceuticals and started autoimmune disease research to the completion of the IL-6 inhibitor research project. We focused on his research and thinking processes in the application of the IL-6 mechanism to autoimmune disease therapy. Ohsugi has been involved in autoimmune disease drug research for a long time in Chugai Pharmaceuticals and was

the research project leader on the IL-6 inhibitor from the initial conception of the idea to commercialization. Therefore, we considered that sufficient valuable information would be obtained for the analysis by tracing Ohsugi's research and thinking processes. In addition, we analysed the books and articles written by Ohsugi and recorded his other interviews to understand his research and thinking processes.

In the case of Company A, we interviewed O, a researcher who was involved in the entire IL-6 drug discovery research process and past related research studies. We also interviewed H, who had conducted immunology research at Company A for a long time and was a research leader by the middle stage of the IL-6 research project. We conducted two interviews with O ranging from one-and-a-half to two hours; the first included two team members who were involved in the same research while the second was with O alone. The interview with H lasted for two hours. We requested O to describe the detailed process and considerations made in concluding that IL-6 was applicable to thrombocytopenia therapy, including previous related research. We asked H to describe his long-term immunology research history, as well as research and thinking processes, from his initiation of immunology research to the change in research leadership of the IL-6 research project. At the interviews, O provided Company A's internal documents that describe the details of the IL-6 drug discovery research project, mainly highlighting the process used to determine the applicability of IL-6 made by A, who was the leader of the IL-6 drug discovery research project. Furthermore, we were provided with Company A's 'lessons to be learned' documents to review the IL-6 project after it was terminated to confirm the detailed processes. We also analysed the books and papers written by H that describe the IL-6 related and previous research projects. The evaluation of the drug application potential of IL-6 was first performed by H, and then a revision was conducted by A. The above interviews and documentations enabled us to analyse the formation of each individual researcher's drug target selection capability and the interaction with organizational management (see Table 1)

Data analysis

We generated case narratives describing how each drug discovery researcher evaluated the drug application potential of the IL-6 mechanisms and why they reached the judgements they did. We also included their past research and the deductive thinking backgrounds that affected their

Table 1. Data sources

Data source	Details
Interviews	✓ Direct interviews with Ohsugi conducted twice for 2 hours each time. ✓ Direct interviews with O conducted twice, the first included two other research team members for 2 hours while the second was with O alone for 1.5 hours. ✓ Direct interview with H conducted for 2 hours.
Books, websites, and papers	✓ <i>Birth of New Drug Actemra</i>, Ohsugi (2013). ✓ <i>Present Immunology Stories</i>, Kishimoto and Nakashima (2007). ✓ <i>Miracle of Antibody Medicine and Innate Immunity</i>, Kishimoto and Nakashima (2009). ✓ <i>Cytokine Hunting</i>, Japanese Society of Interferon and Cytokine Research (2010). ✓ Web-based interview of Ohsugi, (2010) <i>Nikkei Business Online</i>, 16 June, available at http://business.nikkeibp.co.jp/article/tech/20100607/214809/ (accessed May 2020). ✓ Review article Ohsugi (2007). ✓ Article by H (2010) 'IL-6', <i>Biotherapy</i> 14,10, pp.1025–44.
Internal documents	✓ Minutes of the internal meeting of Company A where A decided the clinical application of IL-6. ✓ Internal document of Company A, <i>Written Summary of IL-6 Development</i>. ✓ 'Lessons to be learned' document internally prepared by Company A to review the IL-6 drug discovery project. ✓ Internal publication of Company A, <i>50 Years Research History of Company A</i>.

judgement in the narrative. To verify the validity and reliability of the data, Ohsugi, O, and H were asked to read the narrative and confirm the accuracy of the details of the events and our interpretations. We extracted the researchers' considerations and judgements on how the IL-6 mechanism was applied to drug application and the reasons they arrived at their determinations. In addition, we extracted the past research background information that contributed to the considerations (Table 2). We performed a cross-case comparison of the extracted contents and discussed the factors that contributed to the formation of drug target selection capability.

Case example: IL-6-related drug discovery

The detailed research processes in determining the IL-6 mechanism as a drug target by the research teams of Chugai Pharmaceuticals and Company A are described in Appendix 1.

Results

The narrative was analysed using the method described in the data analysis section. The results of the analysis are summarized in Table 2. Briefly, in the case of Chugai Pharmaceuticals, Ohsugi, the leader of the research team, considered that suppression of B cell activation by the blockade of IL-6 effect could be a novel therapy for autoimmune diseases based on his own discovery derived from

Table 2. Summary of comparative cases

	IL-6 for thrombocytopenia	Tocilizumab
'Evaluation of IL-6 signaling as drug target' in cases	Application of IL-6 action to thrombocytopenia therapy, which failed at Ph.2 because of insufficient balance of efficacy and safety	Application of IL-6 inhibition to autoimmune disease therapy, which succeeded in clinical trials and acquired approval
Reasons for evaluation	Demand of academic researcher who identified platelet-increasing action of IL-6 Decision that protein preparations would easily have become drugs in the haematology field previously Internal company opinion of not wanting to treat IL-6, which was identified by the company, as an etiological factor in disease	Insight that 'suppression of B cell activation suppresses the causes of autoimmune disease and could serve as a therapy' obtained from research by Ohsugi
Research background that fostered the evaluation of IL-6 signaling	H initiated immunology research from the 1970s and developed lentinan and IL-2 as cancer immunotherapies ↓ H sought new immune cytokine that affected B cells in collaboration with Osaka University aimed at identifying next potential therapeutic ↓ The leader of the collaboration was switched from H to A, who was a researcher in a different field. ↓ No haematological research background existed in Company A, but A decided to develop IL-6 for the treatment of thrombocytopenia based on recommendations from academia, clinical development feasibility, and company politics (as described in the above box).	Ohsugi initiated drug discovery research into autoimmune diseases from 1970 ↓ Ohsugi analysed and uncovered Lobenzarit action mechanism ↓ Ohsugi studied the contribution of immune cells to autoimmune diseases under Gershwin from 1978 and discovered that autoimmune diseases develop by B cell activation ↓ Ohsugi began searching for a B cell suppressor as a drug for autoimmune disease ↓ Ohsugi learned of the discovery of IL-6 and that its suppression was the B cell suppressant effect he was seeking

long-term research experience in autoimmune disease therapy and the action mechanisms of drugs. In contrast, A, the research leader of Company A, did not have research expertise in immune diseases. The selection of IL-6 for thrombocytopenia was based on an academic researcher's recommendation, ease of clinical development, and internal politics. The comparison of both cases suggests that relevant scientific insights gained from investigating disease etiology and existing drug action mechanisms are effective skills for drug discovery researchers to evaluate novel physiological mechanisms and correctly select drug targets.

Discussion

Importance of drug target selection capability for competitive drug discovery

Although both Chugai Pharmaceuticals and Company A studied the same physiological mechanism, the difference of drug application of the mechanism led to both the successful development of a blockbuster drug and failed drug development. In both cases, the research leader of the project determined the disease indication for which the IL-6 mechanism was applied. Therefore, the difference in the drug target selection capability of the two leaders affected the company's competitiveness. The contribution of this finding to existing theories (bridging scientist and realized absorptive capacity) is argued in the conclusion.

Fostering processes of individual researcher's drug target selection capability

The efficacy of new drugs must be better than those being used in existing therapies. In addition, side effects of new drugs must be minimal and a sufficient margin between efficacy and safety must be maintained in humans. Physiological mechanisms/molecules selected as a drug target must meet the above criteria when modulated by drug compounds. Therefore, drug discovery researchers must have adequate knowledge that modulating the target physiological mechanisms/molecules would lead to greater efficacy than that achieved by existing drugs; further, they should be able to predict correctly the safety aspect of modulating the targeted physiological mechanisms/molecules. The case comparison of this study shows that the above two capabilities of drug discovery researchers are necessary to enable them to evaluate the drug target potential of physiological mechanisms.

In the case of Chugai Pharmaceuticals, Ohsugi had enhanced his understanding of the pathological mechanisms that trigger autoimmune diseases through the analysis of action mechanisms of anti-immune drugs during his early research career. Through subsequent investigations, he discovered that the super-activation of B cells was essential for triggering autoimmune diseases and, therefore, sought inhibitors of B cell activation. This research background fostered Ohsugi's realization that IL-6 was a B cell activating factor that could be a drug target for autoimmune diseases, and, further, that the suppression of IL-6 activity was a therapeutic option.

The capability to evaluate the drug application potential of physiological mechanisms is not easily obtained by researchers. Hirano, who identified IL-6 and its signal transduction mechanism, was not convinced that IL-6 signal inhibition would be effective in autoimmune diseases. Even the researcher who was responsible for the basic research findings could not determine whether they could be linked to a drug application. Therefore, familiarity with basic research in clarifying physiological functions and mechanisms does not necessarily indicate the ability to determine properly the potential of drug application of the physiological mechanisms. This means that strengthening potential absorptive capacity (Zahra and George, 2002) does not guarantee the reinforcement of drug target selection capability.

In the case of Company A, a researcher who did not have a haematology research background determined the application of IL-6 for thrombocytopenia by making a simple prediction based on the platelet-increasing action of IL-6. The determination was not based on a comprehensive understanding of the etiology of thrombocytopenia. The fact that the platelet increase in mice

was weak and subsequent comments, such as ‘a little more in-depth research could have clarified that IL-6 was not a substance like thrombopoietin’, revealed that the application selection was not conducted by properly predicting the efficacy and safety based on a comprehensive understanding of the etiology of the targeted diseases.

Regarding the safety risk assessment, the comprehensive understanding of diseases and existing drugs by researchers determined the success or failure of the evaluation of drug application potential of the physiological mechanism/molecules. Gershwin, who supervised Ohsugi during his studies in the United States, did not expect B cell suppression to be sufficiently safe for patients with autoimmune diseases. However, Ohsugi had investigated various action mechanisms of autoimmune disease drugs and understood that drugs affecting the entire immune system could be used in humans. Therefore, he was able to predict correctly that modulating B cells alone would lead to an acceptable safety profile. On the other hand, A at Company A underestimated the safety risk of IL-6, although the flu-like syndrome was an easily predicted side effect considering that IL-6 is the protein found to activate the immune function. This risk underestimation led to the failure of the clinical development. It is hard to predict an acceptable safety risk in the haematology field without sufficient research experience in haematology drugs.

Our case study suggests that the comprehensive understanding of disease etiology by drug discovery researchers, as well as knowledge of existing drug action mechanisms, is critical to fostering researchers’ drug target selection capability to make correct judgements of the drug application potential of physiological mechanisms/molecules. When drug discovery researchers’ selection of drug targets is based simply on the function of physiological mechanisms and they have an insufficient understanding of diseases and existing drugs, they often fail to select appropriate physiological mechanisms that meet efficacy and safety standards.

Interaction between drug target selection capability of individuals and organizational management

In the case of Company A, H had succeeded in a few drug discovery cases in immunology before joining the IL-6 research project; therefore, Company A had acquired strong drug discovery capabilities in immunology. H joined the collaborative research project on the identification of IL-6 aimed at developing novel factors with activity on B cells. Specifically, agents with action mechanisms different from those of existing drugs that act on T cells were sought in exploiting the factors for drug discovery. Company A would have developed the idea of applying the IL-6 mechanism to autoimmune disease therapy if H had continued with the IL-6 research project.

However, Company A changed the leader of the IL-6 research project. As a result, a researcher who lacked experience in immunological drug discovery conducted an inadequate evaluation of the drug application potential of the IL-6 mechanism, which led to incorrect efficacy and safety expectations. This suggests that drug target selection capability occurs in individual researchers and is not attained at an organizational level. It would have been a reasonable strategy for Company A to invest in collaborative research with Kishimoto’s laboratory to leverage their strong immunology drug discovery research capability. However, they changed their research leader at the drug discovery application stage for IL-6; this is considered to have resulted in a loss of drug target selection capability.

Conclusion

Implications for theory development

We believe that the importance of drug target selection capability found in our study extends the concept of the ‘bridging scientist’ proposed by Gittelman and Kogut (2003). The literature suggests that the scientist who bridges basic science and innovation is crucial for product development in the biotechnology industry. However, more specific features of bridging scientists, such as the nature

of their capability and factors forming the capability, have not been investigated. Our study suggests that one important capability for bridging basic science and innovation in the drug discovery arena is selection of physiological molecules/mechanisms that are appropriate as drug targets. We propose that the drug discovery researchers' capability to select appropriate drug targets is formed by long-term research experience that leads to a comprehensive understanding of disease etiology and existing drug action mechanisms.

Our finding also contributes to the extension of 'realized absorptive capacity' (Zahra and George, 2002). The literature has conceptualized the capability to transform and exploit the acquired external knowledge for product innovation as realized absorptive capacity. Our study suggests that drug target selection capability is one of the realized absorptive capacities in drug discovery that transforms externally discovered novel physiological molecules/mechanisms into new drug innovation. Because drug target selection capability is achieved by more specific research focusing on disease etiology and the action mechanisms of drugs, rather than pure basic research experience, it is hard to achieve; therefore, once achieved, it could be the source of competitiveness. Considering that absorptive capacity is usually studied at organizational level, it is worth emphasizing that drug target selection capability is an individual capability (Apriliyanti and Alon, 2017).

Implications for managerial practice and public policy

It takes time to nurture drug discovery researchers. The company needs to encourage their researchers to continue disease research in one specific disease field for a long time to increase their capability to evaluate the therapeutic potential of physiological mechanisms/molecules in that discipline. When a company changes its disease focus in drug discovery, it should hire drug discovery research experts who are familiar with the new focus disease field, rather than shifting internal researchers who have been studying other diseases. We also need to consider that investing in research on diseases and mechanisms of therapeutic drugs over many years is a significant burden for pharmaceutical companies. A potentially helpful strategy would be for the government to assist them by establishing a public research institution or organizational division dedicated to researching disease causes and action mechanisms of therapeutic drugs. This could create an environment to nurture researchers who have the capability to succeed in drug target selection.

Study limitations

A limitation of this study is that the discussions on the analyses of these case examples may not be generalizable. It is necessary to examine the validity of our assertion using quantitative methods by translating the degree of understanding of disease etiology and existing drug action mechanisms into proxy variables, in addition to accumulating case examples. The proposed processes that foster drug target selection capability are necessary conditions, but other possible processes should also be examined. Further, it is still questionable whether all drug discovery researchers can acquire the capability to perform drug target selection by conducting long-term research on disease etiology and drug action mechanisms. Further, the characteristics required of researchers for capability formulation remain to be clarified.

References

- Apriliyanti, I. and Alon, I. (2017) 'Bibliometric analysis of absorptive capacity', *International Business Review*, 26, pp.896–907.
- Baba, Y., Shichijo, N. and Sedita, S. (2009) 'How do collaborations with universities affect firms' innovative performance? The role of "Pasteur scientists" in the advanced materials field', *Research Policy*, 38, 5, pp.756–64.

- Bioscience Innovation and Growth Team (2004) *Bioscience 2015 Entire Executive Summary*, available from www.bioindustry.org/bigtreport/index2.html (accessed November 2011).
- Cockburn, I. and Henderson, R. (1996) 'Public-private interaction in pharmaceutical research', *Proceedings of the National Academy of Sciences*, 93, 239, pp.12725–30.
- Cockburn, I. and Henderson, R. (1998) 'Absorptive capacity, coauthoring behavior, and the organization of research in drug discovery', *Journal of Industrial Economics*, 46, 2, pp.157–82.
- Cohen, W. and Levinthal, D. (1990) 'Absorptive capacity: a new perspective on learning and innovation', *Administrative Sciences Quarterly*, 35, pp.569–96.
- Comroe, J. and Dripps, R. (1976) 'Scientific basis for the support of biomedical science', *Science*, 192, 4235, pp.105–11.
- Cook, D., Brown D., Alexander, R. *et al.* (2014) 'Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework' *Nature Reviews Drug Discovery*, 13, pp.419–31.
- DiMasi, J., Feldman, L., Seckler, A. and Wilson, A. (2010) 'Trends in risks associated with new drug development: success rates for investigational drugs', *Clinical Pharmacology and Therapeutics*, 87, pp.272–7.
- Dimitrov, D. and Marks, J. (2009) 'Therapeutic antibodies: current state and future trends – is a paradigm change coming soon?', *Methods in Molecular Biology*, 525, pp. 1–27.
- Edmondson, A. and McManus, S. (2007) 'Methodological fit in management field research', *Academy of Management Review*, 32, 4, pp.1246–64.
- Eisenhardt, K. and Graebner, M. (2007) 'Theory building from cases: opportunities and challenges', *Academy of Management Journal*, 50, 1, pp.25–32.
- Erlanson, D., Fesik, S., Hubbard, R. *et al.* (2016) 'Twenty years on: the impact of fragments on drug discovery', *Nature Reviews Drug Discovery*, 15, 9, pp.605–19.
- Fabrizio, K. (2009) 'Absorptive capacity and the search for innovation', *Research Policy*, 38, 2, pp.255–67.
- Fabrizio, K. and Di Minin, A. (2008) 'Commercializing the laboratory: faculty patenting and the open science environment', *Research Policy*, 37, 5, pp.914–31.
- Folkersen, L., Biswas, S., Frederiksen, K. *et al.* (2015) 'Applying genetics in inflammatory disease drug discovery', *Drug Discovery Today*, 20, 10, pp.1176–81.
- Furukawa, R. and Goto, A. (2006) 'The role of corporate scientists in innovation', *Research Policy*, 35, 1, pp.24–36.
- Galizzi, J., Lockhart, B. and Bril, A. (2013) 'Applying systems biology in drug discovery and development', *Drug Metabolism and Drug Interactions*, 28, 2, pp.67–78.
- Gittelman, M. (2016) 'The revolution re-visited: clinical and genetics research paradigms and the productivity paradox in drug discovery', *Research Policy*, 45, 8, pp.1570–85.
- Gittelman, M. and Kogut, B. (2003) 'Does good science lead to valuable knowledge? Biotechnology firms and the evolutionary logic of citation patterns', *Management Science*, 49, 4, pp.366–82.
- Hertzberg, R. and Pope, A. (2000) 'High-throughput screening: new technology for the 21st century', *Current Opinion in Chemical Biology*, 4, 4, pp.445–51.
- Hess, A. and Rothaermel, F. (2011) 'When are assets complementary? Star scientists, strategic alliances, and innovation in the pharmaceutical industry', *Strategic Management Journal*, 32, 8, pp.895–909.

- Hirano, T., Yasukawa, K., Harada, H. *et al.* (1986) 'Complementary DNA for a novel human interleukin (BSF-2) that induces B lymphocytes to produce immunoglobulin', *Nature*, 324, 6092, pp.73–6.
- Holmes, A., Bonner, F. and Jones, D. (2015) 'Assessing drug safety in human tissues – what are the barriers?', *Nature Reviews Drug Discovery*, 14, pp.585–7.
- Japanese Society of Interferon and Cytokine Research (2010) *Cytokine Hunting*, Kyoto University Press, Kyoto (in Japanese).
- Kirchmair, J., Göller, A., Lang, D. *et al.* (2015) 'Predicting drug metabolism: experiment and/or computation?', *Nature Reviews Drug Discovery*, 14, pp.387–404.
- Kishimoto, T. (2005) 'Interleukin-6: from basic science to medicine – 40 years in immunology', *Annual Review of Immunology*, 23, pp.1–21.
- Kishimoto, T. and Nakashima, A. (2007) *Present Immunology Stories*, Kodansha Publishing, Tokyo (in Japanese).
- Kishimoto, T. and Nakashima, A. (2009) *Miracle of Antibody Medicine and Innate Immunity*, Kodansha Publishing, Tokyo (in Japanese).
- Kuwashima, K. (2006) *Management of Uncertainty*, Nikkei BP Publishing, Tokyo (in Japanese).
- Morgan, P., Brown, D., Lennard, S. *et al.* (2018) 'Impact of a five-dimensional framework on R&D productivity at AstraZeneca', *Nature Reviews Drug Discovery*, 17, pp.167–81.
- Munos, B. (2009) 'Lessons from 60 years of pharmaceutical innovation', *Nature Reviews Drug Discovery*, 8, pp.959–68.
- Munos, B. (2016) 'Biomedical innovation: lessons from the past and perspectives for the future', *Clinical Pharmacology and Therapeutics*, 100, 6, pp.588–90.
- Nadeau, J. and Dudley, A. (2011) 'Systems genetics', *Science*, 331, pp.1015–16.
- Nagano, K. and Higashisaka, K. (2016) 'Promotion of drug discovery research by utilizing omics technology', *Yakugaku Zasshi*, 136, 2, pp.143–4.
- Nagaoka, S. (2016) *New Drug Discovery and Development*, Nikkei BP Publishing, Tokyo (in Japanese).
- Nishimoto, N. (2006) 'Interleukin-6 in rheumatoid arthritis', *Current Opinion of Rheumatology*, 18, 3, pp.277–81.
- Ohsugi, Y. (2007) 'Recent advances in immunopathophysiology of interleukin-6: an innovative therapeutic drug, tocilizumab (recombinant humanized anti-human interleukin-6 receptor antibody) unveils the mysterious etiology of immune-mediated inflammatory diseases', *Biological and Pharmaceutical Bulletin*, 30, 11, pp.2001–6.
- Ohsugi, Y. (2013) *Birth of New Drug Actemra*, Iwanami Shoten Publishing, Tokyo (in Japanese).
- Okuyama, R. (2017) 'Importance of tacit knowledge in incremental innovation: implications from drug discovery cases', *Journal of Strategy and Management*, 10, 1, pp.118–30.
- Plymoth, A. and Hainaut, P. (2011) 'Proteomics beyond proteomics: toward clinical applications', *Current Opinion in Oncology*, 23, 1, pp.77–82.
- Powell, W., Koput, K. and Smith-Doerr, L. (1996) 'Interorganizational collaboration and the locus of innovation: networks of learning in biotechnology', *Administrative Science Quarterly*, 41, 1, pp.116–45.
- Rosenberg, N. and Nelson, R. (1994) 'American universities and technological advance in industry', *Research Policy*, 23, 3, pp.323–48.

- Savino, R., Paduano, S., Preianò, M. and Terracciano, R. (2012) ‘The proteomics big challenge for biomarkers and new drug-targets discovery’, *International Journal of Molecular Sciences*, 13, 11, pp.13926–48.
- Scannell, J. Blanckley, A., Boldon, H. and Warrington, B. (2012) ‘Diagnosing the decline in pharmaceutical R&D efficiency’, *Nature Reviews Drug Discovery*, 11, pp.191–200.
- Smietana, K., Siatkowski, M. and Moller, M. (2016) ‘Trends in clinical success rates’, *Nature Reviews Drug Discovery*, 15, pp.379–80.
- Stokes, D. (1997) *Pasteur’s Quadrant: Basic Science and Technological Innovation*, Brookings Institution, Washington, DC.
- Stranger, B., Stahl, E. and Raj, T. (2011) ‘Progress and promise of genome-wide association studies for human complex trait genetics’, *Genetics*, 187, pp.367–83.
- Swinney, D. and Anthony, J. (2011) ‘How were new medicines discovered?’, *Nature Reviews Drug Discovery*, 10, pp.507–19.
- Tralau-Stewart, C., Wyatt, C., Kleyn, D. and Ayad, A. (2009) ‘Drug discovery: new models for industry–academic partnerships’, *Drug Discovery Today*, 14, 1/2, pp.95–101.
- Toole, A. (2012) ‘The impact of public basic research on industrial innovation: evidence from the pharmaceutical industry’, *Research Policy*, 41, 1, pp.1–12.
- Varmus, H. (2010) ‘Ten years on – the human genome and medicine’, *New England Journal of Medicine*, 362, 21, pp.2028–9.
- Van der Sijde, M., Ng, A. and Fu, J. (2014) ‘Systems genetics: from GWAS to disease pathways’, *Biochimica et Biophysica Acta*, 1842, 10, pp.1903–9.
- Yan, S., Liu, R., Jin, H. *et al.* (2015) ‘“Omics” in pharmaceutical research: overview, applications, challenges, and future perspectives’, *Chinese Journal of Natural Medicines*, 13, 1, pp.3–21.
- Zahra, S. and George, G. (2002) ‘Absorptive capacity: a review, reconceptualization, and extension’, *Academy of Management Review*, 27, 2, pp.185–203.
- Zucker, L., Darby, M. and Armstrong, J. (2002) ‘Commercializing knowledge: university science, knowledge capture, and firm performance in biotechnology’, *Management Science*, 48, 1, pp.138–53.

Appendix 1

Detailed case description: IL-6-related drug discovery

IL-6 is a cytokine that plays important roles in immunity and inflammatory reactions. It has a variety of physiological actions, such as stimulation of B cell differentiation into antibody-producing cells, and promotion of chemokine production (Nishimoto, 2006). This cytokine was identified by Tadimitsu Kishimoto and his associates at Osaka University in 1986 (Hirano *et al.*, 1986) and the IL-6 receptor and its relevant signalling mechanism were also demonstrated (Kishimoto, 2005). Immediately after Kishimoto’s group discovered IL-6 and its signalling mechanism, researchers at Chugai Pharmaceuticals and Company A conducted drug discovery research targeting the IL-6 mechanism.

Evaluation of IL-6 as a drug target

The research team at Chugai Pharmaceuticals focused on B cell activation by IL-6 and aimed to develop a therapeutic drug for autoimmune diseases by suppressing this action. The cause of autoimmune diseases had not been completely elucidated at that time. Ohsugi, who was the leader of the Chugai Pharmaceuticals research team at the time, found that autoimmune diseases were induced

by hyperactivation of B cells. Therefore, he considered that the inhibition of IL-6 signaling through blockade of the IL-6 receptor would be effective against autoimmune diseases. Ohsugi and colleagues successfully developed a humanized antibody (tocilizumab), which suppressed the IL-6 receptor. Tocilizumab acquired approval as a therapeutic drug for rheumatism, a representative autoimmune disease, in 2008. The global sales of the drug exceeded one billion Swiss francs in 2013, and it became a blockbuster drug (www.yakuji.co.jp/entry34625.html). The research team at Company A focused on the platelet-increasing effect of IL-6 and aimed to develop it as a therapeutic drug for thrombocytopenia. However, the development of IL-6 was suspended during the phase II clinical trial because of adverse effects involving common cold symptoms.

The research process in determining IL-6 mechanism as a drug target

The research team at Chugai Pharmaceuticals

Ohsugi became aware of IL-6 in 1986 and had started researching a therapeutic drug for autoimmune diseases at Chugai Pharmaceuticals around 1970, soon after he joined the company. Since then, he has been involved in research on various drugs for autoimmune diseases. In the 1970s, Ohsugi was in charge of research on the action mechanisms of Lobenzarit, a therapeutic drug for rheumatism (Ohsugi, 2013). He took a hint from a comprehensive literature search and demonstrated the action mechanism of Lobenzarit, which was unclear at that time (Ohsugi, 2013). He elucidated that the therapeutic effect of Lobenzarit was mediated by its activation of suppressor T cells that inhibit immune responses. Lobenzarit showed insufficient efficacy in patients with rheumatism; therefore, another therapeutic drug for rheumatism with superior drug efficacy was desired.

From 1978, Ohsugi studied abroad under Gershwin at the University of California and researched the relationship between immune cells and autoimmune diseases. Although T cell research was active at that time, Ohsugi worked on an experiment to examine the hypothesis that hyperactivation of B cells causes autoimmune diseases. He demonstrated that autoimmune diseases were triggered by the hyperactivation of B cells, not T cells, using a gene-manipulated mouse model. Based on these findings, Ohsugi believed that the suppression of B cell functions would be the fundamental therapy for autoimmune diseases: ‘The drug which regulates B cells would be a fundamental therapeutic for autoimmune diseases’ (Ohsugi, 2013, p.21).

Against this idea, Gershwin opined that ‘Suppression of B cell functions leads to immunodeficiency in patients.’ Ohsugi further hypothesized:

Current immune suppressive agents affect immune cells in an overall manner. B cell selective suppression may cause fewer side effects and therefore be more suitable for drugs. (Ohsugi, 2013, p.21)

Specifically, drugs that suppress the entire immune function, such as methotrexate, were used to treat autoimmune diseases, such as rheumatism, at that time, and Ohsugi considered that a B cell-specific mechanism would be safer than non-selective drug mechanisms.

Following his return to Japan, Ohsugi began searching for a B cell suppressor to develop as a new therapeutic drug for autoimmune diseases. Ohsugi recalls:

I said to everyone, ‘It is not suppressor T cells. The next anti-rheumatism drugs are those that directly affect B cells’. Then, people said, ‘Let’s do that.’ (*Nikkei Business Online*, 16 June 2010, available at <http://business.nikkeibp.co.jp/article/tech/20100607/214809/>, accessed May 2020)

No established evaluation system existed for compounds with such actions, and although he continued with his search through trial and error, no B cell-suppressing compound could be found. In 1986, Kishimoto and his associates identified IL-6 as an activation factor of B cell differentiation in patients with intra-atrial myxoma which manifests autoimmune disease-like symptoms. Ohsugi learned from the presentation and considered that ‘IL-6 inhibitor will be an innovative anti autoimmune disease drug which regulates B cells.’ He intuitively felt that IL-6 is the substrate to hyperactivate B cells, and

therefore, its suppression was the B cell suppressant activity he had been seeking. Ohsugi immediately proposed a joint research project on IL-6 suppression to Kishimoto. The concept of IL-6 as a drug development target for the treatment of autoimmune diseases could not be easily fathomed.

Hirano, the leader of basic research on IL-6 at Kishimoto's research laboratory, later opined that:

I was not convinced that the IL-6 could be a contributing factor for autoimmune diseases until we acquired research findings that the genetically modified mice with the mutated IL-6 signal naturally triggered symptoms similar to those of rheumatoid arthritis in later years. (Japanese Society of Interferon and Cytokine Research, 2010, p.163)

Ohsugi subsequently noted that:

I would imagine there were not many who would have thought of daring to search for a suppressor, based on the concept that an IL-6 suppressor could become a therapeutic drug for autoimmune diseases at this point in time, when we only had knowledge based on what we could gather from patients with intra-atrial myxoma. (Ohsugi, 2013, pp.35–6)

Although it was clear that the IL-6 had a relationship with the symptoms of autoimmune diseases, which was observed in intra-atrial myxoma, the extent to which rheumatoid arthritis and the IL-6 were related could not be interpreted based on the paper. (*Nikkei Business Online*, 16 June 2010, available at <http://business.nikkeibp.co.jp/article/tech/20100607/214809/>, accessed May 2020)

In fact, no party other than Chugai Pharmaceutical was interested in participating in a joint research project with Kishimoto on IL-6 suppression (Kishimoto and Nakajima 2009, p.121). Ohsugi further noted:

I thought of the concept because of my many years of research on the mechanisms of pathogenesis with mice afflicted with autoimmune diseases. (Ohsugi, 2013, p.36)

This was something that we could see only because we were engaged in research for decades using experimental mice; this demonstrates how important it is to steadily continue with basic research. (*Nikkei Business Online*, 16 June 2010, available at <http://business.nikkeibp.co.jp/article/tech/20100607/214809/>, accessed May 2020)

Kishimoto and his associates were encouraged by the high level of research conducted by Ohsugi and his associates on autoimmune diseases and decided to accept the offer to participate in the joint research. After the joint research began, Kishimoto and his associates successively demonstrated the signal transduction mechanisms of IL-6 via the IL-6 receptor. Simultaneously, Ohsugi and his group made efforts in the search for a suppressor, and an approach to inhibit IL-6 signalling by blocking the IL-6 receptor with an inhibitory antibody was considered. The IL-6 receptor antibody was prepared for research by Kishimoto and his associates and was subsequently administered to mice by Ohsugi and his associates, who discovered that it suppressed autoimmune reactions. The antibody provided by Kishimoto and his associates was then engineered for human use through a joint effort between Chugai Pharmaceuticals and the MRC Laboratory in the UK. This led to the development of tocilizumab, which was carefully investigated in animals for efficacy and safety, later confirmed in humans through clinical trials, and finally introduced to the market.

The case of the research team of Company A

H at Company A initiated immunology research from the 1970s. He was deployed in the National Cancer Center and succeeded in identifying lentinan as the immunopotentiating component of *Lentinus edodes* under the guidance of top immunology and biochemistry researchers at that time. Lentinan is the substrate that directly activates macrophages, leading to T cell activation. It was first clinically developed and marketed as an anticancer immunotherapy that demonstrated life-prolonging effects in

humans. Subsequently, H explored substances that promoted T cell differentiation to develop a new cancer immunotherapy with increased efficacy in combination with lentinan. H and colleagues identified the target molecule (IL-2) and showed its pharmacological effects in tumour-bearing mice. IL-2 was subsequently developed and marketed as an anti-cancer drug for certain types of cancer.

H made outstanding achievements in drug discovery in the immune field, and so Company A increased its investment there and initiated collaboration with the research group of Kishimoto at Osaka University, which had achieved major advances in immunology at the time. Because lentinan and IL-2 were factors acting on T lymphocytes, H's group became interested in a protein that affected B lymphocytes, the other cell population that plays a role in immune responses. H aimed to identify another immunopotentiating cytokine as the next potential therapeutic. Hirano of Kishimoto's group at Osaka University found that a putative B lymphocyte differentiating factor, which was later identified as IL-6, had been derived from T cells. H's group and Hirano and colleagues jointly attempted to clone IL-6. However, in the middle of the study, H was abruptly relieved of joint research responsibilities, which were transferred to T. H was sent to a university in the United States for three years under the direction of the company. Therefore, he was unable to contribute significantly to the study of IL-6. Against this backdrop, a senior manager of Company A stated that 'He did not have good chemistry with the management.' H was understandably unhappy: 'I was angry about feeling exiled.'

IL-6 was subsequently identified and reported in 1986 as described above. Simultaneously, T was directed to study abroad, and the research team leader of Company A was changed to A. Prior to being involved in IL-6 research, A was a researcher in a different pharmacological field. A was entrusted with investigating IL-6 drug discovery applications. During the same period, various academic researchers began investigating the physiological action of IL-6. Among them, Ishibashi of Fukushima Medical University found that IL-6 has platelet increasing action. At that time, there were no researchers in Company A familiar with haematology research, but A opined that, since granulocyte-colony-stimulating factor (G-CSF) and erythropoietin (EPO) had previously been developed for use as protein preparations in haematology, IL-6 could also be developed as a haematological drug. The platelet increasing action of IL-6 was not very strong, causing an approximately 20% increase in mice. However, based on the strong recommendation of Ishibashi and others, it was decided that clinical development would proceed towards its use in thrombocytopenia. In Company A, a proposal was made to develop an autoimmune disease drug by inhibiting IL-6, which enhances antibody-producing capacity. However, researchers at Company A, who had discovered the noteworthy protein IL-6 ahead of anyone else in the world, were reluctant to consider it a deteriorating factor. In addition, resources were not abundant and concentration was necessary. A finally decided to develop IL-6 as an indication for thrombocytopenia and not to explore IL-6 inhibition in immunity.

In 1992, an IL-6 clinical study was initiated, but flu-like symptoms manifested as adverse reactions in administered patients, and its development was discontinued. IL-6 was identified as an immunopotentiating factor that acts on B cells, and thus was expected to cause inflammatory reactions and produce flu-like symptoms. However, interferons, which have similar action, have also been used as drugs, and the adverse reactions were considered resolvable. In subsequent years, it was repeatedly indicated by Company A that:

the biggest reconsideration was that while we found novel substance over other companies, we had adhered too much to the platelet-increasing activity, and had left no capacity to investigate backup research ideas on IL-6 inhibitors or other related targets.

In the interviews, H was adamant about what had gone wrong:

IL-6 does not increase during bleeding, therefore a little more in-depth research could have clarified that IL-6 was not a substance like thrombopoietin, the endogenous platelet-increasing factor. The initial aim in the immune field was off, and we failed in making developments with the action which was unexpectedly found. We failed because we did not listen to the opinions of on-site researchers who had cultivated their expertise over many years and accepted instead whatever university researchers and our superiors said.