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Issues in and Proposals for Facilitating Drug Discovery by Collaboration between Academia and Industry 2017

- In the Trend of Rapidly Advancing Science -

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Subcommittee on Pharmaceuticals Development
Jun-ichiro Inoue, Chairperson
Yuji Imaizumi, Vice-chairperson

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Introduction

In the United States, the rise of many bioventure companies in the late 20th century forced major pharmaceutical companies to abandon their conventional "closed" product development policy exclusively based on the drug discovery research on their own seeds and generated a new paradigm for drug discovery, i.e., translation of research results from academia (e.g., universities) to pharmaceutical industry via bioventure companies. Similarly in Japan, pharmaceutical companies experiencing a deadlock in new drug development based on "closed" policy have come to seek for seeds from research results obtained by the academia. Such academic-industrial collaboration is termed "open innovation." However, since venture companies have not yet taken root in Japan, efficiency of academic-to-industry translation is far from satisfactory and successful cases of so-called "drug discovery from academia" (development of innovative pharmaceuticals derived from scientifically important basic research results) are still rare.

The existence of bottlenecks (also known as "The Valley of Death") has been noted at multiple steps in a series of process from identification of seeds candidates by basic researchers to clinical trials. The objectives of this Subcommittee on Pharmaceuticals Development were to specifically examine "bottlenecks at earlier stages (from selection of seeds candidates by basic researchers, determination of direction/strategy of drug discovery, to initiation of collaboration with industry)" and to discuss countermeasures for them from the scientific viewpoint. This is because, although selection and evaluation of seeds are key points to successful drug discovery, most of the basic researchers from the academia who possess promising seeds are likely to be not familiar enough with strategies for real drug discovery (including translational research required for drug discovery, timing of publication, and effect of intellectual property rights). On the other hand, the industry side does not fully understand the basic researcher's way of thinking about research and tends to somewhat strongly demand what it expects from academia. Furthermore, while there are so many public or private projects for drug discovery support that have a role in guiding basic researchers towards the most efficient strategy for drug discovery, these projects are expected to play their role even more effectively.

The Basic Act on Science and Technology states that basic research "brings about the discovery of new phenomena, breakthroughs in understanding them, and creative technological innovations; but that it is also difficult to predict what results basic research will yield from its inception, and that its results do not always have a practical application." This means that the results of basic research do not always lead to drug discovery research and require polishing to attract industrial interest. This is the origin of mismatch in academic-industrial collaboration. In fact, a report[(1)] states that "the academia considers newly identified biologically active substances/disease-specifically expressed factors as promising drug discovery seeds, while the industry considers only those with favorable proof of concept (POC) study results (i.e., with proven potential as new drugs) as drug discovery seeds (partially modified from the original text)." In other words, discovery of scientific interest or discovery deserving publication in high-level scientific journals is sufficient to excite basic researchers but, from the industrial viewpoint, this does not provide an immediate starting point for drug discovery. The aforementioned "bottlenecks at earlier stages" seem to be attributable to such difference in values regarding research results between academia and industry. Key information essential for making drug discovery as business includes target validation to demonstrate an association with disease, clinical predictability, safety, and competition of intellectual property rights. If the industry required disclosure of all such

information from basic researchers for implementation of drug development, drug discovery from academia in Japan would not work well. In particular, while target validation of biopharmaceuticals (e.g., vaccines, antibodies) is often feasible even in the academia, drug discovery research starting from chemical compounds would be difficult for the academia. Accordingly, this report focuses on compound-based drug discovery and highlights the importance of target validation and clinical predictability. Issues of biopharmaceuticals in a broad sense (including cellular and tissue-based products and genetically modified products) require distinct perspective for discussion and are therefore beyond the scope of this document.

Tables 1-3 summarize achievements of Drug Discovery Support Network (Department of Innovative Drug Discovery and Development, iD3) of Japan Agency for Medical Research and Development (AMED), the control platform of Platform for Drug Discovery, Informatics, and Structural Life Science (PDIS) (an AMED program), and Drug Seeds Alliance Network Japan (DSANJ) (organized by Osaka Chamber of Commerce and Industry). In either case, an approach to increase the percentage of out-licensing to industry further would be essential in the current situation. Establishment of AMED represents Japan's national aim towards drug discovery of academic origin. We expect that publication of discussion at this Subcommittee will inform many basic researchers of strategies required for drug discovery, provide industry with exact recognition of the current situation in academia, increase the cases of efficient academic-industrial collaboration and launch of promising venture companies from academia targeting drug discovery, and eventually realize as many drug discovery cases from Japan as possible. We also hope that this report will provide PMDA and other organizations engaged in activities related to regulatory science (RS) with an opportunity to recognize issues associated with drug discovery from academia, the process upstream to RS-related activities.

Table 1 Achievements of Drug Discovery Support Network (iD3)
(as of the end of August 2017)

Support stage	Number of cases	Percentage
Drug discovery support to promising seeds	70	100 %
Out-licensing to industry	2	2.9 %

Table 2 Achievements of Platform for Drug Discovery, Informatics, and Structural Life Science (PDIS) control platform (as of the end of May 2016)

Support stage	Number of cases	Percentage
Total number of projects committed	600	100 %
Acquisition of advanced lead compounds Acquisition of POC Acquisition of clinical trial (candidate) compounds	48	8.0 %
Out-licensing to industry Joint research projects with industry	16	2.7 %

Table 3 Achievements of Drug Seeds Alliance Network Japan (DSANJ)
(as of the end of May 2017)

Support stage	Number of cases	Percentage
Organization of business meetings	730	100 %
Agreements of joint research, etc., concluded with industry	39	5.3 %

[References]

(1) Inagaki O. Expectation for the drug development activity in academia. YAKUGAKU ZASSI, 2013 133(2) 213-219.

1 Dissociation in view between industry and academia
- Why proposals from academia on drug discovery research are unacceptable to industry -

1.1 Most members of the academic community are amateurs in drug discovery

1.1.1 Interest of Japanese academia in drug discovery

The majority of academic researchers aim at clarification of truth in life and investigation into the cause of a disease basically from scientific interest. While understanding of needs in routine clinical practice and conducting their own basic research in full consideration of translation to future clinical practice are strongly recommended in research projects supported by AMED and other organizations, such attitudes are not likely to be fully penetrating into the academic community. In particular, it is natural for young researchers to aim at publishing their results as soon as possible in a scientific journal with an impact factor as high as possible, getting new research grants, and developing their own research. On the other hand, the number of academic researchers expecting that their own research results will lead to successful drug discovery has been presumed to be increasing. However, most academic researchers seem to either hesitate to step into the drug discovery process by themselves in fear of reduction in research efficiency or have no idea of what to do after stepping into the drug discovery process.

1.1.2 Lack of drug discovery-related education and frameworks for drug discovery support in the academia

In Japan, education on the drug discovery process in the academia has been poor in most research fields, except for pharmacy and some fields in engineering. Furthermore, entrepreneur education that provides the basis for launching a venture company is still underdeveloped compared with that in Europe and the United States. Particularly in medical schools (faculties of medicine) and graduate schools of medicine in Japan, sufficient education time was not allocated to the concept of intellectual property rights essential for drug discovery research and only limited opportunities for obtaining basic knowledge regarding patents were provided. Although education on intellectual property rights and education for nurturing entrepreneurship are currently promoted as a part of the university or graduate school curriculum,[(1)] the generation of researchers now active in the forefront of research have missed opportunities for such education. As a consequence, some of such researchers still do not fully understand that public presentation of research results makes them “publicly known” information for which a patent shall not be granted. Accordingly, these researchers lack basic knowledge and preparedness required for academic-industrial collaboration and fail to present attractive research proposals that stimulate the development motivation of pharmaceutical companies, which may be the principal cause for why proposals from academia on drug discovery research are unacceptable to industry. However, even if education programs on drug discovery process and intellectual property are offered at universities, it is unavoidable that academic researchers are amateurs in drug discovery. Rather, establishment of supporting frameworks linking the research of academic researchers as amateurs to formal drug discovery research is essential.

Based on the Basic Act on Science and Technology established in 1995, the Act on the Promotion of Technology Transfer from Universities to Private Business Operators (established in 1998) installed several Technology Licensing Organizations (TLOs) spreading all over Japan. In addition, Academic-industrial-governmental Collaboration Coordinators to moderate

academic-to-industrial technology transfer were recruited. Overall, TLOs failed to achieve sufficient technology transfer except for the field of engineering, and most of the established TLOs were deactivated. According to "Basic Strategies of Academic-industrial-governmental Collaboration to Promote Innovation" established in 2012, University Research Administrators (URAs) as a new research management human resource indirectly supporting/promoting research activities at universities were assigned to some of the national universities to reinforce research activities at universities. Since then, URAs have been rapidly diffusing among public and private universities. The URA systems are involved not only in pre-award operations (e.g., acquisition of research grants) but also in post-award roles (e.g., matching) as Academic-industrial-governmental Collaboration Coordinators to function in application of research results.[(2)] On the other hand, "Platform Project for Supporting Drug Discovery and Life Science Research (Platform for Drug Discovery, Informatics, and Structural Life Science)" was discussed as a drug discovery support organization in the Third Science and Technology Basic Plan (FY 2006-FY 2010) and implemented as a 5-year project by the Ministry of Education, Culture, Sports, Science and Technology from FY 2012 [(3)]. This project has been transferred to AMED since FY 2015 and re-launched as a new system in FY 2017. These activities are expected to provide footholds for building up a new era when drug discovery projects from academia become more acceptable to industry, etc., or academia per se implements the earlier stages of drug discovery with the aid of support, etc., by the Platform. Such recruitment of external human resource (URAs) and the support project are expected to function as supporting frameworks linking the research of academic researchers as amateurs to formal drug discovery research.

1.2 Lack of target validation and clinical predictability

Development of pharmaceuticals is discontinued most frequently at Phase II, the development stage for acquisition of POC. The reason for development discontinuation is lacked efficacy in 50% or greater of the cases. In fact, while the probability of successful transition to the next phase from any phase other than phase II is 60% or greater, the transition probability from Phase II to Phase III is reported to be the lowest (39%).[(4)] In a survey of clinical trials that failed between 2011 and 2012, the most frequent reason for failure at Phase II was efficacy (in 59% of cases), followed by safety (in 22% of cases).[(5)] While safety issues will be discussed below (see "2.1.4 Acquisition of data with assured reliability"), this report focusing on "bottlenecks at earlier stages" describes mainly on efficacy in this section. One possible reason for lack of efficacy is the selection of a molecule not appropriate as a drug discovery target. Accordingly, it is important to verify in advance whether the selected target molecule has sufficient qualification as a drug discovery target. Development of pharmaceuticals is a process for identifying a drug discovery target and narrowing down the selection of drug candidate compounds acting on the target by various assessments. In this process, confirmation that the identified drug discovery target is a molecule actually associated with a human disease (e.g., playing an important role in maintenance of physiological functions, involved in pathogenesis, etc.), i.e., so-called "target validation," is crucial.

The objective of target validation is to demonstrate an association of the target molecule with disease by: 1) clarifying its functions in cells, animals, and human as a part of basic research; 2) demonstrating an association between the identified functions and pathology in test systems using animal models, etc.; 3) clarifying an association between the target molecule and human

pathology using clinical samples obtained from patients; and 4) finding biomarkers, as necessary, that enhance clinical predictability. Conducting 1) to 4) allows prediction of which patient groups the drug to be developed is indicated for. Biomarkers provide crucial weapons in evaluating how closely preclinical data obtained in cells and laboratory animals reflect the clinical conditions. Furthermore, if an inhibitor of the target molecule is identified, this compound may be utilized as a tool in basic research to obtain a rich set of peripheral information on the target molecule. In the industry, the amount of resources allocated to basic research (such as identification of the target molecule and functional analysis thereof) are limited: such basic research is the contribution from academia most keenly expected by industry. Access to clinical samples and clinical data is much easier from academia than from industry.

On the other hand, conducting tests in multiple evaluation systems at a single laboratory in the academia may not always be feasible. In addition, data obtained in rodents may not always be translated into clinical usefulness in human: for example, pharmaceuticals acting on the central nervous system require evaluation in small primates such as marmosets as well. Drug discovery projects from the academia should desirably be transferred to pharmaceutical companies by contracts, as early as possible, including open innovation to increase the rate of success at the following drug development stages. If appropriate collaboration with a pharmaceutical company is not feasible, utilization of a public system for drug discovery support or joint research with another academic sector may be necessary.

While a reported disadvantage of research by the academic sector in preclinical studies in general (including target validation) is low reproducibility,[(6)] successful examples of drug discovery from academia in Japan based on the clear target validation will be described in Section 2 (see “2.1.3 Successful drug discovery from academia based on the clear target validation and clinical predictability”).

1.3 Lack of eligibility of screening systems

When the right choice of target is made in a drug discovery proposal from academic researchers, what matters next is eligibility of screening systems to be used. Situations regarding eligibility of screening systems may greatly vary depending on the subject of drug discovery: low-molecular-weight compounds or biopharmaceuticals (vaccines/antibodies and nucleic acid/peptide drugs). However, lack of eligibility of screening systems is an issue common to drug discovery subjects of both types and will be discussed in Section 2.

1.4 Difference between acquisition of intellectual property sought by the industry and the current situation

Ensuring an outcome termed “intellectual property” (including patents) in exchange of research investment is crucial to the pharmaceutical industry as a representative R&D oriented business type.

1.4.1 Particularities in drug patents

Development of pharmaceuticals involves peculiar intellectual property management. In the electric, semiconductor, or automobile industries, a single product is covered by thousands of patents and shared use of a single patent termed “standard patent” with competitors is often noted.

In contrast, each pharmaceutical product is covered by a very small number of patents.[1] As a consequence, establishment of individual patents greatly influences business operations of each pharmaceutical company as the patent owner.

Table 4 highlights particularities of the pharmaceutical industry in Japan regarding patents compared with other business types.

In the pharmaceutical industry, the number of patents acquired per company is not large. However, patents in the pharmaceutical industry have the following features. The patent productivity (number of patents acquired per million JPY research cost spent) is extremely small, which indicates that the amount of investments per patent acquired is extremely large. The period between the start of product development and launching of the product (development period) is expected to be longer (10-17 years) in developing new drugs containing novel active ingredients. In addition, both the practical term of patent[2] and profitable period[3] are longer than those for other business types. However, due to existence of periods for clinical trials and regulatory review, a longer patent life does not yield monopoly profits for an extremely long time after product launching.

Table 4 Comparison for patents between business types

	Patent productivity	Integrity of research and development	Patent applications (Domestic/Overseas)	Duration of development period (months)	Practical term of patent (months)	Duration of a profitable period (months)
Pharmaceutical industry	0.007	28.4%	24.6/40.5	78.4	47.4	94.1
Food industry	0.021	2.6%	12.9/8.6	16.6	33.7	44.2
Chemical industry	0.023	13.3%	65.5/80.1	42.9	42.5	95.8
Automobile/automobile parts industry	0.038	8.6%	239.5/102.9	36.7	31.0	52.9
Electrical machinery industry[note)]	0.050	3.5%	238.9/310.4	26.3	30.1	69.8
Information service industry	0.112	19.1%	63.0/130.9	19.9	21.2	43.6

(Reference) Extracted from "Survey of Research Activities of Private Corporations (2016) [NISTEP REPORT No.173] p.76-100, National Institute of Science and Technology Policy, Ministry of Education, Culture, Sports, Science and Technology Japan, May 2017. (published in Japanese)

Note) Includes all electric machinery/equipment manufacturers other than those manufacturing electric components/devices, electronic circuits, electronic application equipment, and electric measuring instrumentation.

1.4.2 What is lacking in previous efforts made by the academia?

In the academia in Japan, importance of patent application has been recognized and TLOs involved in "technology transfer from the university" have been installed at academic institutions all over Japan. This framework is considered to be effective for early gathering of research results obtained at the academia and increasing the number of patent applications from academia. However, its contribution to promotion of practical application including technology transfer to industry is not sufficient. Due to increasing costs of patent application as well as increased expenses for patent maintenance, TLO organizations at Japanese academic institutions are being consolidated.

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1 Patents involved in development of pharmaceuticals include substance patents, formulation patents, process patents, and use patent (granted for indications and pharmacological actions). Among these, a substance patent is the firmest basic patent. In general, the superiority in drug development is secured by substance patent.

2 A period between the launch of a new product and the launch of a similar product covered by a circumventing patent

3 A period between the launch of a product and end of the patent maintenance period (20 years but may be extended up to a maximum of 25 years for pharmaceuticals)

Furthermore, in patent/intellectual property divisions of Japanese academic institutions, there is increasing tendency to allocate the budget mainly to costs for patent application and patent right acquisition (review request), with little amount of budget allocated to pre-application competition survey and patent application survey (patent survey) essential for patent establishment. As an alternative, checking the "Decision" section in an international patent search report issued after overseas patent application is chosen as the general way to determine whether to allocate the budget to further patent application (e.g., PCT international applications). Moreover, financial support for patent applications from academia provided by the national government (mainly by Japan Science and Technology Agency (JST))[7] tends to be reduced. Although need for patent search is recognized, specific patent search by the academic sector has not been sufficiently conducted. As a consequence, most universities make patent application, particularly PCT international application, only when support from JST or a joint research partner company funding patent application costs is available. It seems rather difficult for universities to pay expenses related to intellectual property (excluding personnel costs) with incomes obtained from intellectual property rights.

In a survey conducted by the Ministry of Education, Culture, Sports, Science and Technology Japan in FY 2015,[8] the number of licensed patent rights, etc., and the amount of income therefrom steadily increased to 2.4 times and 1.9 times as much as the values in FY 2010, respectively, as shown in Table 5. Thus, it is obvious that utilization of intellectual properties owned by Japanese universities has been rapidly promoted. However, based on the data regarding the status of licensed patent rights, etc., by institution (including universities) obtained by the aforementioned survey, the relationship between the number of persons in charge of practical operations related to intellectual property and patents owned at the top 12 universities in the ranking of "income from licensed patent rights, etc." (Table 6) suggests that the number of universities likely to be capable of affording expenses related to intellectual property including personnel costs may be extremely small. Accordingly, it could easily be inferred that the patents related to drug discovery might be much less profitable. On the other hand, the same survey data also demonstrate that profitable patents do exist, such as those owned by healthcare-related universities/faculties and related to regenerative medicine (including iPS cells) or utilization of natural products for drug discovery. To enhance patentability and usefulness of inventions/research results from healthcare-related universities including drug discovery, AMED has proposed a policy to strengthen its support for intellectual property departments of universities (including dispatch of intellectual property specialists and patent survey).[9] By utilizing public support, etc., universities are expected to achieve greater advancement in creation of patents utilized by the pharmaceutical industry more easily in the field of drug discovery as in other fields.

Table 5 Change in the number of and income from licensed patent rights, etc.

Category	National universities, etc.		Public universities, etc.		Private universities, etc.		Total	
	Number of patents	Patent income (1,000 JPY)	Number of patents	Patent income (1,000 JPY)	Number of patents	Patent income (1,000 JPY)	Number of patents	Patent income (1,000 JPY)
FY 2010	3,721	1,135,417	145	38,034	1,102	272,276	4,968	1,445,727
FY 2011	4,371	885,399	134	39,146	1,140	167,055	5,645	1,091,600
FY 2012	7,204	1,101,331	163	45,456	1,441	411,056	8,808	1,557,843
FY 2013	7,893	1,822,683	230	73,121	1,733	316,077	9,856	2,211,881
FY 2014	8,554	1,525,519	210	71,640	2,038	394,425	10,802	1,991,584
FY 2015	9,722	2,118,909	245	80,078	1,905	485,366	11,872	2,684,353

* "Number of licensed patent rights, etc." indicates the number of licensed or assigned patent rights (including those at the stage of "right to obtain patent").
* Rounded off at the first decimal place.

Table 6 Achievements regarding patents in FY 2014 by academic institution

	Name of institution	Number of patent applications	Number of licensed patent rights, etc.	Income from licensed patent rights, etc. (unit: 1,000 JPY)	Number of patents owned	Number of licensed patent rights	Number of patent rights earning running loyalty income	Number of persons in charge of practical operations*	Number of researchers
1	University of Tokyo	657	2,386	553,112	2,499	1,029	99	>= 50	6,565
2	Kyoto University	546	854	370,952	1,470	437	108	>= 50	5,113
3	Osaka University	462	617	165,629	1,429	213	114	>= 50	4,603
4	Keio University	157	259	147,857	654	124	24	>=10, <20	2,500
5	Kyushu University	382	271	132,757	1,024	127	92	>= 50	3,507
6	Nagoya University	278	349	100,672	1,072	167	41	>= 50	3,019
7	Nihon University	83	218	86,401	484	114	92	>=10, <20	4,091
8	Tokyo Medical and Dental University	78	131	70,424	209	30	2	>=10, <20	1,416
9	Mie University	60	13	66,805	242	9	2	>= 50	1,054
10	Tohoku University	381	454	66,363	2,466	259	174	>=20, <30	4,004
11	Kitasato University	54	6	61,080	268	15	2	0, <10	1,833
12	Sapporo Medical University	21	32	50,839	50	0	4	0, <10	779

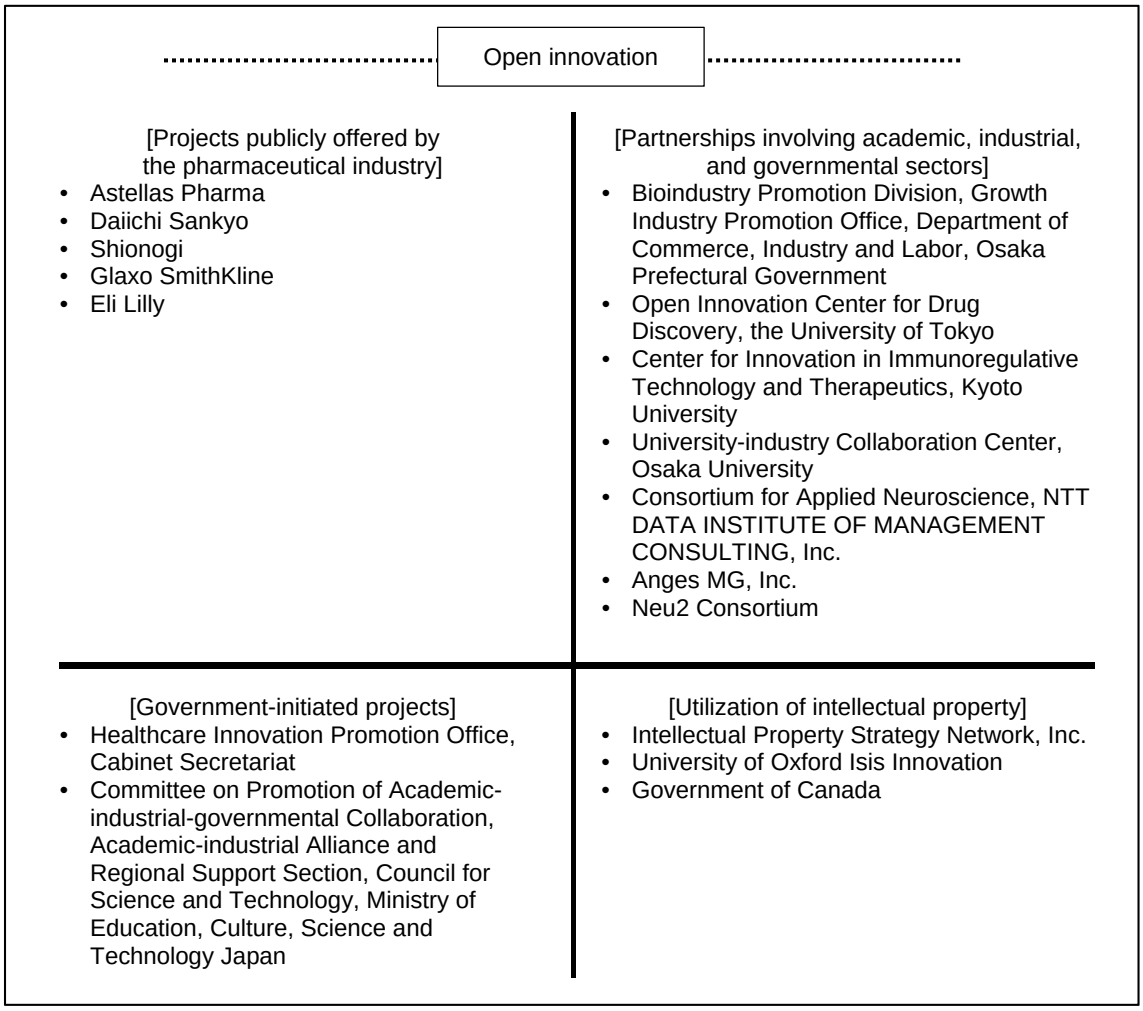
* Calculated for the top 12 institutions in the descending order of "income from licensed patent rights, etc."
* A "person in charge of practical operations" is defined a person affiliated with a post in charge of academic-industrial-governmental collaboration (faculty member, coordinator, URA, etc.) and engaged in practical operations of academic-industrial-governmental collaboration as his/her main activity. If some part of operations of academic-industrial collaboration (e.g., technology transfer) is outsourced to an external technology licensing organization (TLO), etc., and a single TLO is shared by multiple research institutions, the number of persons affiliated with such a TLO is counted as "persons in charge of practical operations."

1.4.3 Collaboration with industry

There are various types of open innovation across the academic, industrial, and governmental sectors, all achieving significant advancements in recent years (Fig. 1). There had previously been substantial discrepancies in the concept of collaboration between pharmaceutical industry and

academia. However, since 2000, expanding expenses for new drug creation and reduced success rate of drug development have propelled the movement of the pharmaceutical industry towards promotion of research and development in drug discovery by introducing external resources (research results from academia, in particular) with the aid of open innovation.

Figure 1 Classification of open innovation projects by companies and academic institutions[10]



* Partly modified from the original.

For the academic sector, the key to successful collaboration in “open innovation in drug discovery” with the industry lies in “marketing efforts” towards industry based on the awareness of “difference between the self and others” (differentiation): to grasp “the status of competition” is important as the starting point. The quickest way to understand the research subjects each company is interested in and the research seeds it has is to search the patents it publishes. This indicates that patent search is important for the academia as well: exact understanding of which company is interested in the field related to the patents owned by the academia is crucial to subsequent successful licensing/assignment of such patents to the industry. Furthermore, application guides for open innovation projects publicly offered by pharmaceutical companies (Table 7) reflect the interest of individual companies. The academic sector demands strategies for

patent right acquisition and assignment to the industry, etc., and such strategies should desirably be established on the initiative of intramural semi-experts in patents and academic-industrial collaboration (e.g., staff at the department of intellectual property and URAs/coordinators supporting researchers).

Table 7 Examples of drug discovery-related open innovation projects publicly offered by major pharmaceutical companies in Japan

Company	Project name
Asahi Kasei Pharma Corporation	Asahi Kasei Open Innovation 2017
Astellas Pharma Inc.	a-cube
EA Pharma Co., Ltd.	Drug Discovery Research Partnership
Sunstar Inc.	Sunstar Open Innovation Challenge
Shionogi & Co., Ltd	FINDS
Daiichi Sankyo Co. Ltd.	TaNeDS
Sumitomo Dainippon Pharma Co., Ltd.	PRISM
Takeda Pharmaceutical Co., Ltd.	COCKPI-T
Bayer Yakuhin, Ltd	Grants4Targets

(excerpted from the 2017 version of individual corporate websites)

1.5 Difference in territory between academia and industry

The research area where academia has strengths is the development of drug discovery seeds fully utilizing its strength such as advanced scientific power, innovative technologies unavailable from industry, and special animal disease models/research materials. In particular, the conduct of research in a groundbreaking area associated with a high development risk, such as novel mechanism of action (MOA) and drug discovery for orphan drugs, is a major feature of academic research. On the other hand, the area where the pharmaceutical industry has strengths includes its routine operations such as preclinical and clinical studies in general. These operations are difficult for the academia to conduct due to existence of various restrictions. Additional areas where the industry has strengths include the establishment of pharmaceutical profiles as development goals and patent acquisition strategies. Furthermore, scientific decisions with management factors (e.g., decision regarding continuation/abandonment of development) may be another area where the industry has strengths.

1.6 Existence of areas beyond the scope of comprehensive partnership resulting from specialization of the industry

Every pharmaceutical company, either domestic or overseas, has its own strategy for so-called “Concentration in Core Competence” to narrow down the areas of its activities to those where it has strengths or future growth is expected (Table 8). Establishing such a “Concentration in Core Competence” strategy is not limited to major companies but an overall trend in the entire pharmaceutical industry. Factors underlying this trend may be increased difficulties in search for drug discovery seeds as drug candidates, no signs of improvement in probability of successful dug development, and skyrocketing development costs per drug product. Such “specialization” of pharmaceutical companies has generated disease areas where translational research is difficult even if a comprehensive partnership agreement is concluded with a particular pharmaceutical company: the academia should be aware of this fact.

Table 8 Examples of "Concentration in Core Competence" in pharmaceutical companies in Japan

Pharmaceutical company	Priority areas (excerpted from the website of each company)
Takeda Pharmaceutical	We innovate with focus on three therapeutic areas- oncology, gastroenterology (GI), and the neuroscience (central nervous system diseases) - and are engaged in research activities to create really innovative pharmaceuticals.
Eisai	Eisai has identified neurology and oncology as important areas where there are many diseases for which treatments are still not well established and Eisai can find "Ricchi" to become a front runner in. Concentrating our R&D resources in these areas, Eisai is striving to discover new highly effective treatments especially for neurology and oncology.
Sumitomo Dainippon Pharma	Sumitomo Dainippon Pharma's goal is to create innovative pharmaceutical products. Psychiatry & Neurology as well as Oncology represent our focus therapeutic areas containing significant unmet medical needs.
Otsuka Pharmaceutical	Discover new pharmaceuticals related to the central nervous system, in oncology, and in other areas where medical needs remain underserved
Shionogi	Shionogi is focusing on metabolic syndrome, pain, and infectious disease as core therapeutic areas.
Daiichi Sankyo	Defining oncology as a primary focus area, we also aim to create advanced new drugs that revolutionize the SOC by advancing research and development targeting pain management, central nervous system disease, heart and kidney disease, and rare diseases as new horizon areas.
Astellas Pharma	in addition of the fields we have focused on to date, namely urology, oncology, immunology, nephrology, and neuroscience, we have selected muscle diseases and ophthalmology as new focused disease areas for research where we will concentrated our resources.
Mitsubishi Tanabe Pharma	In addition to autoimmune diseases and central nervous system diseases, we also focus on vaccines and orphan diseases and work to discover new drugs that address unmet medical needs. In these ways, we strive to further enhance our presence in areas in which we can leverage our strengths.

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2 The timing for passing the baton from academia to industry and desirable way of collaboration

2.1 What pharmaceutical industry expects from academia

2.1.1 Eligibility assurance of screening systems

(1) Eligibility assurance in screening of low-molecular-weight compounds

If sufficient target validation has been done, patent application from academia followed by joining academic-industrial joint research prior to search for seed low-molecular-weight compounds (by either direct consultation with a pharmaceutical company or application for a drug discovery open innovation project publicly offered by a pharmaceutical company) may be the realistic first choice. When academic researchers conduct primary screening by high-throughput screening (HTS) of a chemical library by themselves for various reasons including seed compounds, the following possible obstacles may arise:

[1] Difficulties in utilization of chemical libraries

With this respect, the situation is being improved rapidly in recent years, as exemplified by Drug-discovery Innovation and Screening Consortium (DISC) by AMED, University of Tokyo Drug Discovery Initiative, RIKEN/National Institute of Advanced Industrial Science and Technology, National Institutes of Biomedical Innovation, Health and Nutrition, and open innovation projects offered by pharmaceutical companies.

[2] Difficulties in development of HTS systems and implementation of HTS by the academia

In using full-scale HTS systems involving at least 100-thousand samples, simplicity and cost performance are required in addition to detection efficiency. It is not easy for the academia to develop its own HTS system. In particular, development of a cellular-level HTS system (including a high-content HTS system) has a high technical threshold. On the other hand, in systems for evaluating actions on activities of purified enzymes, examples of HTS conducted by the academia using public libraries have been rapidly increasing in number On the other hand, in systems for evaluating actions on activities of purified enzymes, examples of HTS conducted by the academia using public libraries has been rapidly increasing in number during recent years.(1) Assurance of accuracy and reproducibility is an essential requirement in drug discovery of low-molecular-weight compounds. However, even if a facility for HTS is owned by the academia, maintenance of the performance of devices with continuous verification of basic accuracy and reproducibility requires a dedicated administrator fully familiar with the HTS system. Furthermore, researchers themselves should master the screening techniques in advance by receiving public supports including HTS training classes.(2) Assuring a budget for HTS implementation costs is also indispensable for academic researchers. Hit compounds obtained by primary screening by HTS almost inevitably contain false-positives. As a consequence, secondary screening is required to verify the dose-response relationship and potency of the hit compounds as well as false-positives.

[3] Difficulties in optimizing hit compounds

The next step for selection of seed compounds from the hit compounds and chemical synthesis of derivatives for optimization involves joint research with or outsourcing to a synthetic chemist. Seed compounds and patent application are often required as prerequisites for getting public support. Patent application upon obtaining seed compounds is a good timing for considering an

application for public support such as AMED and seeking an opportunity for joint research (including a drug discovery open innovation project) with a pharmaceutical company. Patent application by the academic sector alone may be an obstacle to joint research with a pharmaceutical company: instead, joint research including optimization for acquisition of a joint patent is desirable.

On the other hand, the recent situation is becoming more favorable for academic researchers to approach drug discovery. Good examples include drug repositioning and fragment libraries. Drug repositioning aiming at extending clinical application of previously approved drugs are influencing drug discovery per se: construction of chemical libraries containing both approved drugs and unapproved drugs (already tested in clinical trials) has been done by both NIH in the United States and in Japan. Similar libraries of approved drugs and commercially available reagents constructed by the academic sectors for convenience in intramural use are increasing in number. Furthermore, as mentioned above multiple Japanese pharmaceutical companies offer a part of their own chemical libraries for external use.

The concept of fragment library (or scaffold library) consisting of low-molecular-weight pharmacologically active compounds with a molecular weight of 250 or lower has been developed and proved successful.[(3)] Such a library efficiently yields hit compounds after screening of a relatively small number of samples (ranging from several hundreds to several thousands) and is recognized as an effective approach particularly for drug discovery from academia (fragment-based approach to drug discovery, FBDD).[(4)]

(2) Eligibility assurance in screening of biopharmaceuticals (vaccines/antibodies and nucleic acid/peptide drugs)

Development of biopharmaceuticals has been advancing rapidly. Compared with development of low-molecular-weight compounds, development of biopharmaceuticals is achieved far more frequently by academic researchers themselves almost to the step of obtaining the final product. As a consequence, pharmaceutical companies often adopt findings of university researchers as the scientific source for development of new biopharmaceuticals, while cases of launching a venture company of university origin as well as a venture company establishing a basis for development of biopharmaceuticals are also frequent.

Particularly in development of vaccines and antibody drugs, academic researchers who found the drug discovery target and acquired POC for disease treatment are often capable of epitope definition and antibody preparation as well. For screening of nucleic acid/peptide drugs, a situation intermediate between antibodies and low-molecular-weight compounds is assumed. Since the difference between *in vitro* and *in vivo* effects of nucleic acid/peptide drugs is often considered significant, secondary screening in an experimental system using laboratory animals is required. Furthermore, construction of a drug delivery system may be often required.

Eligibility (particularly reproducibility) of screening systems in development of biopharmaceuticals in the academia has not been strictly discussed as in development of low-molecular-weight compounds. However, since development of biopharmaceuticals in the academia involves operations according to non-GMP standards at almost all steps, reproducibility may matter at more advanced steps such as scaling-up of antibody production. An analysis has shown that contribution of venture companies possessing such a series of specialized techniques is significant in drug discovery of nucleic acid/peptide drugs. Overall, the presence of academia

is greater in drug discovery of biopharmaceuticals (vaccines/antibodies, nucleic acid/peptide drugs) than in drug discovery of low-molecular-weight drugs. Figure 2 represents the degree of contribution of various scientific sources to development of new drugs created at pharmaceutical companies (rated in 3 levels) in percentage.(5) This figure indicates that collaboration with universities is more important in development of biopharmaceuticals than in development of low-molecular-weight drugs.

Figure 2 : http://www.jpma.or.jp/opir/research/rs_066/paper_66.pdf

2.1.2 Test systems for target validation and grasping clinical predictability

(1) Test systems using animal models

Not a few model animals of monofactorial and multifactorial diseases have been created and played a certain role in drug discovery research as test systems indicating clinical predictability. On the other hand, many fundamental issues associated with experiments using model animals have been pointed out, including failure to reproduce drug efficacy demonstrated in model animals in human subjects. Accordingly, various experiments described below including those using iPS cells are conducted to evaluate clinical predictability. However, establishment of new model animals is still expected to open the way to development of new drugs, investigation of "eligibility" and "clinical predictability" of animal models appropriately reflecting the clinical profile of target diseases will remain necessary. Furthermore, recent innovative advances in genome editing technologies realized introduction of complex mutations in mice and preparation of tumor cell strains derived from patients in mice such as patient-derived xenografts (PDX): more advanced model animals obtained in a shorter time will serve as a tail wind for drug discovery research.

(2) Test systems using biobanks

Since human samples with appropriate clinical information are essential for clarification of clinical predictability in basic and translational research, importance of clinical samples has been re-recognized and biobank projects has been attracting research interest in recent years. The Ministry of Education, Culture, Sports, Science and Technology Japan installed "Review Meeting on Enrichment and Reinforcement of Research Infrastructure for Realization of Genome Medicine" to investigate the desirable picture of clinical biobank projects in Japan from the aspects of not only research and education but also industrial promotion.(6) In response to the report of this Review Meeting, new frameworks will be launched in Japan as well.

The industry sector is also moving towards collection of patient tissue/samples and search for new drug discovery targets, eyeing joint analytical research with academia. Clinical biobank projects established at university hospitals in anticipation of such a trend are expected to gain recognition, supported by the industrial needs. Demands for clinical biobanks are expected to extend further to disease areas beyond the reach of industry such as rare diseases. For extensive utilization of clinical biobanks, the text of informed consent form that allows for providing samples to extramural researchers (including those belonging to pharmaceutical companies), methods for sample collection that allows comparison of samples collected at multiple institutions by yet another institution, and a unified format of accompanying data are of key importance.

(3) Test systems using iPS cells

In 2012, Dr. Shinya Yamanaka was granted Nobel Prize for Physiology or Medicine 2012 for development of iPS cells. Development of this innovative technology has enabled *in vitro* initialization of cells isolated from patients to prepare pluripotent stem cells capable of differentiating multiple types of cells, which solved a number of essential issues associated with experiments using animal models.[7][8] Particularly, Dr. Junya Toguchida and colleagues of Center for iPS Cell Research and Application, Kyoto University, established iPS cells from peripheral blood of patients with fibrodysplasia ossificans progressiva (FOP), a rare disease with no effective therapy available, and induced their differentiation into cells with the disease-causing phenotype to highlight the effectiveness of iPS cells in drug discovery. Namely, they clarified the pathogenetic mechanism of FOP in cells differentiated from patient-derived iPS cells and identified molecules to be used as the drug discovery target. Furthermore, based on these results, they conducted chemical screening and successfully identified rapamycin as a candidate for therapeutic drug.[9] Utilizing these data, an investigator-initiated clinical trial of rapamycin in FOP was initiated. In the situation that cells with the disease-causing phenotype were not available from patients, the fact that cells induced to differentiate from iPS cells fortunately retained the phenotype closely involved in the pathology of FOP seems to provide the key to great success. Thus, an attempt to construct a screening system by *in-vitro* "reproduction" of the target disease using patient-derived iPS cells is likely to reproduce "clinical profiles of human disease" more exactly than an "animal disease model." Therefore, there is no doubt that iPS cells will serve as a test system with an enhanced clinical predictability. Nevertheless, as in most diseases, it is not easy to determine whether an "acquired" disease may be "generalized" or not. However, solving faced problems one by one will extend the future potentials of iPS cells. In fact, a project regarding application of iPS cells to drug discovery is ongoing, supported by AMED.[10]

(4) Test systems involving *in silico* analysis

So-called *in silico* drug screening utilizing molecular dynamics (MD) computer simulations of three-dimensional structure of the target protein has established an important position in drug discovery. This approach has contributed to development of HIV protease inhibitors, an antiviral agent for influenza (neuraminidase inhibitor) oseltamivir, a tyrosine kinase inhibitor gefitinib, and others. More recently, extensive *in silico* "clinical predictability" studies utilizing additional information on cellular metabolism, etc., incorporated in computers are ongoing. One of the best known systems for *in silico* screening may be "Anton 2," a massively parallel supercomputer under development by an investor D. E. Shaw and his colleagues. Anton 2 is a system specialized in MD calculations and oriented for molecular dynamics simulations of biological macromolecules such as proteins. It consists of many application-specific integrated circuits (ASICs) interconnected by a high-speed network. However, even Anton 2 is difficult to "substitute" tests using actual cells and organisms completely: the importance of experiments in animal models remains unchanged.

(5) Testing methods based on precision medicine and genome-wide association studies

Precision medicine is an approach for selecting the optimal treatment method for individual patients based on analysis of disease-related factors (biomarkers). A number of pharmaceuticals developed in combination with methods for analyzing particular biomarkers (companion

diagnostics[11]) have already been approved as antineoplastic agents, etc. Furthermore, advances in cancer genomic medicine are remarkable: methodologies for gene panel testing that analyzes mutations, etc., in many candidate genes with a next generation sequencer (NGS) are investigated and development of technologies for advanced medicine aiming at more detailed diagnostics and selection of the optimal treatment method is in progress.[12] Information thus obtained will be accumulated in a database for application to selection of existing therapeutic drugs as well as for application to exploration of new drug discovery targets. Genome-wide association studies (GWAS) involving genome-wide exploration of disease-related genes allow identification of disease-related genetic mutations/polymorphisms and provide useful methodologies for disease analysis and exploration of new drug discovery targets. Further advancement is expected if driven by development/improvement of NGS. Most genetic mutations/polymorphisms identified in GWAS are related to the disease diversity or risk factors and may not directly serve as drug discovery targets. However, analysis of additional diseases and organization of collected data will hopefully lead to definition of drug discovery targets and subject enrichment in clinical development.

(6) Test systems involving AI (artificial intelligence)

Since AI is capable of reconstructing the vast volume of latest information and findings accumulated as big data and has a special function of deep learning, application of AI to drug discovery has already been attempted. Presumably in a very near future, proposals aided by AI will be realized not only in drug discovery but also in preclinical studies to verify clinical predictability, formal clinical studies, and even marketing in commercialization.

2.1.3 Successful drug discovery from academia based on the clear target validation and clinical predictability

The following examples represent successful drug discovery from academia, i.e., basic research in Japan leading to successful commercialization of drugs because of clear relationships between the drug and target protein and between the target protein and disease.

(1) Nivolumab (anti-PD-1 antibody): Dr. Tasuku Honjo - Ono Pharmaceutical Co., Ltd. and Bristol-Myers Squibb

Discovery of PD-1 by Dr. Honjo and colleagues dates back to 1990's. Thereafter, the function of PD-1 as the brake on the immune system was identified. With subsequent animal studies eyeing application to cancer treatment, disease association demonstrated in clinical observations (e.g., enhanced expression of PD-1 ligand in clinical cancer, reverse correlation between PD-1 expression and survival in cancer patients) led to successful development.[13]

(2) Mogamulizumab (anti-CCR4 antibody): Dr. Ryuzo Ueda - Kyowa Hakko Kirin, Co., Ltd.

In 2004, Dr. Ueda and colleagues found that a chemokine receptor CCR4 was highly expressed on the surface of tumor cells in patients with adult T-cell leukemia (ATL) and that the prognosis of CCR4-positive patients with ATL was poorer than that of CCR4-negative patients. Furthermore, a low-fucose-type anti-CCR4 antibody with an enhanced ADCC activity was prepared in joint research with Kyowa Hakko Kogyo Co., Ltd (predecessor of Kyowa Hakko Kirin, Co., Ltd.) and was reported to have an excellent therapeutic effect in ATL. Subsequently,

clinical development as a therapeutic agent for ATL was formally initiated and resulted in approval in 2012.[14]

(3) Tocilizumab (anti-IL-6 antibody): Dr. Tadamitsu Kishimoto - Chugai Pharmaceutical Co., Ltd.

Dr. Kishimoto and colleagues reported that "IL-6 was the agent inducing autoantibodies." Chugai Pharmaceutical initiated joint research to explore an inhibitor of IL-6. Tocilizumab is a humanized chimera antibody prepared from mouse anti-human IL-6 receptor monoclonal antibody by genetic recombination. It binds to IL-6 receptor and thereby inhibits binding of IL-6 to its receptor. By this mechanism of action, it exhibits immunosuppressive effects by suppressing physiological actions of IL-6 and serves as a molecular target drug. Tocilizumab is currently used for the treatment of rheumatoid arthritis (RA) and systemic juvenile idiopathic arthritis.[15]

(4) Bosentan (endothelin receptor antagonist): Dr. Masashi Yanagisawa - Actelion Pharmaceuticals

Dr. Yanagisawa and colleagues discovered endothelin and the endothelin receptor inducing potent vasoconstriction. Bosentan suppresses endothelin-induced vasoconstriction by binding to the endothelin receptor and blocking binding of endothelin to the receptor. It is used as a therapeutic agent for pulmonary arterial hypertension. In fact, an excess endothelin level is reported in patients with pulmonary arterial hypertension. A Swiss pharmaceutical company Actelion purchased bosentan from Roche for global development/marketing as a therapeutic agent for pulmonary hypertension.[16]

(5) Fingolimod (S1P receptor antagonist): Tetsuro Fujita - Mitsubishi Tanabe Pharma

Induced by binding of a sphingolipid S1P to the S1P receptor on the surface of lymphocytes, lymphocytes migrate from secondary lymphoid tissue to peripheral blood to be involved in immune response. Dr. Fujita attempted to isolate an immunosuppressive substance from plant worms in a joint research with Taito Co., Ltd. and Yoshitomi Pharmaceutical Industries, Ltd. and found Fingolimod (FTY720), an immunosuppressant that induces internalization of the S1P receptor by binding to the S1P receptor and thereby suppresses binding of S1P to the receptor. After initiation of development by Mitsubishi Tanabe Pharma Corporation, this substance was licensed out to Novartis. While Fingolimod is used for the treatment of multiple sclerosis, many points remain unknown regarding its mechanism of action. A probable mechanism is that Fingolimod may inhibit migration of lymphocytes from secondary lymphoid tissue to reduce the number of lymphocytes migrating to the central nervous system and thereby suppress inflammation and demyelination within the brain and spinal cord[17].

(6) Trametinib (MEK inhibitor): Dr. Toshiyuki Sakai - Glaxo SmithKline (GSK)

Originally analyzing the mechanism of inactivation of a tumor suppressor gene RB (retinoblastoma), Dr. Sakai focused on the fact that RB was inactivated in many cancer cases and proposed chemical screening from the viewpoint of "RB reactivation." An MEK inhibitor trametinib was identified using enhancement of expression of the p15 gene acting on RB activation as an index. Central Pharmaceutical Research Institute of Japan Tabacco Inc. (JT), Dr. Sakai's partner, repeated synthesis of hit compounds using enhancement of expression of the p15 gene as index and successfully found trametinib. In August 2012, 6 years after out-licensing from

JT to GSK, GSK submitted a new drug application of trametinib to Food and Drug Administration (FDA) for the treatment of “unresectable or metastatic melanoma positive for *BRAF* V600E mutation” and was granted marketing authorization in May 2013.[18] After further out-licensing to Novartis Pharma K.K., a combination therapy of trametinib and dabrafenib, a BRAF inhibitor, for the treatment of “*BRAF*-mutated advanced non-small-cell lung cancer” was approved in EU and the United States in April and June 2017, respectively.

(7) Crizotinib (ALK inhibitor): Dr. Hiroyuki Mano - Pfizer

Dr. Mano searched the causative gene for lung cancer under a concept of “suppression of the function of a gene harboring cancer driver mutations like imatinib acting on the BCR-ABL gene in blood cancer” and discovered EML4-ALK. This was a great discovery in basic research entirely breaking the conventional understanding that “epithelial tumors have practically no cancer genes generated by chromosome translocation” and stimulated an intense competition in development of ALK inhibitors by pharmaceutical companies in the world. As a result, Crizotinib of Pfizer was granted marketing authorization at the world's highest speed. Crizotinib is used for the treatment of *ALK*-positive unresectable advanced/recurrent non-small-cell lung cancer and *ROS1*-positive unresectable advanced/recurrent non-small-cell lung cancer.[19]

These brilliant achievements highlight the high level of basic research in Japan. Regretfully, however, 4 out of the 7 substances described above (approximately 57%) were commercialized by pharmaceutical companies outside Japan. This illustrates the importance of a framework linking basic research inside Japan to new drug discovery projects even more clearly. Namely, extraction of problems in academic-industrial collaboration and proposal of solutions thereof is urgently needed.

2.1.4 Acquisition of data with assured reliability

Preclinical studies in compliance with guidelines for development of pharmaceuticals are to be conducted at the stage when a single drug candidate compound is selected after exploratory research. These studies are essentially required for New Drug Application. Toxicology studies (general and special toxicology studies) and safety pharmacology studies must be conducted in compliance with GLP. In addition, pharmacology studies and pharmacokinetic studies (studies to clarify in vivo kinetics (absorption, distribution, metabolism, and excretion) of the test substance) must comply with “Reliability Criteria of Application Data[20].” The conduct of these studies by academic researchers themselves is not realistic with respect to cost, facility, and specialty. However, academic researchers should thoroughly understand that these studies are essentially required for New Drug Application and strictly regulated by guidelines: based on this understanding, they should make full use of the opportunity to conduct these studies in their own drug discovery research.

Of the application data required, pharmacology and pharmacokinetic studies may be conducted by academic researchers and are subjected to reliability survey by PMDA to examine whether the application data are compiled as specified in Article 43 of Enforcement Regulations of The Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices.

[1] Correctness: The data shall be complied correctly based on the results of analysis and studies performed in order to compile the data concerned.
[2] Integrity/Completeness: When results are obtained in analyses or studies specified in the previous item, which cast doubts on the quality, efficacy or safety of drugs in applications, these results of the analyses and studies shall also be investigated and evaluated, and the results obtained shall be entered in the data concerned.
[3] Retainability: The data which form the basis of the data concerned shall be retained until the date when a decision is made for or against the approval.

It should also be noted that written and signed declarations of those responsible for collection and compilation of data for approval applications, stating that all submitted data were collected and compiled in compliance with "Reliability Criteria of Application Data," are required to be attached.

Pharmacology and pharmacokinetic studies to be conducted by academic researchers for commercialization should be conducted considering the aforementioned "Reliability Criteria of Application Data": reproducibility and reliability of data should be valued in the conduct of these studies. Department of Innovative Drug Discovery and development, AMED, sponsoring the iD3 Booster program has published a document on basic concepts in data quality assurance at the stages of basic research and drug discovery research in development of pharmaceuticals.(21) In this document, recording of experimental notebooks, storage of raw data, and other topics are described. The key points include the following: 1) traceability to raw data is assured for every figure and table in each report; 2) both the person who conducted the experiment and date of experiment are identifiable; and 3) inconvenient data are not eliminated in preparing a figure or a table. Combining results of multiple experiments conducted on different days and describing them as if they were obtained in a single experiment should also be avoided. In animal studies, when experiments in the control group and the drug administration group were conducted on separate days as different experiments, describing the results from these experiments as obtained in a single experiment should also be avoided. In conducting a pharmacology study in animals in compliance with "Reliability Criteria of Application Data," determination of the final formulation of drug substance may sometimes be necessary in addition to stability of drug substance in the dose solution and pharmacokinetic studies (involving assay of concentrations of the drug and its metabolites during the process of absorption, distribution, metabolism, and excretion of administered drug to check, for example, if oral absorbability is assured when development of an oral preparation is intended).

2.2 Importance of venture companies and comprehensive academic-industrial partnership agreement

2.2.1 Venture companies

in 2000's, the increase in development and sales of biopharmaceuticals has been remarkable and many of them originate from the activities of drug discovery venture companies. Biopharmaceuticals account for 36% of blockbuster drugs in 2012. In 2015, the sales of biopharmaceuticals amounted to approximately 30% of the total sales of pharmaceutical products, exhibiting an increase in rate greater than that of low-molecular-weight pharmaceuticals.(22)

Insufficient development of venture companies is considered to have directly influenced Japan's inferiority in development of biopharmaceuticals.[23] Among 252 pharmaceutical products approved by FDA in 1998-2007, approximately half of 117 products from the United States were biopharmaceuticals, and 72 were of academic origin. On the other hand, 4 out of 23 products from Japan were of academic origin.[24] In the United States, a reasonable system is extensively functioning to transfer the results of drug discovery research for biopharmaceuticals by academic researchers to the developmental process, via drug discovery venture companies of academic origin or translational research by existing bioventure companies, finally to major pharmaceutical companies for development of pharmaceutical products (Fig. 3). On the other hand, problems related to insufficient collaboration in alliance between pharmaceutical companies and bioventure companies in Japan have been closely investigated, and solutions have been proposed.[25] In addition, a number of national support programs for venture companies (from universities) have been implemented via AMED and JST and are expected to change the situation for the better.

Figure 3 : Current status of drug discovery, etc., originating from Japan[26]

In translational research by venture companies, there are 3 possible patterns of relationship between the venture company and academia: (1) launching a venture company by academic researchers themselves; (2) concluding outsourcing or joint research agreement with a venture company of "drug discovery platform" type; and (3) technology transfer to a venture company aiming at business expansion.

(1) Launching a venture company by academic researchers themselves

Launching a venture company is a form of technology transfer. While some venture companies aim at implementing the entire process from clinical development, application of marketing authorization, to manufacture and sales by their own hands, most venture companies in the pharmaceutical industry are expected to hope a technology transfer to or corporate acquisition by major companies in midway of development. Researchers utilize the fund and know-how thus obtained as capital and plan to launch the next project.

Advantages of launching a venture company include the following: First, a venture company has freedom from regulations and pressure of human relations within the organization of major companies and research institutions. In particular, technology transfer or exclusive licensing from universities, etc., to venture companies may facilitate joint research with major companies. Furthermore, if support from a venture capital is provided, additional investment and technical support may be available along with milestone progress to allow devotion to research for a longer time (compared with financial support from public research funding). In addition, on achievement of intended results, great returns may be obtained by initial public offering or sale of business. To obtain support from a venture capital, it is important to demonstrate the potential of the research to bring innovation to society, although associated with a high risk.

On the other hand, launching a venture company is associated with a number of difficulties. First, team building with experts such as professionals in management is required: however, recruitment of such a specialized human resource is not an easy task. In addition, a substantial

amount of initial investment is required to establish infrastructure of research, etc. Furthermore, continued fund procurement is also required to maintain the organization.

(2) Concluding outsourcing or joint research agreement with a venture company of "drug discovery platform" type

There are venture companies of platform type providing a technological platform for drug discovery such as custom synthesis of peptides and nucleic acids, outsourcing of drug screening, and outsourcing of genetic analysis, etc. Differently from negotiation with a major pharmaceutical company, negotiation with such a venture company goes on by direct dialogue with the top management, which enables quick decision-making. In addition, the venture company per se is oriented toward joint research with academia and has a high affinity with academia.

(3) Technology transfer to a venture company aiming at business expansion

In some cases, a venture company may aim at business expansion by investing a promising external project, utilizing the fund obtained by stock listing, etc., as capital. This is an important component of innovation ecosystem. Again in this case, the venture company is likely to be oriented toward the academia and have a high affinity with academia.

2.2.2 Comprehensive academic-industrial partnership agreement

This is an agreement ensuring presentation of a technical information list at a non-confidential level from academia under a non-disclosure agreement to allow a request of further detailed information on subjects the industry is interested in for future joint research or out-licensing.

Concluding a non-exclusive comprehensive partnership agreement with the industry and regularly disclosing technical information enables timely initiation of joint research. This enables understanding of interest or needs within the partner company.

When entering into a joint research, utilization of research resources (know-how, facilities, etc.) of both parties may accelerate research and development activities. Particularly, in development of low-molecular-weight compounds, construction of academic-industrial cooperative relationship (e.g., exploration of lead compounds to synthetic development to the optimal compound by the industry and evaluation in animal models, etc., by the academia) will accelerate research.

On the other hand, there are some considerations related to comprehensive partnership agreement. There may be possible competition with in-house projects within the partner company and a risk of providing information such as technical know-how. Inversely, disease or technology outside the primary focus area of the partner company may not be selected as the subject of joint research or technology transfer. In particular, there may be a risk that development of seeds related to rare/intractable diseases does not proceed smoothly despite urgent clinical needs.

2.3 Importance of academic-industrial collaboration at an early stage

While organization of human resources, etc., in the academic community toward drug discovery research has been promoted in recent years, mainly at Translational Research Core Centers selected by AMED, neither the amount of experience accumulated in the entire organization nor the number of personnel competent for drug discovery from academia is sufficient at present. Furthermore, considering the aforementioned various situations, the key to successful drug discovery from academia is to start academic-industrial collaboration with an

appropriate industrial partner as soon as possible once academic researchers intend to start drug discovery research.

Through joint research based on academic-industrial collaboration, promotion of effective drug discovery research utilizing the advantages of both parties is expected to be feasible. Although some aspects in drug discovery research may not be sufficiently covered by basic research alone, the authentic academic research for the sake of "pursuit of truth," early starting of joint research with industry will help academic researchers to reach early recognition on what is needed in drug discovery research beyond the scope of basic research. Although some tasks such as compliance with GMP for investigational products are beyond the ability of an ordinary academic laboratory, proper role sharing in joint research (e.g., preparation of test substance in compliance with GMP by the industry and preclinical studies using it to acquire POC for efficacy and elucidate the mechanism of action by the academia) is expected to realize rapid conduct of research. In particular, considering that the conduct of preclinical studies of a low-molecular-weight compound requires its synthesis in kilograms, which is far beyond the capacity of laboratory-scale synthesis, it is necessary for academic researchers to find a company capable of manufacturing the target low-molecular-weight compound at an early stage of research, eyeing future compliance with GMP for investigational products. Furthermore, participation of clinicians in academic-industrial collaboration is important for elucidation of clinical significance of the drug discovery project and feasibility of clinical development.

Another advantage of academic-industrial collaboration may be expected from the standpoint of intellectual property rights. As described earlier, the contents of patent applications from academia are often insufficient. If joint patent application with an appropriate partner company is feasible, missing information in the description of such a joint application document intended as a drug discovery patent is expected to be minimized through review from the viewpoint of the industry sector. In addition, joint application may result in assignment of a part of the patent right. In such a case, support from the industry may be available not only for patent application procedures but also for costs of patent application/maintenance.

When the industry decides on joint patent application, this decision is made after thorough examination on existence of a prior patent as well as feasibility/potential of the research per se. Accordingly, once the industry approves patent application and proceeds to joint patent application, this means that the industry considers the research result as an invention deserving patent protection, and it is likely to continue joint drug discovery research after patent application. Inversely, when the industry considers that joint patent application is impossible, the academia can know the conclusion that further continuation of this drug discovery research is difficult while the research is at an early stage. In this case, the academia can publish the research results as "publicly known information" without wasting time and manpower and move on to another research subject.

On the other hand, there are several considerations in academic-industrial collaboration. Continuous efforts to build up a good relationship with the industry specialized in related areas are needed, because it is expected to be difficult for the academia without a reliable industrial partner to seek for determination on whether the disclosed unpublished data deserve patent protection. In addition, even if joint research is initiated and the research itself is ongoing smoothly as planned, it may be discontinued due to the corporate strategy of the industry. Furthermore, partial assignment of the patent right on joint application may reduce flexibility of

research such as potential collaboration with another company. As will be described below (see "3.1.2 Drug discovery support toward out-licensing to pharmaceutical companies"), enrichment of systems supporting academic-industrial collaboration in drug discovery is rapidly in progress in recent years and active utilization of these systems is desired.

Anyway, when the academia conducts drug discovery research, it should desirably start academic-industrial collaboration as early as possible and ideally decide on joint patent application with partial assignment of the patent right to the industrial partner, because manufacture and sale of the final pharmaceutical product are the role of the industry.

2.4 Importance of mobility of people-to-people exchange between the pharmaceutical industry and academia

In Europe and the United States, move of researchers in the industry to universities or regulatory agencies such as FDA and European Medicines Agency (EMA), etc., or move in the reverse direction is quite common. Such people-to-people exchange not only leads to personal carrier progression and brings change in the drug discovery environment such as construction of networks across standpoints and extension of non-competitive areas in drug discovery.

In contrast, people-to-people exchange in Japan is not as active as in Europe and the United States. In Japan, there were some examples of long-term academic-industrial collaboration in basic research, aiming at clarification of the pathology and subsequent exploration of topics for drug discovery research. Furthermore, researchers in the industry were often sent to academic laboratories for 1-2 years for improvement of research competency in new research area or as a part of human resource development. Such exchange not only allows the introduction of state-of-the-art science into the industry but also is effective in human network development between researchers from the industry and academia. In many cases, this has resulted in construction of long-term human relations not motivated by self-interest. In addition, active exchange between research laboratories in the industry and clinical laboratories in the academia enables the industry to know at an early stage of drug development what kind of drugs are needed in clinical practice and utilize this information in exploration of research topics. Furthermore, recent environmental changes in the pharmaceutical industry, e.g., change in the corporate strategy, has led to reduction in scale or even closure of research centers, resulting in increased mobility of researchers and increased surplus facilities. In some cases, an ex-worker of the pharmaceutical industry gets a position at a University-industry Collaboration Center or aims at launching of a venture company. Moreover, converting surplus facilities of pharmaceutical companies to open laboratories for utilization by academic researchers would contribute to activation of people-to-people exchange. On the other hand, the industry tends to reduce resource allocation to basic research (e.g., limit the destination of basic research resource allocation to priority areas). Launching of joint research with academia in such areas and participation of researchers in the industry in such joint research will be useful in raising the standard of drug discovery power in the entire Japan.

In people-to-people exchange between the industry and academia, determination of valid price for the contribution of individual parties in drug discovery, if any, will lead to activation of people-to-people exchange. The academia should claim its contribution within a valid range, while the industry should in turn bear the claimed expense.

The "cross-appointment system" allows a single researcher to conclude employment agreements with two or more organizations among universities, public research institutions, and

private corporations and to be engaged in activities under the responsibility of individual organizations. Active introduction of this system has been included in national strategies such as "Japan Revitalization Strategy Revised in 2014" and "Comprehensive Strategy on Science, Technology and Innovation." The Ministry of Economy, Trade and Industry and the Ministry of Education, Culture, Sports, Science and Technology Japan have compiled basic frameworks and considerations of the cross-appointment system.[27] In the future, utilization of the cross-appointment system is expected to stimulate mobility of people-to-people exchange.

While people-to-people exchange per se should be considered from a global viewpoint, one possible reason for inactive global people-to-people exchange may be substantial differences of Japanese social environment from that in Europe and the United States (e.g., Japan is not an English-speaking society). How to accomplish globalization in Japan under various restrictions is a big challenge.

2.5 Collaboration in drug discovery for multifactorial diseases and development of advanced medicine

In cancer of some types, a single genetic mutation is known to be involved in tumor cell growth and tumor exacerbation (driver mutation). For example, fusion of two genes, bcr and abl, due to chromosome translocation (Philadelphia chromosome, Ph chromosome) is observed in approximately 20% of patients with acute lymphoid leukemia (ALL). Accurate diagnosis to detect Ph chromosome is the key to prescription of therapeutic drug for this condition (imatinib). Namely, if a disease is caused by abnormality in a single molecule, the target of clinical development is easily defined. However, many diseases such as lifestyle diseases (hypertension, diabetes mellitus, dyslipidemia) and dementia (e.g., Alzheimer's disease) are caused by multiple factors. Both genetic and environmental factors are of key importance in development of multifactorial diseases. Pathological analysis involving whole-genome analysis and metabolomics analysis is in progress and its application to diagnosis of and drug development for multifactorial diseases is expected. When the effect of a drug on a single factor is examined in patients with a multifactorial disease, the subject population may contain one subpopulation with complete response and the other subpopulation with no response. A large sample size and a long follow-up period are required to demonstrate efficacy of a therapeutic drug for a multifactorial disease.

On the other hand, in most of the multifactorial disease, an underlying illness is already present in apparently healthy individuals. Some actions taken at this stage might eliminate the onset of signs and symptoms. For example, appropriate therapeutic/preventive intervention at the stage of mild cognitive impairment (MCI) prior to the onset of dementia is said to induce disease recovery or delay the disease onset.[28] In addition, intervention at the stage of prehypertension or impaired glucose tolerance is reported to prevent the subsequent onset of hypertension and diabetes mellitus.[29] Thus, in dementia and lifestyle diseases, "preemptive medicine" involving appropriate therapeutic intervention in the high-risk population identified by presymptomatic testing to prevent the onset of symptomatic disease is expected to be important in the future.

However, in preemptive medicine, it is uncertain at present whether the subject will develop a symptomatic disease in the future. Demonstration of the effectiveness of an approach based on the concept of preemptive medicine requires an extremely large sample size and a prolonged follow-up period. Both genetic predispositions and environmental factors are critical factors to be

considered in preemptive medicine. Clinical development of therapeutic drugs in a subject population with predispositions for a particular disease (identified by disease prediction based on genetic and environmental factors possessed by individuals) would be more efficient, if possible.

In drug discovery for the treatment of multifactorial diseases and development of preemptive medicine, efficient alliance between research resources owned by the academia (e.g., data of cohort studies and other clinical studies, biobanks) and the industry will be of key importance.

2.6 Considerations in patent application from academia

The importance in intellectual property has been mentioned under "1.4 Difference between acquisition of intellectual property sought by the industry and the current situation" in Section 1. Considerations in patent application from academia will be described below:

2.6.1 Strategy-based patent application

In recent years, importance of patent application has been recognized at universities as well. However, due to lack of detailed strategies for intellectual property toward commercialization and insufficient investigation on description/scope of the patent and the timing of its application, the patent application, although with considerable effort, may fail to exhibit its full value in some cases. Among healthcare-related patents, patents protecting products such as pharmaceuticals and medical devices are the most important. Accordingly, strategic elaboration on the timing of patent application based on thorough consideration of its objective/intention, i.e., product development, is essential. It should also be noted that, since pharmaceuticals are covered by a relatively small number of patents, it is important to construct a strategy for each application regarding description/scope of application, timing of application, and term of existence based on consideration of the significance and objectives of individual patents. Furthermore, the academic sector will also demand strategies for patent right acquisition and future assignment to the industry, etc.

2.6.2 Careful preparation

As mentioned above, survey of the competition status should always be conducted on patent application. In drug discovery research, there are almost always prior research and applied or acquired patents. If a patent application containing any previously applied content has been filed without a prior survey, there may be a risk of receiving a warning document from a prior inventor after publication of the filed patent with subsequent interception of the whole research results (which was obtained after prolonged efforts) by the prior inventor. Results of such a competition survey are important on the occasion of discussion with the partner pharmaceutical company.

It should also be noted that academic researchers tend to prepare patent specifications covering extensive concepts with a limited number of examples. However, failure to properly respond to the patent examiner's comments after request for examination may be interpreted as failed proof of "patentable innovative concept" and apparent demonstration of "literal publicly known art," resulting in damage to the patent that would serve as "basic application." A framework for sharing an idea of a new drug conceived by academic researchers with representatives of a pharmaceutical company as soon as possible, requesting a competition survey, and discussing the description of patent application together may also be necessary.

While academic researchers tend to consider patent application as a goal of strategy for intellectual property, it is important for them to recognize that the entire contents of the research

will be open to the public 1.5 years after filing of patent application. Since the greatest achievement for academic researchers is to secure scientific priority, preparation such as publication of research results as a scientific article simultaneously with patent application will be necessary. To allow addition of related data newly obtained by article revision, etc., to the patent, the article should desirably be completed within 1 year after patent application when addition of examples based on "Priority Claim Based on Japanese Patent Application" is feasible.

2.6.3 Measures for coping with delay in publication and public presentation of results

If relevant research results are published in a scientific journal, publicly presented at a scientific meeting, or posted on the internet prior to patent application, the research results lack novelty, making acquisition of patent containing them impossible. Since it is self-evident that competition for "the world-first achievement" is the nature of basic research, any delay in publication of the achievement due to patent application would be a great loss to basic researchers. Accordingly, a method must be devised for rapid patent application and elimination of delay in publication. Without involvement of the industry, the researcher alone or in collaboration with the TLO will prepare a patent application dossier. While the industry applies for full resource patents, the scope of university research allows only patent applications for partial outputs (such as screening patents, etc.) instead of patent right acquisition covering final products in many cases. Furthermore, according to an expert's opinion,[1] there is an established pattern in patent application in the field of life science and patent claims to be included in the application can be assumed in advance when a research is planned. Consequently, if prepared properly, filing a patent application prior to publication of scientific article when the research data is obtained is less difficult and achievable more quickly than expected. However, in application of a partial output patent, it is difficult to determine the range of research results that can be included in a valid patent and this should be considered in combination with a plan for joint research built on patents. Namely, rapid allocation of the content included in a patent and data to be published as a scientific article is essential. In this sense, in case of either a partial output patent or a full resource patent, collaboration with experienced experts in intellectual property related to drug discovery affiliated with the industry would realize strategic article publication and patent application. Also, considering that collaboration with the industry is not always feasible for university researchers, development of human resources competent with the role of the aforementioned experts by the academia or recruitment of such human resources from the industry by stimulating mutual personnel exchanges with the industry may be an effective measure.

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3 Current status and future of systems supporting drug discovery of academic origin

3.1 Current status of support systems

3.1.1 Support for search for seed compounds - University of Tokyo Drug Discovery Initiative

To conduct drug discovery research based on low-molecular-weight compounds, platform facilities such as large chemical library facilities and high-throughput screening (HTS) devices are essential. Conventional lack of such platform facilities in the academia had previously interfered with initiation of drug development based on low-molecular-weight compounds. To overcome such situation, “Target Protein Research Program” (FY 2017-FY 2011)[(1)] and “Platform for Drug discovery, Informatics, and Structural life science” (FY 2012-FY 2016)[(2)] projects were implemented.

(1) Large chemical library facilities

By the aforementioned two projects, a large chemical library facility available for academic researchers was established at University of Tokyo Drug Discovery Initiative. As of March 2017, more than 280-thousand compounds are collected in the compound warehouse and a system providing a number of characteristic groups of compounds (e.g., groups of compounds focused on particular biomolecular species, groups of compounds with known pharmacological activity) on request has been constructed. Recently, compounds from the industry are also collected and a system to facilitate collaboration with pharmaceutical companies is being established from the initial stage of development.

(2) Provision of compounds and screening support

Compounds and compound databases are provided not only for national/public universities, private universities, and public research institutions but also for the industry. The total number of projects committed by University of Tokyo (alone or in collaboration with the member universities of the aforementioned control platform) amounts to 499 as of March 2017, while the number committed by all members of the control platform of PIDS (Platform for Drug Discovery, Informatics, and Structural Life Science) is 600 (see Table 2).

Prior to providing compounds, advice on the screening method and how to obtain definite hits are provided as a part of user support operations under strict confidentiality. The opportunities of this advisory discussion are provided by multiple experts who have long been engaged in drug discovery screening in the industry and functioning very effectively. Implementing HTS requires techniques and concepts entirely different from those employed in screening of a smaller number of compounds. The advisory discussion covers topics such as settings for counter assays and higher-order screening methods. To obtain reproducible definite hits, the quickest way is to attend a technical workshop in addition to obtaining advice from experts. Chemical Screening Workshops are held for general (novice) users: since the 1st workshop in 2011, a total of 21 workshops have been held to date.

(3) Open-access screening devices/facilities

Most researchers implementing HTS in academia did not possess their own devices required for the purpose. At present, HTS devices are installed not only at University of Tokyo Drug Discovery Initiative but also at Hokkaido University, Tohoku University, Kyoto University,

Osaka University, Kyushu University, and Nagasaki University: all of them are available for open access.[3]

(4) Future perspectives and issues

Regarding search for seed compounds by the academic sector, the industry sector seems to have 2 alternative opinions. One is “The academia has only to conduct basic research. There is no need for replicating the way of the industry”; the other is “If we could find any compound reacting with unique target molecules possessed by the academia, this would substantially facilitate subsequent research toward drug discovery and could be of great help.” The former complaint might be ascribable mainly to low-quality data long provided by the academia. The latter expectation is obvious from the fact that several ten-thousands (not just several) of compounds possessed by the industry are offered for screening by the academia. What should the academia do to obtain high-quality screening data sufficient to convince the industry? The long-term answer is enrichment of drug discovery education at the university, while the short-term answer is utilization of human resources from the industry. In contrast to Europe and the United States, mobility of people-to-people exchange between the academia and industry is minimal in Japan. For successful search for seed compounds, not only enrichment of hardware such as chemical libraries and screening devices but also recruitment of excellent human resource are essential.

3.1.2 Drug discovery support toward out-licensing to pharmaceutical companies - AMED (iD3) and DSANJ

Every Japanese university has been making efforts in enrichment of education/support systems for academic researchers to promote academic-industrial collaboration. In addition, researchers can expect the following support covering from the initial stage of drug discovery to the clinical stage.

(1) Support for obtaining lead/hit compounds from promising target molecules discovered by the academia

Drug Discovery Support Network[4] (AMED)

This is Japan’s first drug discovery support system that involves a firm collaboration system constructed with RIKEN, National Institutes of Biomedical Innovation, Health and Nutrition, and National Institute of Advanced Industrial Science, etc., and provides all-Japan support to research for practical application aiming at creation of innovative new drugs based on excellent research results from universities and public research institutions. This support system is intended for drug discovery seeds with a high potential for practical application generated at universities, etc. and mainly covers from exploratory research to preclinical development.

The iD3 Booster[5] (comprehensive drug discovery support program) (AMED)

This program offers strategies for intellectual property, strategies for research, and a platform for drug discovery technology, etc., to researchers who possess drug discovery seeds considered to have a high potential for practical application, at the expense of AMED. The support available from this program ranges from methods for searching/identification of lead/hit compounds to out-licensing to the industry, through profiling/validation of target

functional molecules, HTS at Drug-discovery Innovation and Screening Consortium (DISC),[6] and preclinical studies, etc.

Drug Discovery Navi[7] (consultation program for free) (AMED)

To accelerate practical application of excellent research results (drug discovery seeds) generated at universities and public research institutions, highly experienced drug discovery coordinators affiliated with Department of Innovative Drug Discovery and Development, AMED, respond to various consultations from researchers engaged in drug discovery research.

Basis for Supporting Innovative Drug Discovery and Life Science Research, BINDS[8] (AMED)

Aiming at practical application of excellent results obtained in life science research in the form of pharmaceutical products, etc., this program establishes and maintains large-scale facilities such as synchrotron radiation facilities (SPring-8, Photon Factory), cryo-electron microscopes, chemical libraries, and next generation sequencer for active open access (joint usage). In addition, this program provides a strong backup from supporting researchers skilled in cutting-edge technologies such as structural analysis, protein production, search for chemical seeds/lead, structural development, genomic analysis, and *in-silico* screening for the promotion of research by external researchers. The organization for this program consists of the following units competent with support ranging from basic research, target validation, screening, to structural development.

- Platform Function Optimization Unit
- Structural Analysis Unit/Structural Analysis Area
- Structural Analysis Unit/Protein Production Area
- Chemical Seeds/Lead Search Unit/ Library Screening Area
- Chemical Seeds/Lead Search Unit/ Structural Development Area
- Biological Seeds Search Unit
- *In-silico* Unit

(2) Chemical libraries available to academia

University of Tokyo Drug Discovery Initiative (see “1-1 Support for search for seed compounds”)

Supports construction of a system for cooperation between the academia and pharmaceutical industry by demonstrating successful identification of lead/hit compounds.

National Institute of Advanced Industrial Science and Technology / Technology Research Association for Next Generation Natural Products Chemistry Natural Products Library[9]

RIKEN Chemical Bank[10]

Kitasato University Omura Natural Compound Library[11]

National Institutes of Biomedical Innovation, Health and Nutrition Antibody/Nucleic Acid Library, Medicinal Plant Library,[12] AMED DISC[13] (an AMED program collecting compounds from 20 pharmaceutical companies)

AMED Next Generation Drug Discovery Seeds Library Construction Project[14];

This project promotes construction of a library of compounds, etc., (with a molecular weight of approximately 500) expected to have an inhibitory effect on protein-protein interaction (PPI).

(3) Approach from pharmaceutical companies to eliminate mismatches between their own needs and the academia

Based on their own needs, individual pharmaceutical companies make their efforts to recruit ideas on research and drug discovery (open innovation) extensively or offer a part of their own chemical libraries for open access. These approaches are implemented in the form of joint research with each pharmaceutical company and characterized by inclusion of access to technical resources related to drug discovery and compounds owned by the company. Such efforts are listed as "Information from the Industry" by AMED for open access,[(15)] allowing researchers to obtain information from this one-stop information service.

There are also attempts to provide compounds from the pharmaceutical industry to the academia. In the "Joint Open INnovation of drUg repoSitioning" (JOINUS) program, three Japanese pharmaceutical companies (Astellas Pharma, Mitsubishi Tanabe Pharma, and Daiichi Sankyo) have started a joint attempt to collect compounds either subjected to clinical trials or whose development was suspended/discontinued immediately prior to clinical trials and provide them as a chemical library.[(16)] Although the structures of these compounds are not disclosed in principle, information on their mechanism of action and major in-vitro activities are provided together with clinical and preclinical data previously collected. Accordingly, use of this library is expected to realize a clinical trial after a shorter preclinical development period compared with development of entirely novel compounds. Although with restrictions such as non-disclosure of structural information, such attempts are expected to expand in scale in the future.

(4) Support for out-licensing of research results from the academia

The following are examples of an approach from academia to the pharmaceutical industry and an inverse attempt to establish the environment facilitating the industry's access to promising research results.

Support for out-licensing of research results offered by the iD3 Booster program of AMED has been described above. Here, Drug Seeds Alliance Network Japan (DSANJ), a project organized by Osaka Chamber of Commerce and Industry, is additionally described. This program consists of 2 parts, [1] database program and [2] business meeting program. DSANJ Biz Meetings Categorized by Target Diseases are held as a part of the business meeting program and contribute to partnering between the academia and pharmaceutical industry. Each Biz Meeting offers an opportunity for matching by delivering the researcher's idea to the representative of a pharmaceutical company in advance and providing an opportunity for interview, for example. The achievements of DSANJ program shown in Table 3 demonstrate a substantial success.

(5) Support for the conduct of clinical trials initiated by the academia and venture companies

In establishing plans for studies/clinical trials required between the final stage of candidate selection for pharmaceuticals, etc., and mainly the initial stage of clinical development (POC), understanding of advanced regulations are essentially required. When academic researchers plan to conduct a clinical trial as an investigator-initiated trial, various research grants from AMED, research grants provided to Core Clinical Research Hospitals, and support from Center for

Clinical Trials, Japan Medical Association are expected. In addition, PMDA has also enriched its consultation programs since April 1, 2017 as follows.

[1] RS General Consultation (free): Checks for eligibility of the proposed consultation items for RS Consultation on R&D Strategy; explains details and procedures of the RS Consultation Program on R&D Strategy.

[2] Prior Assessment Consultation (RS Consultation on R&D Strategy) (free): Summarizes issues in consultation items; verifies the contents of data to be submitted.

[3] Face-to-face Consultation (RS Consultation on R&D Strategy) (charged): The review team of the responsible Reviewing Office examines the submitted data, transmits the official opinion of PMDA in response to individual consultation items regarding future clinical trials and regulatory submission, and provides specific guidance and advice.

3.2 Future of support systems

(1) Funding for Research to Expedite Effective drug discovery by Government, Academia, and Private partnership (GAPFREE)

GAPFREE is an academic-industrial-governmental collaboration program offered by AMED and involves conclusion of pair-wise agreements between the academic, industrial, and governmental sectors as illustrated in Fig. 4. Namely, AMED receives research grants deposited from the partnering pharmaceutical company, pools them with funds from the national government (the figure shows funds from the Ministry of Health, Labour and Welfare as an example), and outsources the R&D project it has accepted to the academic institution proposing it. Then the pharmaceutical company and academic institution conclude a joint research agreement defining how to handle the research results, etc., using a template format for agreement[17] provided by AMED, which is a unique feature of this program.

Figure 4： http://yss.umin.jp/elements/pdf/slide_kusama.pdf

In most cases, the academic institution with which the pharmaceutical company intends to collaborate in drug discovery research is a medical institution, a potential customer purchasing pharmaceutical products from the pharmaceutical company (see also “3.3 Support at the clinical phase as an existing strategy and related issues”). This situation makes direct negotiation between these two parties difficult. Involvement of AMED in [1] matching of research seeds and needs, [2] proposal of a template format for joint research agreement, and [3] management of research progress has realized joint research between the academic and industrial sectors as equal research partners. While the academic and industrial sectors have their own fields of expertise as already described, the GAPFREE program eliminates gaps between the academic, industrial, and governmental sectors by constructing a system for complementary academic-industrial partnership and is capable of promoting research in a larger scale by offering a greater amount of research grant than AMED or the partnering pharmaceutical company alone. Making full use of these advantages, this program is expected to promote practical application of seeds from the academia.

The GAPFREE program accepted a number of research projects for exploration of drug discovery targets by offering 2 opportunities for open recruitment in FY 2015 and FY 2016. All

accepted research projects involve identification and verification of drug discovery targets by the academic sector using clinical samples obtained by prospective clinical research to realize drug discovery research with improved clinical predictability at an early stage of development. Each project underwent matching on the initiative of AMED prior to application.

A possible issue related to the GAPFREE program is the concern that research based on the unconventional way of thinking characteristic of academic researchers might not be feasible. Academic freedom of research is in a trade-off relationship with out-licensing of research results to the industry. Although the basic design of GAPFREE program involves seeds-needs matching on the initiative of AMED to make full use of research questions from academic researchers prior to launch of joint research on a subject agreed by the academic and industrial sectors, gaps still remain. Another possible issue is the concern of limitations in research policy and publication of research results. There is a trade-off relationship between a strategy for intellectual property and publication of research results. In general, if the strategy for intellectual property and out-licensing policy is not definite, researchers are forced to be conservative and all research results must be kept closed. While a prerequisite of the GAPFREE program is that research results obtained are open to the public in principle (because each research project is partly supported by funds from the national government), the strategy for intellectual property in each joint research project depends on the strategy for intellectual property of the partnering pharmaceutical company from the start of joint research. Accordingly, there is room for decision making and discussion between the academic and industrial sectors on publication of research results. In addition, the GAPFREE program eliminates efforts of the academic sector for patent application and negotiation on out-licensing of research results.

(2) Acceleration Transformative Research for Medical Innovation by Industrial-Academic Collaboration (Basic Scheme [ACT-M], Setup Scheme [ACT-MS])

ACT-M and ACT-MS are systems offered by AMED to support R&D by industrial-academic collaboration for construction of collaboration networks between universities, etc., and pharmaceutical companies/hospitals, etc., as well as smooth and effective transfer (entry into the practical application process) of technological seeds from the academia to the industry (pharmaceutical companies), involving open recruitment of research proposals.[(18)]

ACT-M is intended for joint research and development by industrial-academic collaboration based on research seeds from the academia covering a wide range of stages from the end of basic research to early phase of clinical research (up to Phase I). Among the candidate subjects of support by ACT-M, ACT-MS specifically focuses on “set-up” research and development aiming at polishing up the “challenging technological seeds” of academic origin to a level compatible with out-licensing based on a business model presented by the industry.

The aforementioned programs are devised in hope that they will help penetration of understanding of translational research into the society and quicker return of academic research results to the society as pharmaceutical products, through construction of mutual win-win relationships across researchers and institutions from the academic, industrial, and governmental sectors based on understanding of and respect for the standpoint of each other.

(3) Implementation-oriented education of academic researchers and graduate students

Opportunities for systematic learning of topics to be considered in conducting research oriented to development of pharmaceuticals and for putting them into practice should be provided not only to academic researchers but also to graduate students expected to lead future drug discovery research. Educational programs focusing on methods for development of pharmaceuticals/medical devices aiming at providing solutions based on medical needs, such as SPARK (for pharmaceuticals and diagnostics)[19] and Biodesign (for medical devices)[20] offered at Stanford University in the United States, seem to conform to this purpose. Continued enrichment of opportunities for learning through interaction with researchers from the industrial sector may be essential.

As already described, supports for drug discovery from academia are extensively provided ranging from the exploratory stage to the clinical stage. One probable reason for failure to find a business partner is market size of the target disease. So-called “rare diseases” and “ultra-rare diseases” may correspond to such cases. To ensure successful matching with a partner pharmaceutical company in orphan drug development as well, further enrichment of public support to provide appropriate incentive is expected. Regarding measures for development of pharmaceuticals for rare cancer, see the report of Subcommittee on Control of Rare Cancer of PMDA Science Board submitted in this Fiscal Year.

Support Program for Orphan drug prior to the Designation[21] (AMED)

To promote development of orphan drugs prior to and after the conduct of a clinical trial involving first administration in human subjects by R&D oriented pharmaceutical companies, etc., aiming at acquisition of marketing authorization thereof, this program provides financial support for a definite amount of the development cost as a part of environmental arrangement for realizing the goal.

3.3 Support at the clinical phase as an exit strategy and related issues

3.3.1 Positioning of the clinical phase as an exit strategy

It goes without saying that establishing strategies with clearly defined “exits” corresponding to individual research stages and providing practical support are important in supporting research for seeds of academic origin. Out-licensing to the industry at an earliest possible stage is ideal as a goal for one of such supporting strategies. On the other hand, one of the strengths of medical research is extraordinary enthusiasm for so-called “reverse-translational research” starting from patients in front of each researcher, briefly “starting from issues found in clinical practice, clarifying the mechanism by basic research, and finally providing feedback to clinical practice.” Accordingly, clinically-based researchers today often have a strong devotion to conducting clinical research by themselves. However, exploratory researches are often conducted as clinical research and not as a clinical trial, mainly due to lack of research funds, need for research achievement, and transition to the clinical phase required as a milestone for continuation of public research grants upon interim assessment, etc. In addition, the industry often requires acquisition of POC in human subjects by academic researchers as a condition for the conduct of a clinical trial, due to profitability or other reasons. Accordingly, support for the clinical phase has been demanded as an exit strategy for the academia.

3.3.2 Desirable way of support - Issues in RS consultation on R&D strategy [(22)] from the standpoint of academia

Upon transition to clinical development (clinical trials), a substantial loss of time may occur even after acquisition of clinical POC for various reasons, including insufficiency of preclinical data (e.g., quality studies, toxicology studies), redoing of preclinical studies required due to noncompliance with GLP, insufficient investigation of product specifications, and others. To ensure efficient face-to-face consultation involving scientific discussion, PMDA conducts prior assessment consultation (free) in advance to summarize issues in consultation items and verify the contents of data to be submitted. However, the academia's understanding of face-to-face consultation as well as RS consultation on R&D strategy for development plan, etc., is not always sufficient. While a written record is prepared for each face-to-face consultation, it seems that the subjects of consultation items are not definite enough to be advised appropriately. In RS consultation on R&D strategy, close collaboration with AMED and Translational and Clinical Research Core Centers would allow presentation of more specific methods and options to academic researchers regarding how to conduct development depending on the characteristics of the seeds at a very early stage. This could greatly contribute, as a consequence, to discovery and early development of promising medical seeds in Japan. In drug discovery from academia, cellular and tissue-based products, in particular, require collaboration with the industry in most cases. However, development of such products is associated with a problem of difficulty in charging development costs to the industry due to their limited marketability. A major obstacle to drug discovery from academia is insufficient investigation of formulation and pharmacokinetics observed very frequently. Accordingly, a system for providing advices regarding investigation of formulation and pharmacokinetics at an early stage of development based on brochures and experiences of approved drugs is also desirable.

On the other hand, it is not easy for a single university to accumulate human resource, facilities, and know-how required for development of pharmaceuticals and medical devices. In addition, different universities have different fields of expertise and mutual sharing of their knowledge will potentially yield better results. Collaboration with Translational and Clinical Research Core Centers and Core Clinical Research Hospitals and efforts to inform researchers of the need for early RS consultation on R&D strategy as well as knowledge on RS consultation on R&D strategy itself are continuously needed. And thereby nurturing the "development mind" of researchers on how to promote development of medical seeds is considered necessary for early practical application of innovative medical seeds.

3.3.3 Conflict of interest (COI)

When academic researchers conduct clinical studies for acquisition of POC in human subjects and other purposes, appropriate management of COI is required for reliability assurance of research results. More specifically, COI management is required in the following cases: [1] a researcher possessing the patent right for the compound to be commercialized is also an investigator of its clinical trial; [2] the patent right for a compound to be commercialized is transferred to a venture company, but an investigator of its clinical trial is an executive of the venture company; and [3] issues related to intellectual right of the compound to be commercialized are cleared, but ~~the establishment of~~ the venture company sponsoring its clinical trial has been financially supported by the university where the compound was discovered. In fact,

since a number of misconducts were disclosed in 2013-2014 in multiple clinical studies in which pharmaceutical companies were involved, the Ministry of Health, Labour and Welfare started development of a law to restore the reliability of clinical studies in Japan. As a result, The Clinical Studies Act was promulgated on April 14, 2017 to come into force within a period not exceeding one year from the day of promulgation. According to this Act, the principal investigator of a "Specially Designated Clinical Study" (a clinical study of pharmaceuticals, etc., not granted approval or used off-label and a clinical study of pharmaceuticals, etc., provided with research funds from a Marketing Authorization Holder thereof) is required to conduct it in compliance with Standards for the Conduct of Clinical Studies (e.g., monitoring, COI management), notify/publish the Protocol containing the aforementioned information to the Minister of Health, Labour and Welfare, and store the records related to the Specially Designated Clinical Study. Furthermore, an Authorized Clinical Studies Review Board authorized by the Minister of Health, Labour and Welfare shall review the Protocol and countermeasures for diseases, etc., and the Ministry of Health, Labour and Welfare may issue an Order for Improvement based on this Act. Since this Act is applied to ongoing clinical studies, researchers should try to assure reliability of data including COI management, based on related laws and regulations as well as notifications, etc. to be issued in the future.

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4 Conclusions and perspectives

Initially, the subject of discussion at this Subcommittee was “Bottlenecks in Drug Discovery form the Academia.” However, as described under “Introduction,” this Subcommittee focused on “bottlenecks at earlier stages (from selection of seeds candidates by basic researchers, determination of direction/strategy of drug discovery, to initiation of collaboration with the industry)” among bottlenecks present at multiple steps between identification of seeds candidates and clinical trials. While the industry appears to assume researchers conducting translational research as “the academia,” this report deals with issues related to drug discovery attempts by basic researchers familiar with experiments in the cellular level and experienced a little in simple experiments using laboratory animals. In this sense, this report focuses on a different range of aspects from those of conventional reports covering clinical studies and even regulatory science. Therefore, the title of this report was determined as “Issues in and Proposals for Facilitating Drug Discovery by Collaboration between the Academia-and Industry 2017.”

In recent years, counting items related to intellectual property (e.g., patent application) as “performance” in performance reports submitted to research grant providers has been established as a rule and AMED, a national organization established aiming at practical achievement in the field of healthcare, has come to play a role in research funding. For better or worse, such circumstances have placed basic researchers in a new environment where they can no longer ignore practical application of research results in addition to simple scientific interest. Opinions of basic researchers such as “Science should be purer.” or “The essence of basic research lies in free exploration of unexpected discoveries (i.e., serendipities).” are absolutely right and admit no doubt. Nevertheless, while maintaining such standpoints, knowledge of process to drug discovery is likely to significantly change the probability that “unexpected discoveries in basic science” result in “contribution to welfare of human beings in the form of drug discovery and development of treatment methods.”

Pharmaceutical companies have abandoned “closed” product development policy and come to seek for seeds from the academia in the name of “open innovation,” while the academia is making “marketing efforts” toward the industry to offer their seeds. In this way, the frequency of interactions between the academic and industrial sectors has been increasing. Dissociation in view between the industry (that exists depending on profits obtained from drug development) and academia (that has continued the pursuit of science) inevitably occurred, as described in Section 1.

The first and greatest dissociation in view between the industry and academia occurs on **target validation and clinical predictability**.

In brief, the key point is whether sufficient preclinical POC required for transition to clinical trials has been obtained or not. What is required is to answer the following questions very hard to answer: “Is it really effective in human subjects?” or “Is it supported by reproducible data obtained in test systems closely related to the target disease?” Even if the academia claims that the target has been identified successfully, whether it is really linked to the cause of disease should be validated. If the confidence in mechanism (CIM) is not obtained, the medical evidence supporting involvement of the new factor in disease is considered insufficient. The fact that basic

research results presented by the academia rarely provide such a full set of supporting evidence convincing the industry causes this dissociation in view between the industry and academia.

The next dissociation in view between the industry and academia occurs on **acquisition of intellectual property and grasping of the status of intellectual property.**

They are issues of critical importance to the industry seeking for profits. Nevertheless, from the academic viewpoint, it is not too much to say that they are issues never recognized previously and little recognized currently. In reality, these processes are essential for the academia as well to obtain profits in the form of loyalty.

The importance of and methods for elimination of such difference in view between the industry and academia have been described in Section 2. The importance of academic-industrial collaboration at an early stage is obvious: more efficient and rapid progress of the drug discovery process will be realized if the academia is familiar with the point sought by the industry and the industry understands the academic way of thinking. Furthermore, organizations supporting the academia and organizations mediating matching of the industry and academia to minimize the dissociation in view between the industry and academia have been described in Section 3. Although there was not enough time to aggregate opinions of researchers utilizing these organizations for inclusion in this report, we expect that efforts of individual organizations to accept feedbacks from users will realize more careful and generous support.

Considering the current situation that further progress in out-licensing of drug discovery research from the academia to the industry is desired despite the existence of various supporting organizations and efforts such as establishment of TLOs at universities, the following proposals are presented, looking at the future perspective, to stimulate and encourage future drug discovery from academia:

[1] High-quality education and human resource development in drug discovery research and management thereof in the academia
[2] High-quality education and human resource development in administration of intellectual property in the academia
[3] High-quality education and human resource development in research ethics in the academia
[4] High-quality education and human resource development in administration of biobanks in the academia
[5] High-quality education and human resource development in launching and administration of venture companies in the academia
[6] Development of human resource specialized in industrial-academic collaboration in both the academia and industry
[7] Activation of bidirectional people-to-people exchanges between the academia and industry utilizing a cross-appointment system, etc.
[8] Recruitment of leaders in human resource development in (1) to (6) by (7)
[9] Construction of a system for boosting the launch of venture companies without fearing exposure to risk
[10] High-quality support provided with high flexibility by PMDA and other organizations supporting drug discovery
[11] Utilization of AI in drug discovery and management thereof

As a future image of the relationship between the industry and academia, we expect mutual win-win development maintaining an “equal relationship retaining the characteristics of both parties.” However, looking at the rapid changes of the times, we feel that “the university and industry will merge” in the near future and the time will come when these two parties need not be aware of difference in position between them.

Although this report failed to cover all issues in drug discovery from academia, it summarizes major issues faced by basic researchers achieving medically important discoveries and aiming at drug discovery. It also presents proposals with an eye toward a future image of drug discovery from academia in Japan. We hope this report will boost drug discovery from Japan.

5 Terminology

Term	Complete representation	Explanation (in Japanese)
Entrepreneur education		Education for nurturing entrepreneurship
Seeds		Chemical compounds and proteins that are potential candidates for pharmaceuticals.
Target validation		To validate whether a disease-related gene or protein identified by basic research is valid as the target of actual treatment or drug discovery.
Biomarker		A biological indicator. An indicator representing biological information numerically and quantitatively to allow a quantitative grasp of biological changes *in vivo*.
Lead		A compound that has some suboptimal features as a therapeutic agent but is likely to deserve testing in clinical studies after improvement by proper chemical modification. Exhibits efficacy in an animal model with a full set of ADMET (absorption, distribution, metabolism, excretion, and toxicity) data available.
CIM	confidence in mechanism	Confidence that the molecular mechanism of the target is linked to the actual treatment due to drug efficacy in knockout animals, siRNA or disease animal models. (cited from the website of RIKEN Program for Drug Discovery and Medical Technology Platforms (DMP))
COI	conflict of interest	Conflict of interest
DISC	Drug-Discovery Innovation and Screening Consortium	Drug-discovery Innovation and Screening Consortium Chemical libraries offered by industry members are screened for drug discovery seeds (drug discovery targets) supported by the iD3 Booster program. Industry members are provided with feedbacks of screening results to improve the potential of practical application.
EMA	European Medicines Agency	European Medicines Agency
FDA	Food and Drug Administration	Food and Drug Administration
GLP	Good laboratory practice	Good Laboratory Practice
GMP	Good Manufacturing Practice	Good Manufacturing Practice
PCT application		International patent application based on the Patent Corporation Treaty (PCT)
PMDA	Pharmaceuticals and Medical Devices Agency	Pharmaceuticals and Medical Devices Agency
POC	Proof of Concept	Proof of efficacy as pharmaceuticals
TLO	Technology Licensing Organization	Technology licensing organization

Member List of the Facilitating R&D of Academia-originated Pharmaceuticals

As of April 1,2017

Hiroyuki Arai
Professor, Graduate school of pharmaceutical sciences, The University of Tokyo

Yoshihiro Arakawa
Professor, Tsukuba Clinical Research and Development Organization, Faculty of Medicine, The University of Tsukuba

Jun-ichiro Inoue
Professor, Division of Cellular and Molecular Biology, The Institute of Medical Science, The University of Tokyo

Yuji Imaizumi
Professor, Vice President, Nagoya City University

Shigeru Ohta
Professor, Graduate School of Biomedical and Health Sciences, Hiroshima University

Takayoshi Okabe
Professor, Drug Discovery Initiative, The University of Tokyo

Hiroyuki Kusuhara
Professor, Laboratory of Molecular Pharmacokinetics, Graduate School of Pharmaceutical Sciences, The University of Tokyo

Jun Kunisawa
Project leader, Laboratory of Vaccine Materials, National Institutes of Biomedical Innovation, Health and Nutrition

Toshio Goto
Director, Program for Drug Discovery and Medical Technology Platforms, RIKEN

Toshiyuki Sakai
Professor, Department of Molecular-Targeting Cancer Prevention, Graduate School of Medical Science, Kyoto Prefectural University of Medicine

Masataka Sata
Professor, Tokushima University

Motoharu Seiki
Research Professor, Kanazawa University／Professor Emeritus, The University of Tokyo

Tohru Takashi
Director, Division of Strategic Research and Evaluation, Department of Innovative Drug Discovery and Development, Japan Agency for Medical Research and Development

Kyosuke Nagata
President, University of Tsukuba

Shuichi Furuya
Deputy Managing Director, Vice-Director and Professor of Neutron Therapy Research Center, Okayama University

Kazuo Matsubara
Professor and Director, Department of Clinical Pharmacology and Therapeutics, Kyoto University Hospital