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A Strategic Translational Research System for Drug Discovery in Tottori University

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ABSTRACT

The probability of successful drug discovery is declining, and research and development costs are increasing. To solve these problems, pharmaceutical companies tend to in-license seeds from venture companies and academia. Therefore, academia's role in drug discovery is extremely important. Tottori University started a "Next-Generation Research Support Project (Strategic Research Support Project)" in 2020, developing a translational research system to promote drug discovery. In this project, we established a research and development infrastructure, such as seed registration, construction of drug research and development support, and research fund allocation. The registered seed were converted into project, and the project implemented this research and development system, and evaluated and verified its results. Twenty-two seeds were converted into projects and portfolios were constructed. Research funds were allocated to eight prioritized projects. Each project raised the research and development stages. From the overall portfolio, one project with the Japan Agency for Medical Research and Development (AMED) Drug Discovery Booster Project, and three projects with Seeds A of the AMED Translational Research Strategic Promotion Program were adopted. Additionally, a new low-molecular weight chaperone drug against GM1-gangliosidosis was out-licensed to an overseas pharmaceutical company. The strength of this system was the strategic allocation of research funds and the accompanying support that leveraged internal and external resources with the PM and researchers at its core. This system achieved certain results in promoting drug discovery; however, resource optimization of specialized personnel needs to be strengthened in the future. In this report, we summarized the efforts of translational research in Japan and around the world. In addition, the translational research efforts of Japanese academia and Tottori University were compared and the current status was summarized.

Key words drug discovery; open innovation; translational research

Recently, science and technology have made remarkable progress, including the elucidation of the causes of diseases through genomic science and development of various modalities, such as antibodies and regenerative medicine. The research and development of drugs for rare or intractable diseases with highly unmet medical needs are also ongoing. However, the probability of successful drug discovery is declining and research and development costs are increasing. To solve these problems, pharmaceutical companies worldwide are adopting an open innovation strategy wherein they focus their basic research on their own areas of expertise and in-license seeds from venture companies and academia.[1–5] Therefore, the role of academia in drug discovery is extremely important, and academia must strategically and efficiently "bridge" these seeds to pharmaceutical companies for practical applications in clinical settings. National Institute of Health (NIH) define translational research as the process of converting observations made in the laboratory, clinic, and community into interventions that improve the health of individuals and the public—from diagnostics and therapeutics to medical procedures and behavioral changes.[6] In the 2000s, countries worldwide began to note the significance of translational research for innovation in the medical field, and thereafter, an effective research support was implemented.

In response to the growing momentum of drug discovery in academia, Tottori University established a policy to promote drug discovery in 2020. However, the Tottori University does not have an established

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Abbreviations: AMED, Japan Agency for Medical Research and Development; BINDS, Basis for Supporting Innovative Drug Discovery and Life Science Research; CTSA, Clinical and Translational Science Awards; DDS, Drug delivery system; FDA, US Food and Drug Administration; GLP, Good Laboratory Practice; HTS, High throughput system; IP, Intellectual Property Specialist; MEXT, Ministry of Education, Culture, Sports, Science and Technology; NIH, National Institute of Health; PDX, Patient Derived Xenograft; PM, Project manager; POC, Proof of Consent; TLO, Technology Licensing Organization; TPP, Target Product Profile; URA, University Research Administrator

system that comprehensively promotes and supports drug discovery. Therefore, Organization for Research Initiative and Promotion in Tottori University started a "Next-Generation Research Support Project (Strategic Research Support Project)" for two years from 2020. The objective of this project was to 1) promote drug discovery, 2) allow teams to construct and validate the support system for drug discovery, and 3) acquire external funds and intellectual property based on the results of this project. Additionally, Tottori University established "Vision 2030" in July 2021, which includes the promotion of drug discovery. The University Research Administrator (URA) is responsible for the management of the Next-Generation Research Support Project (Strategic Research Support Project) and optimizing resources to build a system for promoting drug discovery. A project manager (PM) was assigned to each project and the principal researcher and PM led each project. Furthermore, we established a drug research and development infrastructure that utilized internal and external resources. A system for a drug seed discovery was also established. In this project, we strategically allocated research funds to priority projects and promoted joint research and out-licensing by matching pharmaceutical companies through open innovation. Through these efforts of two years, we evaluated and verified the results and problems associated with "Next-Generation Research Support Project (Strategic Research Support Project)." This article summarizes the efforts in Japan and around the world regarding translational research. It will also compare translational research efforts in Japanese academia with those at Tottori University to summarize the current state.

TRANSLATIONAL RESEARCH SYSTEM IN EACH COUNTRY

In the United States, the 252 drugs approved by the US Food and Drug Administration (FDA) during the period 1998–2007, 72 were of academic origin. In contrast, four out of 23 drugs from Japan originated from academia.[7] Efforts such as seed development, operations, and personnel training in translational research in each country are different, and each has its own characteristics as shown in Table 1. Europe and the United States started translational research support projects in the 1970s, and have refined them up to the present, resulting in current system. On the other hand, Japan started the support project in 2007 and is currently in the third phase. In Japan, support system and education related to drug discovery and entrepreneurship falls behind that in

Table 1. Summary of main translational research system in each country

Country	Organization	Project	Objective	Start year
Japan	AMED	Translational research program[8, 9]	1) Develop translational research support institutes and nurture seeds through institutes 2) Create innovative pharmaceuticals and medical devices by efficiently transferring excellent basic research results from academia to clinical research and practical application by utilizing translational research support institutes	2007
US	NIH	Clinical and Translational Science Awards (CTSA)[10]	Establishment of foundations for integrated translational research in academic institutions and hospitals 1) Human resource development 2) Cooperation with stakeholders, and cooperation between bases 3) Improvement of an integrated research environment 4) Construction of methodology and research process 5) Promotion of information science that contributes to translational research	2006 (NIH started the support in 1980s)
Germany	Fraunhofer Gesellschaft e.V.[11]	–	Creation of corporate innovation through research in pre-competitive areas 1) Commissioned research from companies 2) Licensing of patents acquired as research results 3) Giving back to society by starting a business with the inventions and new services created 4) Supplying researchers to industry 5) Providing state-of-the-art facilities to companies	1970s
UK	Government	Catapult program[12]	Building a base for technological innovation that leads the world in specific technical fields	2010 (Government started the support in 1990s)

Europe and the US, and education from the perspective of intellectual property is also insufficient. At present, education on intellectual property and entrepreneurship is being gradually promoted,[13–15] but such an education is not sufficient. Owing to the lack of support system, basic knowledge and necessary arrangements for industry–academia collaboration, the current situation does not allow academia to propose the seeds that attract pharmaceutical companies. Especially in academia, uncertainties in target validation and screening assay systems, inadequate target product profiles (TPP), lack of non-clinical data packages, and weaknesses in intellectual property strategies are the major obstacles when negotiating with pharmaceutical companies.

In Japan, the Ministry of Education, Culture, Sports, Science and Technology (MEXT) has established translational research support bases for three terms since 2007, and these bases have been pursuing drug discovery. As a result of these efforts, academia has been encouraged to change its minds for the practical application of seeds, and the number of seeds supported by bases has increased. In addition, the Japan Agency for Medical Research and Development (AMED) organized the Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS), which aims to bridge excellent basic research results to drug discovery and other practical research.[16] BINDS provides compound libraries, support optimization of hit compounds, and structure–activity relationship analysis, etc. AMED has achieved 36 seeds for non-clinical Proof of Consent (POC), 12 seeds for clinical POC, 47 seeds out-licensing to companies, and 15 pharmaceutical approvals in 2021.[17] Furthermore, AMED started the "Translational Research Program" in 2022, which provides a research grant to promote the translational research and create innovative drugs.[11]

ACADEMIA TRANSLATIONAL RESEARCH SYSTEM IN JAPAN

In Japan, 11 universities or hospitals are certified as translational research support institutes by the Ministry of Education, Culture, Sports, Science and Technology.[18] The translational research support institute is required to have 1) a regulatory affairs staff, 2) a non-clinical (safety/kinetics) quality control staff, 3) a research article quality control staff, 4) biostaticians, and 5) an intellectual property management staff, while having an organizational structure the same as or similar to any pharmaceutical company. The Clinical Research, Innovation and Education Center at Tohoku University Hospital, one of the translational research support institutes, has 11 departments and 2 units for the promotion of translational research and clinical research, and is operated by 120 staff members.[19] Other translational research support institutes such as Okayama University and Osaka University, also have support systems of the same scale as Tohoku University.[20, 21] At these institutes, researchers and specialists form teams under the AMED Translational Research Program to promote translational research (fostering seeds and promoting open innovation) based on research and development strategies.[22] They are also obligated to assist non-certified institutes. In addition, even at medium-sized universities, specialists are assigned within the university to independently promote translational research. According to a survey conducted at 31 medical research institutes with medical schools in Japan, the average number of personnel supporting industry-university collaboration at any one institution was 19.8.[23] Among them, the average number of industry-academia coordinators and technical staff was 3.4. The average number of intellectual property personnel was 2.7. It has also been reported that 58% of all patents filed independently by universities, etc. negotiated out-licensing to companies. The number of industry-university collaboration support personnel, which averages 3.4 people per institution, is presumed to be unreliable because industry-university collaboration support operations cover a wide range of areas, such as patent applications, licensing, contracts, and compliance. As a comparison with the situation of overseas academia at five US universities (Massachusetts Institute of Technology, University of New Mexico, Stanford University, UC San Diego, California Institute of Technology), the average number of personnel in the department responsible for technology transfer among industry-academia collaborations is 32.4 per institution, a big difference between Japan and the United States.[24] In 2017, the total intellectual property income of US universities was about 321.9 billion yen, while that of Japanese universities was about 4.3 billion yen,[25] and this systemic difference may be related to income disparity. Small universities such as Tottori University also aim to promote translational research; however, due to the lack of resources and support organization within the university, sufficient support cannot be provided, and researchers are currently proceeding with research and development on their own or need help from an external organization. A Technology Licensing Organization (TLO), an organization that patents university research results and transfers the technology to companies, was established at university or region. Shikoku TLO and Niigata TLO are independent from universities and are working to promote bridging of intellectual property from universities in the Shikoku region and Niigata

Prefecture, respectively.[26, 27]

TRANSLATIONAL RESEARCH SYSTEM IN TOTTORI UNIVESITY

The translational research system in Tottori University consisted of the following four elements: 1) seed registration system and portfolio, 2) research fund allocation, 3) enhancement of drug research and development and 4) industry–academia collaboration.

Seed registration system and portfolio

In "Next-Generation Research Support Project (Strategic Research Support Project)", a seed consultation and registration system was constructed based on the progress of research and development, as shown in Fig. 1. Registered seed was reviewed by the URA with the objective of the contents and progress of the seed, and it was converted into research and development project as the result of review. The target development stage was that the target molecules had been verified. Thirty seeds were registered during the two-year period of this project, and 22 seeds that were targeted for the system were converted into projects. The portfolio also includes seeds from the Faculties of Engineering and Agriculture, and the recognition of this system has progressed throughout the university. Five projects were in the area of neurology, 10 in oncology, 4 in other diseases, and 3 in biomarkers or drug delivery systems (DDS).

Research fund allocation

A scheme for the strategic allocation of research funds to prioritized projects selected by the URA was established (Fig. 2). The researcher and PM who was assigned to each project prepared the research plan, which was reviewed by the Research Strategy Evaluation Committee, and its adoption was decided based on the relevance of target, novelty, relevance of research and development plan, stage, and risk. A total of 8 projects were selected in 2 years (Table 2). In 2020, five projects were prioritized, and their research funds were allocated. One of the projects was selected for the "AMED drug discovery booster project," so research funding allocation ended in 2020. In 2021, in addition to the ongoing projects from 2020, three new projects were selected, and their research funds were allocated. Furthermore, research funds were allocated flexibly and strategically, such as by making additional allocations (five times) based on project progress during the middle of the year. In the AMED translational research program, six support schemes are set according to the research development phase, and research funds are

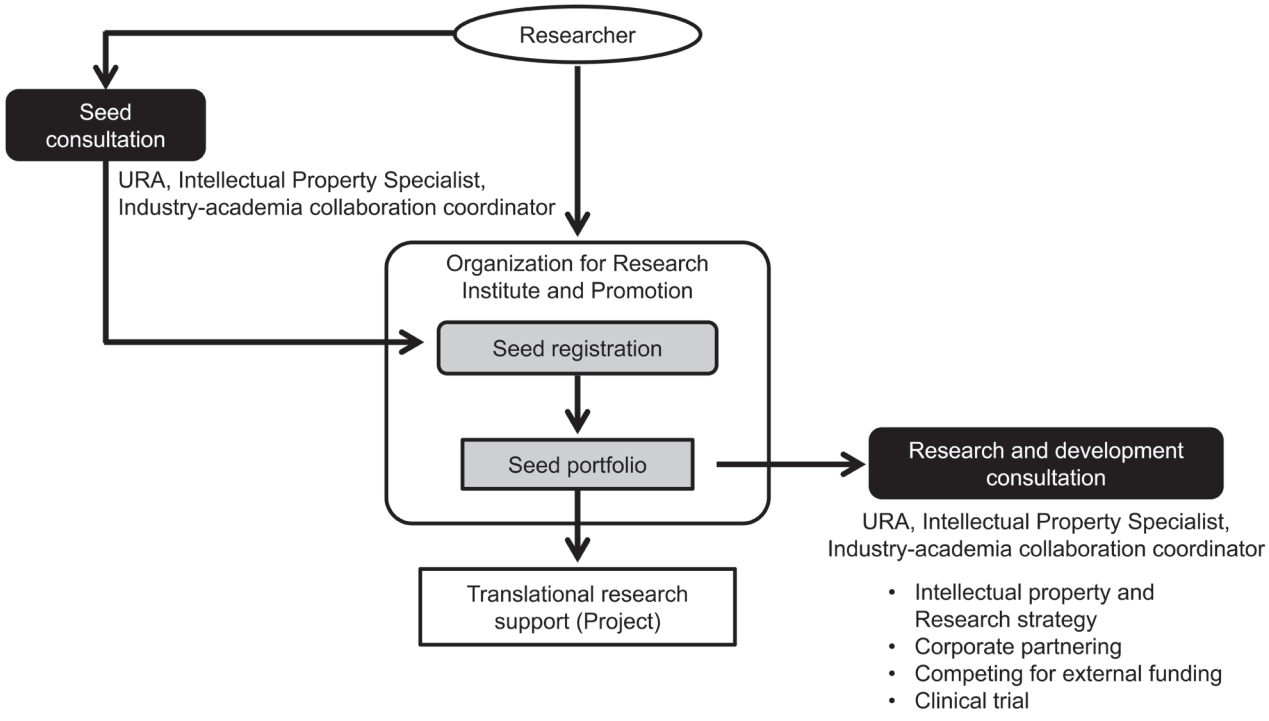

Fig. 1. Seed registration system. Establish a seed registration system, provide consultation on seed according to research and development stage, and comprehensively manage and support from seed cultivation to translational research, clinical trials, out-licensing, and commercialization. URA, University Research Administrator.

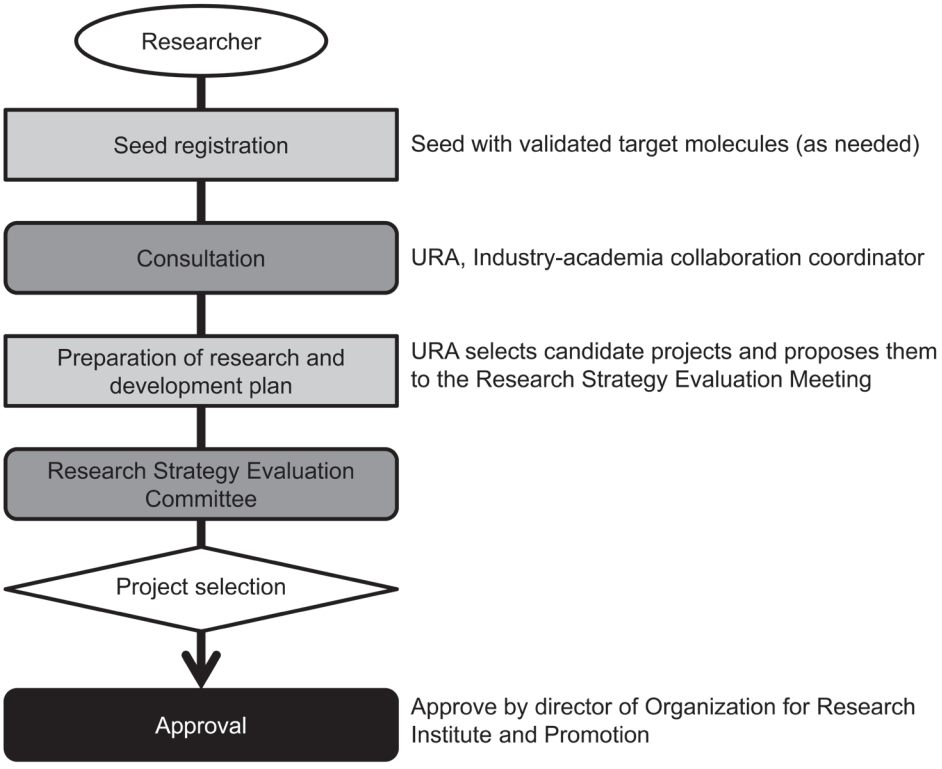

Fig. 2. Strategic research funds allocation.

Table 2. Summary of the eight prioritized project

ID	Researcher	Target disease	Modality	Research Fund (yen) (FY)
20-1	Faculty of Medicine	Tumor, Diabetic retinopathy	Low molecular	4,000,000 (2020–2021)
20-8	Organization for Research Institute and Promotion	Mucopolysaccharidosis	Low molecular	1,500,000 (2020)
20-9	Faculty of Medicine	Chronic active Epstein-Barr virus infection	Low molecular	3,500,000 (2020–2021)
20-15	Faculty of Medicine	Malaria	Low molecular	4,000,000 (2020–2021)
20-19	Faculty of Engineering	Pancreas cancer	Nucleic acid	4,000,000 (2020–2021)
21-1	Faculty of Medicine	Multiple myeloma, Auto immune disease	Low molecular Anti body Peptide	1,000,000 (2021)
20-28	Faculty of Medicine	Solid tumor	Oncolytic virus	1,000,000 (2021)
20-5	Faculty of Medicine	Solid tumor	Low molecular	1,000,000 (2021)

allocated according to a wide range of development phases, from the stage of aiming for patent applications to the stage of aiming to obtain clinical POC. AMED or translational research support institutes evaluate the research and development plan and adopt the research fund. In general, domestic and overseas research institutions allocate research funds through open application system in their universities, but our system differs in

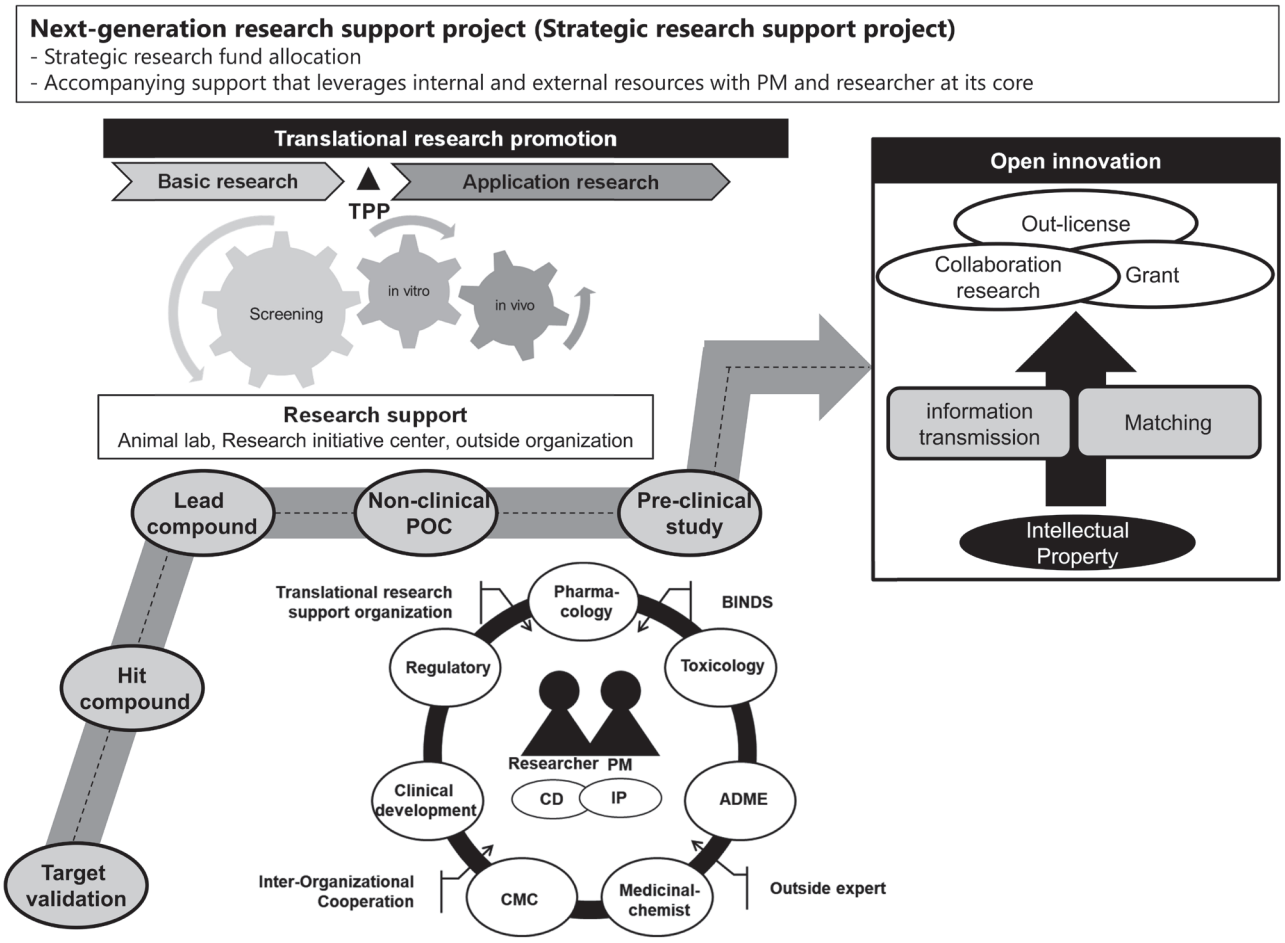

Fig. 3. Drug research and development support system. Strategic research funds allocation, seamless support for translational research through co-creation between researchers and support organizations and strengthening of industry–academia collaboration (Open innovation). ADME, absorption, distribution, metabolism and excretion; CD, Industry–academia collaboration coordinator; CMC, Chemistry, Manufacturing and Control; IP, Intellectual Property Specialist.

that funds are allocated top-down to prioritized projects. This strategic allocation of research funds is one of its characteristics.

Enhancement of drug research and development

Before initiating the "Next-Generation Research Support Project (Strategic Research Support Project)", researchers had been conducting drug research and development independently and had little knowledge of methods for research and development. As a result, they could not prepare appropriate development strategies and did not know what kind of specialized human resources they would need. Although the total number of specialists who provide translational research support is 4 at Tottori University (namely 1 PM, 1 intellectual property manager, and 2 industry–academia collaboration coordinators), we optimally allocated resources within the university and started to provide support (Fig. 3). First of all, the PM was assigned to the research and development project, and a project team was formed centered on the researcher and PM. By forming a team, the PM and researcher were able to develop an optimal research and development strategy that included a research and development schedule, leveraged internal and external resources, boosted external funding acquisition, and supported open innovation. Under the research and development strategy, the PM supported decision-making and the overall management of the project's status and research expenses, and functioned as a bridge between researchers and support organizations (accompaniment support). In addition, a team could use a newly constructed system that seamlessly implemented a series of research and development roadmap, from basic and applied research to non-clinical POC acquisition research. Additionally, intellectual property and alliance experts within the university were allowed

Table 3. Achievement of the eight prioritized project

ID	Target disease	Achievement
20-1	Tumor, Diabetic retinopathy	- Consult with BINDS (screening assay system) - Construct screening assay system
20-8	Mucopolysaccharidosis	- AMED Drug Discovery Booster Project adoption - Construct screening assay system
20-9	Chronic active Epstein-Barr virus infection	- Obtain compound library from BINDS - Complete 1st screening and obtain hit compounds - Start in vitro 2nd screening
20-15	Malaria	- Compound screening using the mushroom library owned by Faculty of Agriculture - Isolate compound that hit by 1st screening - Start plasmodium falciparum growth inhibition study
20-19	Pancreas cancer	- Patent application - Seeds A of the AMED Translational Research Strategic Promotion Program adoption - DSANJ Digital Bio Conference (eight companies)
21-1	Multiple myeloma, Auto immune disease	- Antibody and peptide creation - Start in vivo study
20-28	Solid tumor	- Creation of animal disease models (glioma)
20-5	Solid tumor	- Construction of screening assay system (on-going)

to join in as necessary. Because of limited resources within the university, a project team could also consult an animal experiment or instrumental analysis expert at the university and maximally use external resources, such as BINDS and translational research support institutes with limited resources at the university. Finally, the project team prepared a non-clinical data package for a proper evaluation of seeds at each research and development stage. In the characteristic drug research and development support infrastructure, all registered projects were advanced research and development to raise the stage under the support system. In the overall portfolio, two projects received support for screening assay system validation and the provision of compound libraries by BINDS. Moreover, one project received BINDS support for the structural expansion of the hit compound. We have also promoted interdisciplinary research and conducted compound screening using a mushroom library owned by the Faculty of Agriculture at Tottori University. Furthermore, nucleic acid medicines synthesized by the Faculty of Engineering were evaluated through joint research with the Faculty of Medicine. For drug discovery projects in the Faculties of Agriculture and Engineering, researchers in these faculties formed a team with researchers in the Faculty of Medicine and received guidance regarding in vitro and in vivo research methods and medical requirements. In addition, medical doctors provided advice on medical needs. The detailed achievements of eight prioritized projects in the "Next-Generation Research Support Project (Strategic Research Support Project)" are listed in Table 3.

Industry–academia collaboration

We also built a system wherein property managers and industry–academia collaboration coordinators could join in the project team. They could provide accompaniment support for industry–academia collaboration depending on the research and development stage under the research and development strategy. A non-clinical data package was used for intellectual property, acquisition of competitive external grants, and collaborative research. One project with the AMED Drug Discovery Booster Project and three projects with seed A (only one project with seed A was adopted in the past three years before initiating our support) of the AMED Translational Research Strategic Promotion Program were adopted during the two-year project period. We have also filed for a patent application. Two projects participated in the DSANJ Digital Bio Conference, and one project participated in the Kihara Foundation BVA Bio Interface; interviews were held with 16 companies. Although this did not lead to joint research at these conferences, we could evaluate the seeds from a company's perspective and obtained useful information for subsequent research and development. In addition, in 2020, the results of "a search for a new low-molecular weight chaperone drug against GM1-gangliosidosis brain pathology," adopted by the AMED Drug Discovery Booster Project in 2017 and out-licensed to Green Cross Corporation, South Korea, helped increase royalties by approximately 25 times in 2021 compared to the previous year. After

that, other seeds were out-licensed to pharmaceutical companies, and royalties are increasing year after year. We were able to organize personnel and support out-licensing by maintaining close communication with the person in charge of intellectual property, contracts, and alliances within the university.

CONCLUSION

For the Next-Generation Research Support Project (Strategic Research Support Project), we constructed a framework for the research and development support system. Funds are allocated top-down to prioritized projects in our system, and this strategic allocation of research funds is one of its strengths. The other strength is accompanying support that leverages internal and external resources with the PM and researchers at its core. Translational research support institute and medium-sized universities can promote translational research as a team with several specialists; however, Tottori University allocated limited resources to key roles to promote translational research. A system that promotes translational research with limited resources and achieves certain results will serve as a model case for other small-size universities. In this system, the URA delegated authority as the PM, and decisions were quickly made. Twenty-two seeds were discovered and converted into projects, and research funds were strategically allocated to eight prioritized projects. Each project could raise the research and development stages. In addition, chaperone therapy for GM1 gangliosidosis can be out-licensed to overseas pharmaceutical company. Although most seeds are at an early stage, we focused on accumulating seeds in diverse areas and explored the possibility of drug development for rare and intractable diseases. Drug discovery is a high-risk and high-return industry and generally takes more than a decade from the initiation of research and development to it being launched to the public for use. In this process, research and development are often forced to discontinue owing to various factors, and the probability of success in drug discovery is low. The success rates of Phases I, II, and III are reported to be 67.3%, 35.9%, and 55.3%, respectively.[28] Development was often discontinued in Phase II to achieve POC, and more than 50% of the reasons for discontinuation were lack of efficacy.[29] Accuracy of target validation can be an important factor in increasing the probability of success in Phase II. To improve the accuracy of target validation, evaluations using animal models that accurately reflect the clinical picture of the disease are important. In recent years, the latest techniques using patient-derived xenografts (PDX) and iPS cells have been developed.[30, 31] In addition, the screening assay system requires more expertise, such as the construction of an appropriate high-throughput system (HTS) and optimization of hit compounds.

When considering out-licensing to a pharmaceutical company, in addition to the accuracy of target validation, it is necessary to fulfill unmet medical needs in clinical practice and ensure the sufficiency and reliability of the data package. From the perspective of risk reduction, various efforts have been made with the advances in science and technology, and certain results have been achieved in terms of launch the innovative new drugs to market.[32] In fact, new drugs have been launched for various diseases, and satisfaction with treatment for lifestyle-related diseases is increasing yearly.[33] As a result, recently, research and development targets tend to shift to intractable and rare diseases areas with several unmet needs. This is the specialty area of Tottori University such as out-licensing of the GM1 gangliosidosis project.

From the viewpoint of data reliability, toxicity and safety pharmacology studies must be conducted in compliance with Good Laboratory Practice (GLP). In addition, efficacy of pharmacological and pharmacokinetic studies must conform to the "Criteria for Reliability of Application Data." Pharmacological and pharmacokinetic studies may be conducted in academia, and it is necessary to summarize the results based on the requirements (accuracy, completeness, comprehensiveness, and preservability) stipulated in Article 43 of the Enforcement Regulations of Pharmaceuticals and Medical Devices Law.

However, there are not enough drug discovery specialists in academia; therefore, it is necessary to promote research and development with experts inside and outside the university as project members, in accordance with the research and development stage. In the "Next-Generation Research Support Project (Strategic Research Support Project)", a project team was formed centered on the researcher and PM. Property managers and industry–academia collaboration coordinators also joined in the project team. Project meetings were conducted frequently, and an optimal research and development strategy was able to be developed. Based on this strategy, a team could make decisions, and utilize external resources efficiently, such as experts in screening assay systems and the synthesis of derivatives in BINDS while receiving low-molecular weight compound libraries in the screening assay. In addition, we participated in a network of translational research support organizations and have been collecting the latest information and mutual support. Strategic allocation of research funds in the university and support

for the acquisition of competitive external grants were conducted as efforts leading to open innovation. We strategically allocated university research funds to key projects as a bridge to the acquisition of competitive external funding. As a result of this strategy, one project was adopted for the AMED Drug Discovery Booster Project and three projects were adopted for Seeds A of the AMED Translational Research Strategic Promotion Program. Furthermore, as early industry–academia collaboration is the key to success in academia-initiated drug discovery, we actively pursued open innovation under the research and development strategy. Open innovation through industry–academia collaboration allows us to evaluate seeds from the perspective of a pharmaceutical company and quickly determine the lack of data in drug discovery. Joint research with pharmaceutical companies is expected to promote effective drug discovery by exploiting each advantage. There are also advantages to industry–academia collaboration from the perspective of intellectual property. There are many cases in which the content of patent applications is inadequate in academia. However, if joint applications can be filed with a company, it will be possible to obtain patents without omission for drug discovery.

Universities have come to recognize the importance of patent applications, but there are cases in which patent applications do not fully demonstrate their value because of a lack of specific intellectual property strategies for commercialization. Therefore, it is important to carefully consider the purpose and intent of product development and strategically plan the application timing. Because pharmaceutical patents are covered by a small number of patents, strategies such as application content, scope, timing, and existence period are important. Academia tends to view patent applications as one of its goals, but it is also important to recognize that all research content will be disclosed within a year and a half after filing a patent application. In addition, it is imperative to recognize that when related research results are published in academic societies, journals, and other publications, the results lose their novelty and patents containing such results cannot be obtained. Based on these points, intellectual property experts accompany support projects and manage the timing of the publication of research results and patent applications in our support system. One project filed a patent application during the project period.

In Japan, translational research by academia is still under development; however, owing to the implementation of policies and projects that promote translational research, the practical application of medical technology originating from academia in clinical settings is also increasing. We built an infrastructure for drug discovery. Other universities are also promoting translational research, but this project is unique in that it strategically allocates research funds and provides accompaniment support through a project team with limited resources. This system will serve as a model case for other small-size universities. Although we have limited resources, it is necessary to improve the system to efficiently promote translational research and out-license it to pharmaceutical companies. Universities must also develop momentum to promote translational research.

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