Analysis and Comparison of the Biotech Startup Ecosystem in the United States and Japan

by

Ayano Kagami

B.S. in Biophysics and Biochemistry
The University of Tokyo, 2005

M.S. in Biophysics and Biochemistry
The University of Tokyo, 2007

Ph.D. in Biophysics and Biochemistry
The University of Tokyo, 2011

Submitted to the System Design and Management Program
in Partial Fulfillment of the Requirements for the Degree of

Master of Science in Engineering and Management
at the
Massachusetts Institute of Technology

June 2019

Signature of Author: Signature redacted
System Design and Management Program
May 15, 2019

Certified By: Signature redacted
Michael A. Cusumano
Sloan Management Review Distinguished Professor of Management
Thesis Supervisor

Accepted By: Signature redacted
Joan S. Rubin
Executive Director, System Design and Management Program

This page is intentionally left blank

Analysis and Comparison of the Biotech Startup Ecosystem in the United States and Japan

by

Ayano Kagami

Submitted to the System Design and Management Program on May 15, 2019,
in partial fulfillment of the requirements for the degree of
Master of Science in Engineering and Management

ABSTRACT

Many regions and cities, including in Japan, are interested in developing a biotech startup ecosystem. Therefore, there are several strategies and policy instruments in Japan to promote medical research and development and collaboration among universities and industries, and to foster entrepreneurship in Japanese society. However, a startup ecosystem is a complicated system because there are many stakeholders and many ways of interactions among them. For this reason, it is assumed that the coordination of many factors, such as governments' policies and the academic and industrial environment, is required to develop the ecosystem. The Greater Boston area, where MIT is located, is a world-renowned biotech cluster. Many countries and cities have been trying to imitate this cluster, but just copying the ecosystem might not work in other cities because the environment surrounding the ecosystem is different from cluster to cluster.

In this study, we analyze and compare the biotech startup ecosystems in the U.S. (Greater Boston and San Francisco Bay Area) and Japan (Tokyo (Kanto region) and Kyoto (Kinki region)) in order to understand the key factors required for developing the ecosystem and to get insights for developing an ecosystem in Japan. We also analyze universities locating within these areas from the standpoint of the interface machinery between academic research and industry. In the analysis, we compare the stakeholders and their network in each cluster and explore the advantages and challenges of Japanese clusters. For universities, we also compare the system of managing the intersection of academic researchers and industries in each university and explore the functions and features of offices involved in the system.

The results of the analysis suggest that the Japanese biotech startup ecosystems have several challenges: the weakness of the network among stakeholders and of the support system for startups; the low level of entrepreneurship and of opportunities to foster it; and the limitation in the capital available. These challenges exist even though there is strong support from the governments and there are well-organized systems in universities for supporting not only collaboration with industry but also startups and student entrepreneurship. Therefore, taking advantage of the system in universities and utilizing them as the community and/or platform for stakeholders in the ecosystem, including the promotion of entrepreneurial education, might help Japanese clusters to develop successful biotech startup ecosystems.

Thesis Supervisor: Michael A. Cusumano
Title: Sloan Management Review Distinguished Professor of Management

This page is intentionally left blank

Acknowledgements

First of all, I would like to thank Prof. Michael A. Cusumano, my thesis supervisor. His exact advice and wealthy knowledge, especially derived from his experience as Vice President and Dean at the Tokyo University of Science helped me a lot in tackling this theme and giving my ideas into shape. It was a precious time for me to work with him. I express my gratitude here.

I would also like to thank the Japanese community in the Greater Boston Area, especially whom I met through my journey for the study. Their knowledge and experience in the biotech ecosystem, their passion to deliver technology to the society, and their ugly on Japanese environment encourage me to push forward on this study.

There are many people who help me to shape the study through discussions. I want to express my appreciation especially to my supervisor during the intern at BioInnovation Labs, LLC (BioLabs) in the summer 2018, Dr. Jean-Jacques Yarmoff. I learned a lot from the discussions with him about the biotech ecosystem in Boston/Cambridge, France, and Japan. I also want thank Dr. Erin L. Scott and Ms. Margaret Chiappetta for having discussions at the beginning of the study. Mr. Takuro Yoshimoto, my college in MEXT, provided me the information on OECD's research related to university-industry collaboration and the suggestions for policy analysis.

Additionally, I would also like to thank my friends in MIT. They inspired me a lot and made my life in MIT priceless not only in the classrooms but also in other activities.

I could not be here in MIT without the sponsorship from Ministry of Education, Culture, Sports, Science and Technology. I appreciate their support and I would like to share and make use of the experience in MIT and the results of this study after I back to the office.

Finally, I need to thank my family in Japan; my father, mother, sister, brother and two grandmothers. I really appreciate their understanding and tremendous supports, even when they had difficult times.

This page is intentionally left blank

Table of Contents

List of Figures

List of Tables

List of Acronyms

AMED	Japanese Agency for Medical Research and Development
CVC	Corporate Venture Capital
GEM	Global Entrepreneurship Monitor
I-Cap	Innovation Capacity
IDE	Innovation Driven Enterprise
INCJ	Innovation Network Corporation of Japan
IP	Intellectual Property
JETRO	Japan External Trade Organization
JST	Japan Science and Technology Agency
E-Cap	Entrepreneurship Capacity
FDA	the US Food and Drug Administration
METI	Ministry of Economy, Trade and Industry
MEXT	Ministry of Education, Culture, Sports, Science and Technology
MHLW	Ministry of Health, Labour and Welfare
NEDO	New Energy and Industrial Technology Development Organization
NIH	National Institute of Health
NSF	National Science Foundation
OECD	Organization for Economic Cooperation and Development
PMDA	the Japan Pharmaceuticals and Medical Devices Agency
R&D	Research and Development
SME	Small/medium-sized Enterprises
SME	The Small and Medium Enterprise Agency
TLO	Technology Licensing Office
VC	Venture Capital

Currency exchange rates used in this study

(OECD.Stat (https://stats.oecd.org), Exchange rates, period-average)

Year	Yen/$
2011	79.807
2012	79.790
2013	97.596
2014	105.945
2015	121.004
2016	108.793
2017	112.166
2018	110.423

1. Introduction

As a country which lacks natural resources, Japan has been allocating a significant amount of budget to science and technology research and development (R&D) both in the government and in industry. The number of researchers is in 3rd place in the world, following the United States and China[1]. Also, sixteen Japanese researchers were awarded Nobel prizes in the natural sciences since 2017 and the number of the applications to the Patent Cooperation Treaty (PCT) is 3rd, again following China and the U.S.[2] Thus, there has been a significant amount of research that has great impact not only in academia but also on the society in Japan.

In addition, greater generation of innovation is needed to overcome the long period of economic stagnation and the aging and shrinking population. Given this background, the expectation for healthcare and medical innovation is huge. The needs for innovation are the same in industry because the rapid development of science and technology is forcing them to change their R&D strategy and to shift from in-house R&D to open innovation. Thus, companies have more interest in academic research and collaboration than ever before.

Therefore, many policy initiatives have been undertaken to boost the innovation based on the strength of academic research in Japan. One of them is the promotion of academia-industry collaboration. For this purpose, the Ministry of Education, Culture, Sports, Science and Technology (MEXT) provides funding to universities, industries, and entrepreneurs for fostering collaboration and enabling the smooth transfer of the fruits from academic research to the society. Another policy is the promotion of startup businesses, especially spin-off startups from academic research. To encourage such businesses, the Japanese government provided $1.5 billion (120 billion JPY) in risk capital from the national budget to universities and the Japan Science and Technology Agency (JST) for investing in university spin-off startups in 2012[3]. Because of the strong desire for healthcare and medical innovation in order to solve the problems of an aging society with increasing medical costs, the Act on Promotion of Healthcare Policy was approved in 2014 and a significant amount of budget for medical R&D has been allocated since then. Several local governments, such as Tokyo, Kawasaki, Kyoto, and Kobe, have been investing in efforts to develop biotech ecosystems as a source of economic growth.

Although Japan has risen in the total ranking in the Global Innovation Index and Tokyo-Yokohama came out on top among the top 100 science and technology clusters, the ranking is 13th among 126 countries[4]. In addition, the ranking is 31st in the creative outputs, though Japan is at the top in innovation quality[4]. These research results suggest that there is a deficiency in the system which converts the academic knowledge to business or social good, despite the governments' policies.

For comparison, the Greater Boston area is a place where universities, high tech companies, and startups (especially in biopharmaceutical industries) have accumulated, and it is one of the U.S,'s top two biotech clusters, along with the San Francisco Bay Area. Thus, an innovation and startup ecosystem has formed in this area. For example, Massachusetts Institute of Technology (MIT) and Harvard University are consistently ranked within top 10 in the several university rankings and Harvard University is top ranked in the number of the highly cited researchers[5]. Five of the top six U.S. hospitals are also in the Greater Boston[6]. Not only top universities and hospitals but also many high-tech companies are located in Cambridge; Google, Amazon, Facebook, and many of the largest pharmaceutical companies, such as Pfizer and Novartis. A large number of entrepreneurs, venture capital firms (VCs) and incubation facilities for startups are also present. In addition, because of historical strength in the biotechnology field and the attraction of top pharmaceutical companies, the Greater Boston area is highly suitable for biopharmaceutical industries. Thus, the biotech startup ecosystem has already formed.

Developing an innovation ecosystem or a startup ecosystem is a complicated process because there are many types of stakeholders and because the environment surrounding stakeholders is different from region to region. In addition, the biotechnology industry is more challenging than other fields because of its high risk and the steep costs. Therefore, comparing the several biotech clusters in the US, including the Greater Boston Area, and the several areas in Japan suggests insights and key actions to develop a biotech startup ecosystem in Japan. In addition, comparison of universities in clusters from the perspective of the functions in the ecosystem might suggest to us how to overcome the challenge in Japanese clusters where there has been difficulty in transforming the achievements in academic research to industries or social good. This is because it is well known that MIT has been playing an important role in forming the ecosystem in Cambridge and also giving tremendous impact to industries by its alumni and researchers.

Therefore, we have analyzed and compared the biotech startup ecosystems in two clusters in the US and two clusters in Japan and also the function of universities in the ecosystem in each region in order to reveal the key actions and insights to develop a successful biotech startup ecosystem in Japanese clusters. In Chapter 1, we provide the motivation and the brief background for the thesis. In Chapter 2, the research questions are discussed for framing the research. In Chapter 3, the backgrounds of policies and the preceding research are reviewed to understand the current environment of the ecosystem and the existing theories related to the innovation and startup ecosystem and the knowledge transfer from academia to industries. In Chapter 4, we discussed and defined the boundary of the biotech startup ecosystem and the specificity of the biotech industry in comparison with other industries. In Chapter 5, the metrics for comparing the biotech startup ecosystem among several cities are discussed and defined. In Chapter 6, the regions and universities we analyze and compare in this research are explored to shed light on the biotech startup ecosystems and to discuss the practical implementation of the desirable policies. In Chapter 7, the stakeholders and their networks in the regions we studied in Chapter

6 are examined and the differences between the U.S. and Japan are explored. In Chapter 8, the functions of universities in the ecosystem are explored and the differences of the systems in the universities we identified in Chapter 6 are analyzed. In Chapter 9, the findings of the research, the policy recommendation for developing the biotech startup ecosystem in Japan, and future work are discussed.

2. Research Questions

In this section, research questions are discussed to shape the focus of the research. As discussed in the previous section, the purpose of this study is to understand the biotech startup ecosystem for better implementation of Japanese policies and actions. Therefore, the comprehensive question of the research directly comes from the purpose.

Q: How can we develop a biotech startup ecosystem in Japan?

To answer this question, comparing the successful biotech startup ecosystem(s) with the ecosystems in Japan. Thus, the first research question is to examine existing biotech startup ecosystems including the ones which recognized as a successful case and the ones which have been trying to establish in Japan.

Q1: What are the weakness and strength of the Japanese ecosystem compared with the successful ecosystem in the U.S.?

The Q1 is the base for figuring out the weakness and strength of Japanese ecosystems to establish policies for developing them. For this purpose, we analyze two clusters in the United States, Boston/Cambridge and San Francisco Bay Area, which are recognized as top biopharmaceutical clusters in the U.S.[7] and also analyze two clusters in Japan, Tokyo (Kanto area) and Kyoto (Kinki Area), which have been trying to develop the biotech ecosystems. To answer this question, we need to explore two following questions.

Q1-1: What is the key element in the ecosystem and how does it impact on the ecosystem?
Q1-2: What is the difference of biotech startup ecosystems in Japan and the U.S.?

The first sub-question approaches to finding the key element of the ecosystem and the impact given by each element to the ecosystem based on the stakeholder analysis and its network analysis by applying MIT's innovation ecosystem model. The second sub-question is the foundation for answering the Q1 based on the stakeholder analysis of each cluster.

Q2: What is the key action(s) for universities in developing the ecosystem in Japan?

The Q2 gives a focus on one of the stakeholders in the ecosystem. As discussed in the previous section, universities are the sources of cutting-edge technologies and innovation and played an important role in the development of the biotech cluster in Boston/Cambridge[8]. In addition, Budden and Murray (2019) mentioned that universities are often the ideal leader for developing regional innovation ecosystem[9]. Thus, exploring the way to developing the ecosystem in Japan by changing universities might be one of the solutions. To answer this question, the following two questions are needed to be explored.

Q2-1: What are the functions of universities in the ecosystem?
Q2-2: What are differences in universities' function and contribution in the ecosystem between the U.S. and Japan?

The first sub-question approaches the function of universities in the ecosystem and the second sub-question approaches the difference between universities in the U.S. and universities in Japan. The relationship between academia and industry have been catching the eye of researchers and governments who want to industrialize the results of academic research. However, Japanese universities seem to be not performing well in this context as noted in the previous part. Thus, the comparison of universities' system in the US and Japan from the aspect of their function in the ecosystem will give us insights about the root of the problem.

3. Literature Review

In this section, innovation ecosystem and policy in the U.S. and Japan, the basis of regional clusters and biotech industries, MIT's approach to innovation ecosystem, and the mechanism of knowledge transfer are reviewed, in order to explore the biotech startup ecosystem in the U.S. and Japan in the following sections.

3.1 Innovation ecosystem and policy

(1) Innovation ecosystem and startup ecosystem

Ecosystem is traditionally defined as a biological community of interacting organisms and their physical environment in Oxford English Dictionary. However, its meaning was expanded to the non-biological situation and the word "ecosystem" is now generally used as a complex network or interconnected system as the analogy of the biological ecosystem.

"Innovation ecosystem" is defined as an interconnected set of people and resources (and their physical environment) that provide the context for Innovation Driven Enterprises (IDEs) to start, grow and scale [10]. In this definition, IDEs are startups whose competitive advantage and growth potential is driven by innovation [11]. On the other hand, the World Bank defines in its report the startup ecosystem as follows:

The combination of people, startups at various stages and other stakeholders and organizations supporting or connecting to these startups, interacting in multiple dimensions to create and scale new startup ventures[12].

Thus, if we focus on innovation generated in startups and implemented through the startup ecosystem, there is significant overlap between the innovation ecosystem and the startup ecosystem.

(2) Innovation policy in the U.S.

In *The Global Competitiveness Report 2018* (World Economic Forum), the U.S. is ranked 1st in Business Dynamics and 2nd in Innovation Capacity (1st is Germany). The score of Business Dynamics is based on the cost and time spend in starting a new business, the attitude toward entrepreneurial risk, companies embracing disruptive ideas, and so on. Innovation Capacity is based on multi-stakeholder collaboration, scientific publications, patent applications, R&D expenditures, buyer sophistication, and so on [13]. Thus, this ranking suggests that the U.S. is a country suitable for innovative business.

Also, it is said, "The United States has long been at the forefront of cutting-edge innovation" in OECD Science, Technology and Industry Outlook 2012. This position is based on the excellent higher education institutions, a large and integrated marketplace, and efficient capital and equity markets [14].

The policy on innovation in the U.S. backs to 1980 when the Bayh-Dole Act and Stevenson-Wydler Technology Innovation Act were established. The Bay-Dole Act is the act for promoting the technology transfer from university to industries and enables entities to apply patents based on research funded by the federal government and to license them to the third party. Because of this act, universities (and inventor) can earn royalty from patents and also are enhanced incentives for technology transfer. As a result, the collaboration between academia and industry, technology transfer and creation of startups have promoted [15].

Stevenson-Wydler Technology Innovation Act was also established in 1980 and determines the way to manage the results funded by the federal government. For example, entities are required to maximize the application of the research result funded by the federal government by transfer to the private sector. In addition, the federal agencies with research institutes are required to allocate more than 0.5% R&D budget to the technology transfer, and entities are required to establish the office for technology transfer and in the case of a institute's R&D budgets exceeds $ 20 million, to employ a full-time officer for technology officer [15]. With these two acts, the technology transfer in the U.S. institute was promoted.

Under President Obama's administration, there are several policies for innovation. Strategy for American Innovation, released in 2009, is for establishing the foundation for sustainable growth and the creation of quality jobs by clarifies the critical roles[1] for the federal government [16]. Based on this strategy, President Obama started in 2011 to celebrate, inspire and accelerate high-growth entrepreneurship throughout the nation [17]. This initiative is based on the idea that startups and entrepreneurs can be engines of job creation and economic growth. It focused on five areas; (1) Unlocking access to capital to fuel startup growth, (2) Connecting mentors and education to entrepreneurs, (3) Reducing barriers and making government work for entrepreneurs, (4) Accelerating innovation from "lab to market" for breakthrough technologies, (5) Unleashing market opportunities in industries like healthcare, clean energy, and education [16].

(3) Innovation policy in Japan

Importance of innovation for economic growth has been mentioned in Japan, the nation lack of natural resources. However, the history of Japanese innovation policy was started almost 10 years later for the U.S. The Act to Facilitate Technology Transfer from Universities to the Private Sector was established in 1998 in order to improve the technologies in industries including new field and to activate R&D activities in academic institutes. With this act, the establishment of the technology transfer offices (TLO) was boosted. In 1999, the system for Bayh-Dole was enacted in the Act on Special Measures Concerning Revitalization of Industry and Innovation in

---

[1] 1) Investment in the building blocks of innovation, such as fundamental research, human capital, and infrastructure. 2) Creation of the right environment for private-sector investment and competitive market. 3) Catalyzing for breakthrough related to national priorities and other grand challenges of the 21st century.

Industrial Activities. This system is based on Bay-Dole Act in the U.S. In addition, the exception on licensing fee for researchers in universities was accepted and faculties in national universities can become to be board members of companies in 2000 [15].

In Growth Strategy 2018, creation of innovation ecosystem through collaboration with universities industries, and government agencies are mentioned and the improvement of universities' management system, the collaboration of academia, industry, and government, and the support for startups are also mentioned for accomplishing the goal[18]. In Integrated Innovation Strategy, established also in 2018, achieving "the most innovation-friendly country in the world" and showing models of problem-solving to other countries as the front-runner of the world are declared as the objectives[19].

In addition, the recent amendment on Act on Improving the Capacity, and the Efficient Promotion of Research and Development through Promotion of Research and Development System Reform (the name is now changed to the Act on Activation of Science, Technology and Creation of Innovation) on December 2018 enables the national R&D agencies to invest startups for commercializing their fruits of R&D.

However, the challenge to fill in the gap between academia and industries and the small number and size of startups based on R&D have been mentioned in Japan. Many policies have been trying to overcome this problem and one of the representative system reorganizations in the funding system happened in medical R&D field. This was the reason for the establishment of the Agency of Medical Research and Development (AMED) in 2015. Currently in Japan, most of the funding to biomedical research is provide by AMED, which corresponds to NIH in the U.S., though AMED doesn't own research institute by itself.

AMED was established in Apr 2015 based on "Japan Revitalization Strategy - Japan is Back-" established in 2013[20]. With the strong push from the government, AMED was assigned as the control tower of the medical research and development, and most of the budget related to the medical R&D which had been managed by three ministries and agencies, i.e. Ministry of Education, Culture, Sports, Science and Technology (MEXT), Ministry of Economy, Trade and Industry (METI), Ministry of Health, Labour and Welfare (MHLW) and their belonging agency related to medical R&D, were integrated to AMED. Its primary objective is providing seamless financial support from basic research to practical application from which medical R&D in Japan had been suffering because the funding programs were provided by three ministries depending on its research stage, such as basic research, pre-clinical research, and clinical research.

Despite of these policies and the fact that Tokyo is ranked top in Innovation Cities Index 2018 and Japan ranked 6th in Innovation Capacity in the Global Competitiveness Report 2018[13], the government still feel needs and challenges for promoting innovation and implementing cutting-edge technology to the society because progressing aging society requires innovation with more speed than current pace. This mind is also same as in local governments especially which located in the rural area with a highly aging community and the national government encourages local governments to boost their economy by utilizing the specialty of the region in Regional Revitalization Strategy. Actually, some prefectures and cities, such as Kanagawa Prefecture, Kawasaki City, Kobe City, Kita-Kyusyu City, have been set their priority on science and technology as their core industry.

3.2 Regional clusters and biotech industries

(1) Regional clusters

Cluster is defined as a geographic concentration of interconnected companies and institutions in a particular field. It includes suppliers and providers of the industry and often extends to downstream of the industry, such as channels and customers, and also to governmental and other institutions, such as universities, consulting firms, and human resource providers[21].

The formation of a cluster is important for companies in competition because clusters help them in accessing to specialized and experienced employees and suppliers and also to specialized information from their community in more easier way than other regions [22]. In addition, linkage among stakeholders within a cluster is more easily recognized and captured.

Clusters also have an important role in innovation. This is because firms within a cluster can perceive new buyer needs more clearly and rapidly and because participation in a cluster gives advantages in perceiving new technological, operating or delivery possibilities. Competition among firms which locate geographically concentrated also reinforce the innovation. These are almost same in new business formation because the existing networks information about opportunities which lower entry barriers for entrepreneurs are the advantage in starting a new business for filling the perceived gaps in a cluster[22].

(2) Biotech clusters in the world

Biotech industries also form clusters around the world. Genetic engineering and biotechnology news (GEN) announces annually the ranking of biopharma clusters in each region, the U.S., Asia, and Europe[7], [23], [24]. As shown in Table 1, the ranking in 2018, Boston/Cambridge and San Francisco Bay Area are the top2 clusters in the U.S. and Japan is ranked 2nd in Asia. Though these rankings are separated by region, the prosperity of top 2 clusters in the U.S. is obvious because of its long history in biotech industries beginning from the 1970s, recombinant DNA technology. Since then, many firms and talents have been accumulating to these two clusters.

Table 1 Top 10 biopharma clusters in 2018 by region

Rank	**US**[7]	**Asia**[23]	**Europe**[24]
1	Boston / Cambridge, MA	China	United Kingdom
2	San Francisco Bay Area	Japan	Germany
3	New York / New Jersey	South Korea	France
4	BioHealth Capital Region [Maryland / Virginia / Washington, D.C.]	India	The Netherlands
5	San Diego	Australia	Spain
6	Greater Philadelphia	Taiwan	Switzerland
7	Los Angels / Orange Country, CA	Singapore	Belgium
8	Raleigh-Durham, NC (includes Research Triangle Park, NC)	Malaysia	Sweden
9	Seattle	Thailand	Italy
10	Chicagoland	Indonesia	Denmark

There are several articles analyzed and compared biotechnology clusters, in Boston/Cambridge, San Francisco Bay Area, the U.S., and Europe. The results suggest that the growth and diffusion of human capital, thus skilled labor and scientific expertise, was the primal determinant of the location and timing in the development of the American biotechnology industry [25]. Venture capital firms are another important stakeholder in the biotech cluster. Not only for investing local biotech companies, but also for navigating the business of a young company, VCs play a strong role in R&D [26]. Thus, in the high-tech based industries like biotech, suppliers of knowledge and funding seem to be essential in developing a cluster.

3.3 MIT approach to innovation ecosystem

(1) Innovation ecosystem and stakeholders

There are historically several models proposing stakeholders required for establishing an innovation ecosystem and they keep changing along with the development of economy and technology. In order to boost an economy, the relationship between industry and government had been focused on the old days. However, with the emerging of knowledge-based societies, the role of a university in innovation have been enhanced and the "Triple Helix" of University-Industry-Government relationship was stated [27].

After that, reality has already changed now. From the analysis of the world's iconic innovation ecosystems, Budden and Murray proposed the five key stakeholders in innovation-driven entrepreneurship ecosystems. The five stakeholders in this model are (1) Entrepreneur, (2) Risk Capital, (3) Corporate, (4) Government, and (5) University (Figure 1). These stakeholders are critical to the success in creating and growing innovation ecosystem. There are also other key players who can be included within the five stakeholders depending on the region's specific circumstance, such as service providers like lawyers and accelerators. [9]

Source: Budden & Murray, 2019[9]

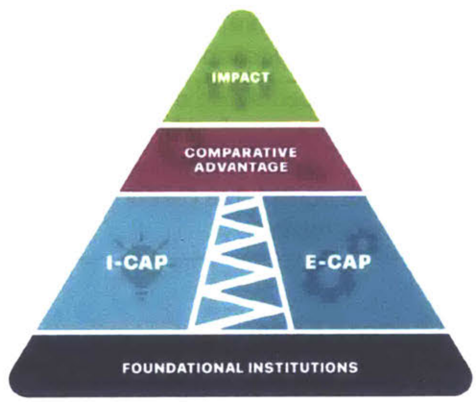
Figure 1 Five stakeholders in innovation ecosystem from MIT's model

Among these stakeholders, all of them can take a leadership role in creating the ecosystem. However, who is the best leader for ecosystem development is another problem. For example, large corporates are rarely regarded as leaders for the innovation ecosystem, but universities are often ideal leaders of a regional innovation ecosystem because of its regionality and longevity to commit the region. Of course, entrepreneurs/risk capital and government can be a leader but there might be limitations in the development stage and pitfalls in taking a lead. [9]

In addition, collective stakeholder leadership is also a key in developing the innovation ecosystem [9]. Thus, not only stakeholders themselves but also the relationships among them are also an important factor in developing the innovation ecosystem and considering them becomes more important in the strategic development of the ecosystem.

(2) The system for innovation-driven entrepreneurship

Budden and Murray also developed a way to analyze the innovation ecosystem systematic way which enables to compare and capture each ecosystem in the world [9], [28]. They break the system into four core elements shown in Figure 2.



Source: Budden & Murray, 2019[28]

Figure 2 MIT's model for innovation-driven entrepreneurship system

The foundational institutions are existing institutions, rules, practices and norms and are important for the capability of the system in investments or leverage on the ecosystem. Innovation Capacity (I-Cap) and Entrepreneurial Capacity (E-Cap) are the twin engines of the system at the next level on the foundational institutions. The comparative advantage which leads to the impact of the system is shaped based on the elements of two capacities and linkage between these capacities. [28]

For two capacities, I-Cap is the capacity of a place to develop innovative ideas and to take them from societal impact and E-Cap is general entrepreneurial capability and conditions for entrepreneurial activity. Each capacity is consisted by five critical inputs; Human Capital, Funding, Infrastructure, Demand, and Culture & Incentives.

Each component is defined as in Table 2, and the metrics for measuring these inputs are summarized in Table 3.

Table 2 Definition of five components of I-Cap and E-Cap

Components	Definition
Human Capital	the appropriate human talent (from within a region, or attracted into a region) with relevant education, training and experience for either innovation or entrepreneurship (or both).
Funding	a variety of types of capital (from the public and private sectors) that support innovation and entrepreneurship both at their origins but also throughout the journey from idea to impact, or start-up to scale-up.
Infrastructure	the physical infrastructure that is necessary to support innovation and entrepreneurship at their different stages - including space as well as equipment required for discovery, production and supply chains, etc.
Demand	the level and nature of specialized demand for the outputs of innovation and entrepreneurial capacities supplied by different organizations in the system.
Culture & incentives	the nature of role models and individuals who are celebrated, the social norms ('culture') that shape acceptable career choices and the incentives that shape individual and team behaviors.

Table 3 Measurements for 5 inputs in I-Cap and E-Cap

Components	I-Cap	E-Cap
Human Capital	Quality of STEM education, STEM Graduate, New PhD graduate, Availability of scientists & engineers, Researchers/professional engaged in R&D	% of school grads in tertiary education, Entrepreneurship perceived capabilities
Funding	R&D expenditure, Public R&D expenditure, Business R&D expenditure	Easy access to loans, ease of credit, Venture capital (VC) availability, VC investment, VC deals
Infrastructure	ICT access, Internet Bandwidth, Production process sophistication, Availability of latest technologies	Electricity & telephony infrastructure, Number of internet users, Logistics performance
Demand	Government procurement of advanced technologies, University-industry research collaborations, Trade, competition & market scale	Buyer sophistication, Domestic market scale
Culture & incentives	Quality of science research institutions, Graduates in science & engineering	Entrepreneurial intention, Fear of failure, Entrepreneurship as a good career choice, High status to successful entrepreneurs Business freedom

3.4 Knowledge transfer from academia to industries

(1) Channels for knowledge transfer

The importance of knowledge-based capital from academia to industries has been increasing, for the competitiveness and addressing the socio-economic challenges by benefitted from research and utilization of research findings to innovation [29]. There are two types of channels in knowledge transfer, one is formal and strong channels and another is informal and weak channels [8].

The formal channels are ones which are transferred by a certain type of legal arrangements. For example, collaborative and contract research, intellectual property transactions, labor mobility and academic spin-offs are categorized to this type of channel in OECD research. On the other hand, informal channels are ones occurred as information spillovers, thus weak connections among participants in a network facilitate this type of transaction, such as conferencing and networking, facility sharing, and recurrent education provided by universities to enterprises or people. The details defined in OECD are shown in Table 4 [8], [29].

Table 4 Types of channels in knowledge transfer and its definition

Channels	Definition
Formal Channels	
Collaborative research	research projects carried out jointly by public researchers and private firms.
Contact research	research that a private firm commissions universities or PRIs to perform.
Academic consultancy	research and advisory services provided by public researchers to industry clients.
Intellectual property (IP) transactions	the licensing and selling of IP generated by universities and PRIs to industry.
Research mobility	both university researchers working in industry and the converse, including temporary assignments.
Academic spin-offs	the entrepreneurial route to commercializing knowledge developed by public research.
Labour mobility	university graduates that join industry.
Informal Channels	
Publication	publication of public research in scientific journals and other specialised media.

Conferencing and networking	interaction between public researchers and industry actors can take place in formal conferences or dissemination events, but also in more informal settings.
Networking facilitated by geographic proximity	informal interactions between public research staff and industry researchers.
Facility sharing	Facility sharing between industry and public research.
Courses and continuing education	Courses and continuing education provided by universities to enterprises, and lectures at universities held by industry employees.

In the OECD's report "University-Industry Collaboration: New Evidence and Policy Options", they find five evidences:

1) The direct contributions of universities and public research institutes (PRIs) to patenting remain modest, but are growing faster than those of inventions from firms.
2) Universities and PRIs increasingly engage in research collaboration with industry.
3) (Physical) proximity to universities and PRIs matter for industry inventions.
4) Startup firms founded by students or academic significantly contribute to commercializing knowledge developed through public research.
5) Labor mobility is a key channel of science-industry knowledge transfer, particularly in some disciplines and industry sectors.

It is also mentioned that which channel is more important is different from industry to industry [30]. Especially in cutting-edge academic discoveries in biotechnology, such as a technique for recombinant DNA, the knowledge was transferred to industry through university spinoffs in many cases [31]. For example, Genentech (founded in 1976 and now a part of Roche), Biogen (founded in 1978) and Amgen (founded in 1980) are all started by researchers in universities. Though, engagement on firms as consultants and/or advisory board members also work as the mechanisms of knowledge transfer in tissue engineering [32].

(2) Knowledge transfer and key stakeholders or relationship in the ecosystem

In addition to channels, there is a shift in the weight of contribution by each stakeholder during the development of the ecosystem. Owen-Smith and Powell (2004) revealed that six public research organizations (MIT, Boston University, Tufts, Harvard, the Dana Farber Cancer Center, Massachusetts General Hospital, and the New England Medical Center) and large corporations not in Boston mainly contributed to connects participants of the network in the early development stage of Boston biotech community (in 1988). However, ten years later (in 1998), the network's centrality shifted to dedicated biotechnology firm (DBFs) and VCs, thus it became a more market-oriented network. They also mentioned that both proximity and cohesion among participants are important in innovation. [8]

Stakeholders and relationship which underpin the ecosystem's network are also different from a cluster to a cluster. The Boston/Cambridge and San Francisco Bay Area are known as the world's largest and most successful biotech clusters, but their feature is different. The Bay Area cluster's network depended on venture capitals. though Boston/Cambridge cluster's network highly dependent on academic research institute at the early stage, as mentioned above. It is possible that the difference of these clusters is derived from the differences in the stage of clusters, but the heavier reliance on non-DBF patents in the citations of Boston firm's prior art than the firms in Bay Area's one also suggested the difference of knowledge source in these regions. [33]

4. Definition and specificity of the biotech startup ecosystem

In this section, the outline of the biotech startup ecosystem is defined and the specificity of the biotech startup ecosystem in comparing other technological fields is discussed to explore the ecosystem afterward.

4.1 Definition of the biotech startup ecosystem

In this research, we focus on the startup ecosystem in the biotechnology and pharmaceutical industry and define the ecosystem in this area as the biotech startup ecosystem. The biotech startup ecosystem could contain the medical device area, but the situation in that area is quite different from pharmaceutical industries (or the pharmaceutical industry is a quite unique area from others). In addition, there are two types of startups; one is the innovation driven enterprise (IDEs) and another is small/medium-sized enterprises (SMEs).[11] Thus, we focus on IDEs and limit the area of the biotech startup ecosystem basically within the biopharmaceutical industries, otherwise, there is a notification.

4.2 Specificity and trends in biotech industries

(1) Specificity of biotech industries

It is often said that biotech startups a high-risk. Of course, most startups fail in all industry areas (the success rate of biotech startups is 13.8%), but biotech startups spend harder time until when it comes to clear whether their business succeeds. [34] In addition, 90% of clinical trials fail to get approval from the Food and Drug Administration (FDA).[35] Even though it goes successfully, more than 10 years are required until when the product is approved by FDA and it costs $2.6 billion in average (doubled from the mid-2000s) until it gets approved. [36] Because of the duration and costs on R&D, it takes long a time until a drug makes money, increase the risk of competition and cause the risk in expiring its patents and reduction of terms which a company is benefited from the patent protection.[37]

In addition to the specificity as the startup businesses, the biotech startup ecosystem also has a characteristic feature in the way of knowledge transfer from universities to industries. While joint research between universities and industries is a predominant way of knowledge interaction in technology-oriented industries,[30] a deep commitment by a scientist to a firm, such as by full employment or university-spinoff startup, is rather important in transferring new academic knowledge in biotechnology.[31]

Thus, in capturing the biotech startup ecosystem, we need to consider the systems which support the specificity of the biopharmaceutical businesses and the channels of knowledge transfer in biotechnology.

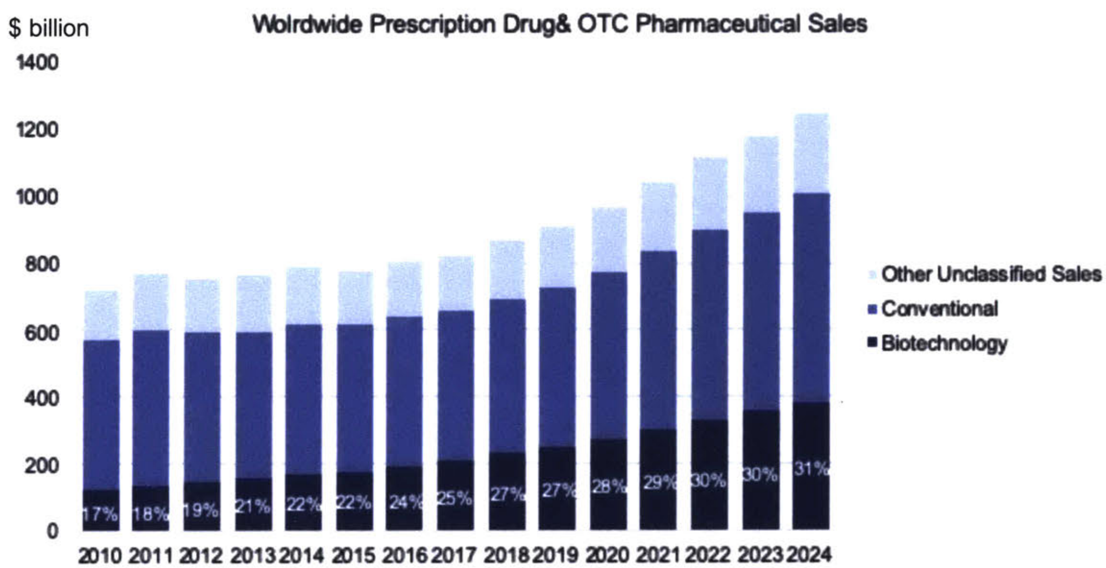
(2) Change in biotech and pharmaceutical industry

The change in the technological trend is inevitable in all industries and affects companies' business model. In addition, the needs for decreasing the cost and duration in developing new drugs makes it critical for pharmaceutical companies to change their R&D strategy. For example, companies collaborate with academia in a more engaging way and result in the increment of R&D budget allocation to collaboration partners from academia and the creation of a new alliance program with academia. Also, portfolio management including M&A and project acquisitions becomes more important in this industry.[37]

Creating innovation centers is another trend for pharmaceutical companies to boost innovation by mixing the internal and external resource including experts within or outside of a company.[37] For example, Pfizer opened Centers for Therapeutic Innovation (CTI) in 2010 to boost academic-industry collaboration and to bridge the gap between early scientific discovery and the translation to developing new medicine by Pfizer's team working side-by-side with academic teams.[38] Johnson and Johnson

(J&J) owns Johnson & Johnson Innovation as a part of the group and incubates and invests biotech startup companies.[39]

In addition, increasing the share of biologics, such as monoclonal antibodies, proteins or peptides (Figure 3) requires pharmaceutical companies to change their R&D model or pipelines because their traditional drugs are based on small molecules and because their R&D system has been optimized for them.[40]



Source: World Preview 2018 Outlook to 2024, Evaluate Pharma

Figure 3 Worldwide prescription drugs & OTC pharmaceutical sales by category[2]

4.3 Biotech startup's process from start to exit

(1) Growing process of a biotech startup

A biotech startup's growth process is almost same as other tech-oriented startups, thought its industry area has some specificity noted above. Table 5 describes what kind of tasks are required in a startup's business and R&D and Figure 4 is the flow chart which shows when each task is required for the business.

[2] ~2017: actual data, 2018~: prediction

Table 5 The task of a biotech startups

Category	**Type of task**	**Specific tasks**
Business Side	Funding	Grant application
		Applying business competitions
		Fundraising from VC (including CVC)
	Human Resource	Recruiting
	Establishing a company	Filing the business
		Finding Advisory Board
	Company exit	Preparing for IPO
		Negotiation for M&A or licensing
	Patent	Patenting
		IP licensing
R&D Side	R&D	R&D for POC
		R&D for patenting
		R&D for IND
	Managing clinical trials	Coordinating clinical trials
		Analyzing the data

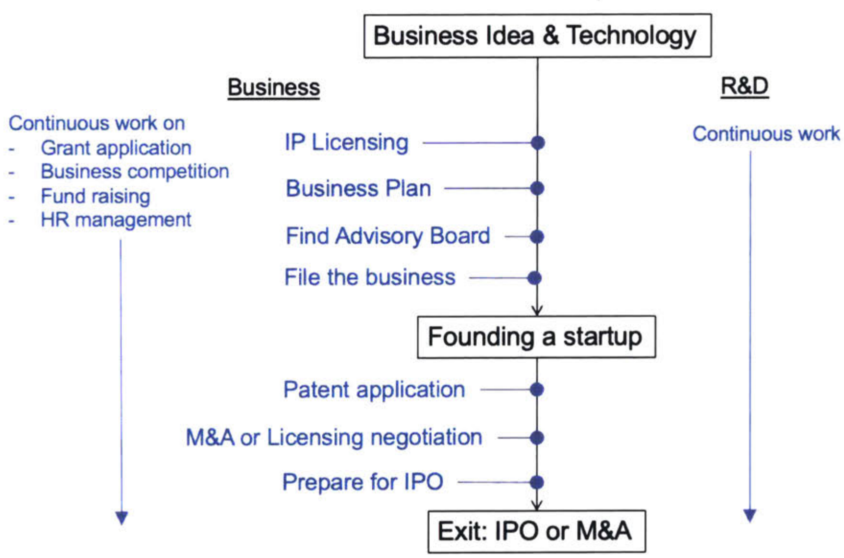


Figure 4 Flow chart of tasks in a biotech startups business

It is apparent from Figure 4 that most of the tasks relating to the management a startup is required temporally and concentrated at the beginning of a business.

Finally, a biotech startup exits, that is it goes public in an initial public offering (IPO) or is sold to a large pharmaceutical company. However, a biotech startup's story doesn't end at this point, it still needs to go forward in the R&D side to get FDA's final approval. Also, the management team has to raise money continuously.

Overall, there are many tasks in the business side at the beginning of a startup's business and an entrepreneur has to learn or be supported to overcome them especially if the founding group doesn't have any background in business. Farther, the beginning phase of a biotech startup is more important than of other industry's startups because a biotech business takes much more time and cost. Therefore, in order to reduce the hurdle in starting a business, several types of supports and/or services are required from entrepreneurs.

(2) Requirements for supporters and supporting activity in the ecosystem

As mentioned in Chapter 3, there are five major stakeholders in the innovation ecosystem. The supports and/or services for startups pointed out above are provided by universities, pharmaceutical companies, and VCs as a part of their business, but such supports are not their primal function in the ecosystem. In addition, there are certain organizations who primarily provide these supports and services to entrepreneurs. Also, these supports are sometimes delivered by the intangible ways, such as word of mouth. This type of knowledge transduction is based on the network, and the network is also sometimes provided by a certain entity which is not categorized into the five stakeholders, such as the association of stakeholders. The function of these entities which are not categorized to five stakeholders plays a more important role in starting a company, especially in the field like biotech where the risk and cost are higher than other areas.

To fill the gap of the five stakeholders' model and the point above, we decided to count "Supporter" as another stakeholder in the innovation ecosystem. The concept of supporter is also mentioned as one of the stakeholders in the ecosystem in some models,[41] and it is sometimes called intermediaries.[42] In these models, supporters are defined as infrastructure, professionals, and network which supports entrepreneurs. For example, law firms support startups in the legal process, such as filing the company and signing the license agreement. The association of stakeholders in the ecosystem is also categorized here because their primary role is networking all the stakeholders including startups and the network could be a key for newcomers in the ecosystem like startups. Therefore, as considering the importance of the supporter's role at the beginning of biotech startup business, we adopt this definition and consider supporters as one of the critical stakeholders. In addition, as mentioned above, some of the functions provided by supporters could be provided by other stakeholders redundantly. We also define it as "supporting activity" and discuss this point in the later section.

5. Metrics in comparing the biotech startup ecosystem

In this section, we'll define the metrics for analyzing and understanding the biotech startup ecosystem including the five stakeholders in MIT's model and the supporters as we discussed above.

5.1 Stakeholders in the biotech startup ecosystem

(1) Supplies and demands of stakeholders in a biotech ecosystem

Table 6 shows the function of six stakeholders in focusing on their demand and supply on the ecosystem. The supplies and demands of stakeholders reveal that the main values exchanged in the ecosystem are technology[3], knowledge, researcher, and money and that the supply of entrepreneur is essential for the risk capital and the supporter. This means they don't have the incentive to be in the ecosystem without entrepreneurs.

Table 6 Supply and demand of six stakeholders in the ecosystem

stakeholders	What they can give to the ecosystem (supply)	What they need from the ecosystem (demand)
Entrepreneur	Technology Knowledge Researcher	Money (including tax deduction) Knowledge Place (lab facilities and office space) Researcher
University	Technology Knowledge Place (including lab facilities) Researcher	Money (including tax deduction) Knowledge
Government	Money (including tax deduction) Place (including lab facilities)	Money (tax)
Corporate	Money Knowledge Place (including lab facilities) Researcher	Technology Knowledge Researcher

[3] In this study, we distinguish technology from knowledge. Technology is the knowledge directly related to business itself and transferred among stakeholders via patents or other contracts. Knowledge is the knowledge not directly related to business and tend to be more supportive activity in business. Knowledge can be transferred not only by contracts but also by word of mouth.

Risk Capital	Money Knowledge	Entrepreneur
Supporters	Knowledge Place (including lab facilities) Opportunity (meet-up etc.)	Entrepreneur

Figure 5 is the stakeholder value network surrounding entrepreneurs and Figure 6 is the whole structure of the network of the ecosystem based on the analysis in Table 6. Figure 6 includes the network other than entrepreneurs and shows that stakeholders are connected mutually. In addition, it shows that researchers and technology are exchanged among entrepreneur, university and corporate.

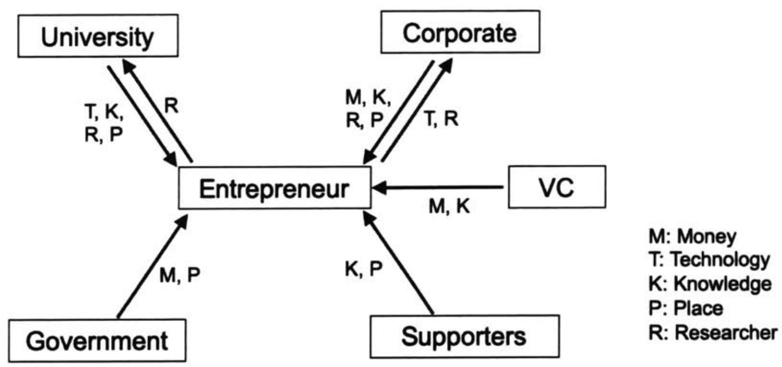


Figure 5 Stakeholder value network surrounding entrepreneurs

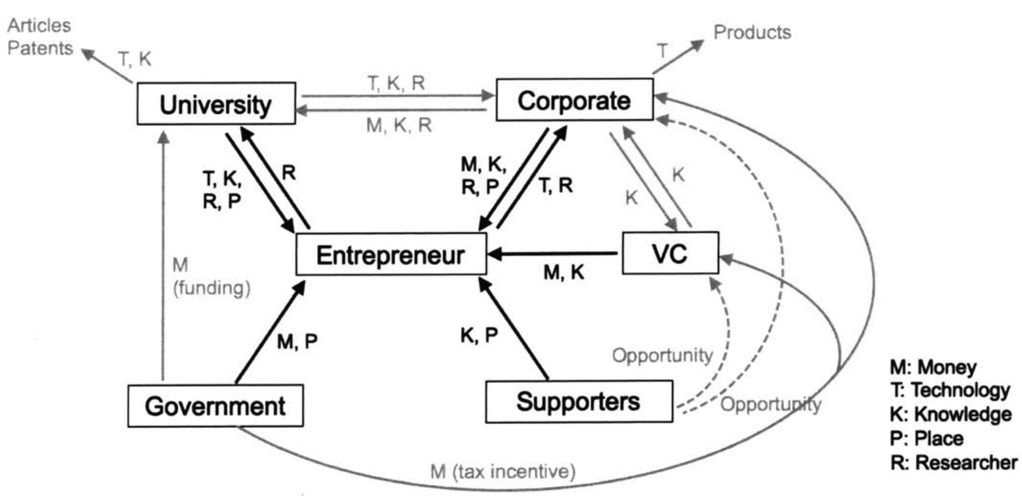


Figure 6 Stakeholder value network of the innovation ecosystem

(2) Stakeholders as organization

Organizations which involves a biotech ecosystem are categorized to six stakeholder's categories as shown in Table 7. It is possible that several stakeholder organizations, such as pharmaceutical companies, have some overlapped function within six categories, but they are categorized to one category based on their original businesses.

Table 7 List of stakeholders as an organization

Stakeholder Category	Organization	Definition
Government	Government	R&D promoting side of the government
	Regulatory Agency	Regulatory side of the government
Corporate	Pharmaceutical Company	Pharmaceutical companies *It is possible that a pharmaceutical company has a function as venture capital (CVC) in addition to their basic business operations and R&D units.
Risk Capital	Venture Capital	Firms providing risk capital to startups
University	University	Academic research institute
	Hospital	The place clinical researches are executed
Entrepreneur	Startup	IDE started by entrepreneurs
Supporters	Organizations of supporters	Firms or organizations which support startups' business or R&D, such as law firms, IP firms, accounting firms, consultants, incubators, accelerators, and R&D outsourcing companies
	Association of all stakeholders	Association(s) which is consisted of (most of) all stakeholders in the ecosystem

For the government, the features of policy in promoting side and regulatory side are different. Therefore, we analyze the policies in promoting side and regulatory side separately.

Universities also can be separated into two types of organizations. Hospital(s) belonging to a university is a place for executing clinical research which is managed by pharmaceutical companies, startups and doctors themselves. Thus, it is different from academic research institutes and some universities don't have a belonging hospital.

Supporters are also the same. As discussed above, there are several organizations could be categorized into supporters, but the feature of stakeholders' association(s) is different from other organizations because their customers are all stakeholders in the ecosystem. Thus, we differentiate them from other organizations.

5.2. Innovation capacity and entrepreneurship capacity in a biotech ecosystem

(1) Metrics used for I-Cap and E-Cap in this research

The measurements for I-Cap and E-Cap in MIT's approach are shown in Table 3. These measurements are used for comparing countries and collected from publicly available data from worldwide research. However, there are constraints in the data available because of the comprehensiveness of the research.

In this research, we focus on the biotech ecosystem in several clusters and universities in the United States and Japan. Thus, it is expected that the more precise metrics which measures I-Cap and E-Cap could be available and that the measurement could be optimized to measure the biotech ecosystem. For example, we can measure R&D expense on medical research and life science area. In addition, measuring I-Cap and E-Cap of universities are important when we focus on the startup ecosystem because universities play an important role in transfer knowledge to industries. For these reasons, we arrange the metrics for I-Cap and E-Cap to measure the biotech ecosystem in the national or local level and university level as shown Table 8 and Table 9. Based on these metrics, we'll analyze and discuss the ecosystem in the following sections. Definitions of each measurements are following.

Table 8 Metrics for capturing I-Cap in the biotech ecosystem

	National/local (regional) level	**University level**
Human Capital	# of universities (per capita/area)	university ranking
	# of top-ranked universities	# of highly cited researchers
	STEM Graduates per capita	# of STEM Graduates
	New Ph.D. graduates per capita	# of New Ph.D. graduates in STEM
	Researchers/Professional engaged in R&D per million populations	# of Researchers/Professional engaged in R&D
Funding	Public R&D Expenditure as % of total R&D expenditure	Amount of public funding in R&D (total and life science/medial)
	Business Expenditure as % of total R&D expenditure	Amount of private funding in R&D (total and life science/medial)
Infrastructure	# of clinical research hospitals	# of patents, licensing and licensing revenue
	# of patents	
Demand	# and ranking of pharmaceutical companies	# of collaborative research with private sectors
	budget on academia-industry collaborative research	
Culture and Incentives	# of Nobel prize winner	# of Nobel prize winner
	# of top10%/1% articles	# of graduates in science & engineering, medical school
	% of graduates in science & engineering, medical school	

Table 9 Metrics for capturing E-Cap in the biotech ecosystem

	national/local (regional) level	**University level**
Human Capital	% of school grads in tertiary education	# of students
		# of classes of entrepreneurship education
		# of spin-off startups
Funding	Incentive for startups (funding, tax incentive)	
	number of venture capitals	
	VC investment	
	VC deals	

Infrastructure	# of incubation office, accelerator, shared-lab, meet-up events	# of incubation office, accelerator, shared-lab, meet-up events
Demand	Market scale in the pharmaceutical industry	Incentives for starting businesses (prize and competition)
	# of pharmaceutical companies	
Culture and Incentives	Entrepreneurial intention	(# or $of) business competition (or prize) in university
	Fear of failure	
	Entrepreneurship as a Good career choice	
	High Status to Successful Entrepreneurs	
	(# or $ of) business competition (or prize) in public/private	

(a) Human Capital

I-Cap

The metrics of I-Cap in Human Capital is chosen for assessing the quality of STEM education and the number of STEM graduates, Ph.D. graduates, and researchers. The quality is substituted by the ranking of universities and the number of the highly cited researchers. The number of students and researchers are adjusted by population.

E-Cap

The metrics of E-Cap in Human Capital is chosen for assessing the number of students who have a potential to be convert into I-Cap population. In addition, the number of entrepreneurship classes and spin-off startups are counted for assessing the opportunity for immersing entrepreneurship.

(b) Funding

I-Cap

The metrics of I-Cap in Funding is same as the metrics in MIT's approach. In the case of a university, the source of research budgets are counted.

E-Cap

The metrics of E-Cap in Funding is also same as MIT's approach. In stead of the availability of VCs, we adopt the number of VCs.

(c) Infrastructure

I-Cap

The metrics of I-Cap in Infrastructure is assessing the outlet of the academia to industries. Thus, here we count the number of clinical research hospitals and patents.

E-Cap

The metrics of E-Cap in Infrastructure is assessing the number of incubation office or share-lab, accelerators, and meet-up events, where people can foster entrepreneurship and expand their entrepreneurial business.

(d) Demand

I-Cap

The metrics of I-Cap in Demand is assessing the demand from industries in human resource and technology. Thus, here we count the budget on academia-collaboration research and the ranking of pharmaceutical companies which affects the potential R&D budgets in industries.

E-Cap

The metrics of E-Cap in Demand is assessing the market scale. Thus, here we count the number of pharmaceutical companies and their market scale. In university, the demand is the given incentives for starting business, such as prize, competition, and evaluation for researchers.

(e) Culture and incentives

I-Cap

The metrics of I-Cap in Culture and incentives is assessing the quality of academic research. Thus, here we measure the number of Nobel Prize laureates and the number of highly cited researchers in the articles. Also, we count the number of graduates in science & engineering and medical schools as same as MIT's approach.

E-Cap

The metrics of E-Cap in Culture and incentives is assessing entrepreneurial intention and environment for fostering entrepreneurship. Thus, here we measure the number of business competition or prizes for startups in addition to the metrics in MIT's approach.

(2) Other metrics evaluating ecosystem

I-Cap and E-Cap measurements discussed above is based on MIT's model. However, compared with the stakeholder network model constructed in Figure 6, some measurements relating to supporters and supporting activities are missing. Thus, we add metrics to evaluate this point from the aspect of I-Cap and E-Cap as shown in Table 10. I-Cap is defined as the number of supporting organizations and the association of stakeholder in the ecosystem, and E-Cap is the number of occasions organized by the association and the accessibility to supporters for entrepreneurs.

Table 10 Metrics for evaluating I-Cap and E-Cap of supporting activities

	I-Cap	**E-Cap**
Supporting activity	# of stakeholders' association	# of events
	# of supporters	Accessibility to supporters

6. Regions and universities analyzed in this research

In this section, we'll figure out which cities and universities are suitable for analyzing the biotech startup ecosystem in the U.S. and Japan and will overview the administrative information about the cities.

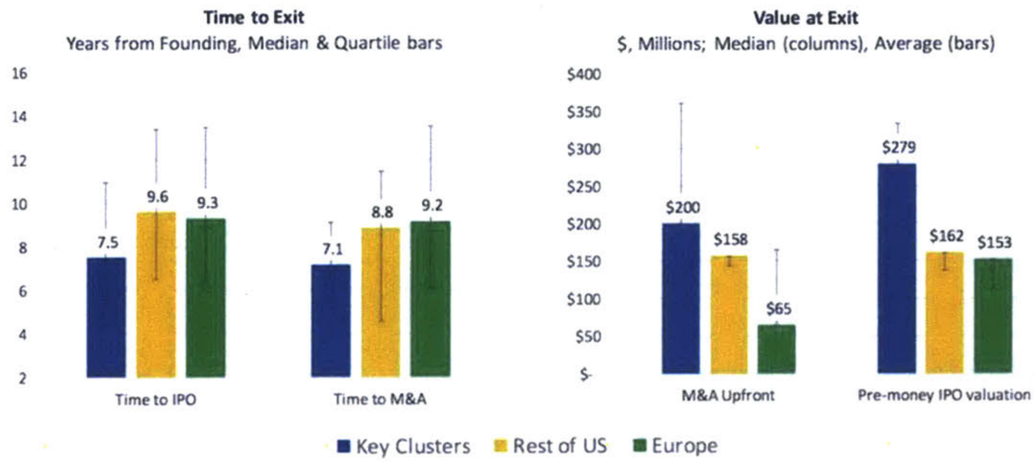
6.1 Selection of regions in the U.S. and Japan

Numerous countries have or try to have biotech clusters to foster biopharmaceutical industries, and Japan is not the exception. Although the national government and some local governments have been trying to foster the biotech ecosystem, Japan is ranked 15th in "The 2016 Scientific American Worldview", which assessed innovation potential in biotechnology over 54 countries. In this ranking, the U.S. is 1st and Singapore (2nd) and Denmark (3rd) follow.[43]

In this research, we will compare the biotech startup ecosystem in the U.S. and Japan by focusing on the difference in the system around the startup especially spin-off from academic research in a university. For this purpose, two cities and two universities in each city both in the U.S. and Japan are chosen in the following process.

(1) Clusters and universities in the United States

As shown before, Boston/Cambridge is ranked as No.1 biopharma cluster in the U.S., and San Francisco Bay Area follows (Table 1). These two regions have been key clusters in biotech because talent and capital related to biotechnology are accumulated.[44] Benefited from the effect of a cluster, the time to exit in these two key clusters were roughly two years faster at the median than other regions, and the average value at exit distributed upwards in the key clusters (Figure 7).



Source: Pitchbook; Key Clusters defined as Massachusetts and Bay Area by BRUCE BOOTH[44]

Figure 7 Exit time and Value at Exit by Region (average: 2013-2016)

The university ranking also gives the plausibility of these clusters. As Table 11 shows, 9 of the top 100 universities in THE World University Rankings 2019 locate in California, and 3 are in Massachusetts.[45] The universities which are ranked in the top 100 in California and Massachusetts are listed in Table 12 and Table 13.

Table 11 Number of universities in Top 100 in THE World University Rankings 2019 by state (US)

State	Number of universities
California (CA)	9
Massachusetts (MA)	3
New York (NY)	3
Pennsylvania (PA)	3
Illinoi (IL)	3
(5 states)	2
(10 states)	1

Table 12 Universities ranked in Top 100 (California)

Rank	Name	Public/Private
3	Stanford University	Private
5	California Institute of Technology	Private
15	University of California, Berkeley	Public
17	University of California, Los Angeles	Public
30	University of California, San Diego	Public
52	University of California, Santa Barbara	Public
59	University of California, Davis	Public

66	University of Southern California	Public
96	University of California, Irvine	Public

Table 13 Universities ranked in Top 100 (Massachusetts)

Rank	Name	Public/Private
4	Massachusetts Institute of Technology	Private
6	Harvard University	Private
74	Boston University	Private

With these facts, we choose two clusters, Boston/Cambridge and San Francisco Bay Area [4], and four universities in these two states (Massachusetts Institute of Technology (MIT), Harvard University, Stanford University and University of California, Berkley (UC Berkley): three private schools, one public school), as the target of analysis in this research.

(2) Clusters and universities in Japan

In Japan, it is obvious Tokyo (Kanto[5]) and Kyoto/Osaka (Kinki[6]) are the two major economic clusters in any area. In addition, Tokyo is ranked 1st, Osaka is 45th and Kyoto is 64th in World's top 100 cities for innovation 2018.[46] Indeed, 10 of 5 Japanese companies in the top 50 global pharmaceutical companies (2017) locate their headquarters or office (not R&D institute) both in Tokyo and Osaka and 5 companies' headquarters are in Tokyo (Table 14).

Table 14 Location of Headquarters or Business Offices[7]

Ranking (World)	Company Name	HQ or Business Base location
20	Takeda Pharmaceutical Company Ltd	Tokyo, Osaka
23	Astellas Pharma Inc,	Tokyo

[4] Alameda, Contra Costa, Marin, Napa, San Mateo, Santa Clara, Solano, Sonoma, and San Francisco.
[5] Ibaraki, Tochigi, Gunma, Chiba, Saitama, Tokyo, Kanagawa
[6] Osaka, Kyoto, Hyogo, Nara, Wakayama, Shiga, Mie
[7] The data source is noted in Chapter 11

26	Daiichi-Sankyo Co., Ltd.	Tokyo
28	Otsuka Holdings	Tokyo, Osaka
32	Eisai Co., Ltd.	Tokyo
38	Chugai Pharmaceutical Co., Ltd.	Tokyo
40	Sumitomo Dainippon Pharma Co., Ltd.	Tokyo, Osaka
45	Mitsubishi Tanabe Pharma Co., Ltd.	Tokyo, Osaka
46	Ono Pharmaceutical Co., Ltd.	Tokyo, Osaka
49	Kyowa Hakko Kirin Co., Ltd.	Tokyo

In addition, 10 of the top 20 universities in THE Japanese University Rankings 2018 locates in Kanto (Tokyo, Ibaraki, and Chiba), and 3 are in Kinki (Kyoto, Osaka, Kobe) (Table 15).[47] The only one university nominated in top 50 in THE World University Rankings was University of Tokyo.[45] The universities which are ranked in the top 20 of Japanese ranking in Kanto and Kinki are listed in Table 16 and Table 17.

Table 15 Location of universities in top 20 by regions and prefectures

Region	(Prefecture)	Number of universities
Kanto		10
	Tokyo	(8)
	Ibaraki	(1)
	Chiba	(1)
Kinki		3
	Kyoto	(1)
	Osaka	(1)
	Hyogo	(1)
Other		7

Table 16 Universities ranked in top 20 (Kanto)

Ranking (Japan)	University	Prefecture	Public/Private
1	The University of Tokyo	Tokyo	Public
4	Tokyo Institute of Technology	Tokyo	Public
9	University of Tsukuba	Ibraki	Public
10	Keio University	Tokyo	Private
11	Waseda University	Tokyo	Private
14	Hitotsubashi University	Tokyo	Public

15	Sophia University	Tokyo	Private
16	International Christian University	Tokyo	Private
17	Tokyo University of Foreign Studies	Tokyo	Public
19	Chiba University	Chiba	Public

Table 17 Universities ranked in top 20 (Kinki)

Ranking (Japan)	University	Prefecture	Public/Private
1	Kyoto University	Kyoto	Public
8	Osaka University	Osaka	Public
18	Kobe University	Hyogo	Public

With these facts, we choose two clusters, Kanto (focusing on Tokyo) and Kinki (Kyoto, Osaka, Hyogo) Area, and four universities in these two areas (University of Tokyo, Keio University, Kyoto University and Osaka University: three public schools, one private school), as the target of analysis in this research.

6.2 Administrative information and basic demographics of Clusters

(1) Administrative information about clusters

In comparing the different cities, metrics sometimes depends on a city's area size, population, and GDP. Table 18 is the basic information about each region in the U.S. and Japan. From the following sections, we'll basically use these numbers in the adjustment is required.

Table 18 Area, GDP and population of each country and region[8]

	US					Japan					
		Massachusetts		California			Kanto		Kinnki		
			Boston /Cambridge		Bay Area*			Tokyo		Kyoto	Osaka
Area (sq km)	9,834,000	20,202.08	141.59	403,466.62	21,500.00	377,962.00	32,236.00	2,104.00	32,856.00	4,623.00	1,901.00
Population (million)	327.160	6.902	0.799	39.557	8.562	126.443	43.248	13.724	20.138	2.599	8.823
GDP (million $)	19,485,394	542,978.80	438,683.9 **	2,797,600.90	837,544.70	5,319,800.40	1,844,728.0	861,993.5	687,477.9	85,468.6	323,080.2
GDP per capita	59,774.00	71,456.00	78,465 **	65,160.00	107,151.30	41,978.00	42,654.64	62,809.20	34,138.34	32,885.17	36,617.96

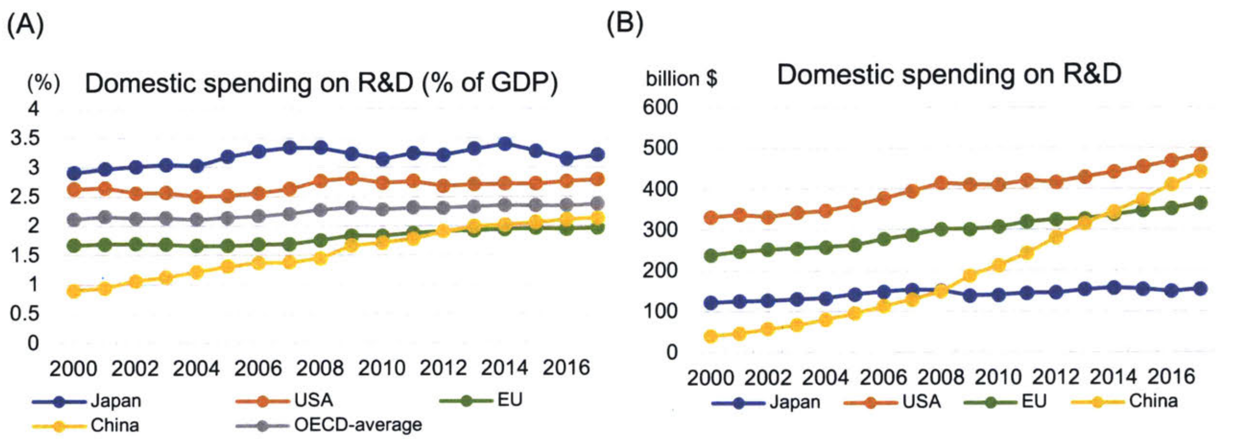
All the data is in 2018, except: population in Japanese regions (2017), national GDP (2017), GDP in US regions (2017), GDP in Japanese regions (2015), GDP capita is calculated from the latest available data.

*San Jose-Sunnyvale-Santa Clara, San Francisco-Oakland-Hayward, Napa, Santa Rosa, and Vallejo-Fairfield MSAs

** Boston-Cambridge-Newton, MSA

(2) Basic demographics surrounding R&D in Clusters

There are several ways to compare R&D activities among countries, but using spending on R&D is one of the basic means. Figure 8 compares the spending on R&D by % of GDP and actual spending. In Japan, the spending is larger than US and China in the % of GDP (Figure 8 (A)), but the actual spending is less and stagnated these 15 years (Figure 8 (B)).



Source: GDP domestic spending on R&D (OECD Stat.[9])

Figure 8 Domestic spending on R&D by countries (2000-2017)

[8] The data source is noted in Chapter 11.

[9] https://stats.oecd.org

The expenditure on R&D is mainly financed by public and business sector. Figure 9 shows the percentage of expenditure financed by the government. Compared with the U.S. and China, the percentage of government expenditure is lower in Japan. In general, R&D expenditure by the business sector is more focused on application and development rather than the public sector's funding. Thus, the reason for the low expenditure on basic research is the high expenditure on R&D by the business sector.

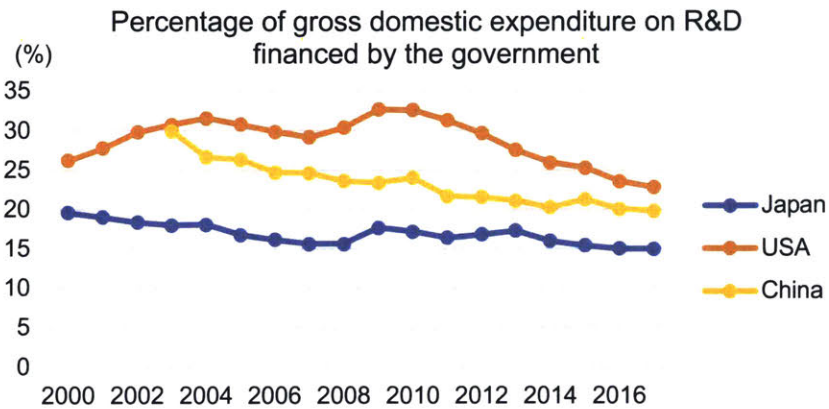


Figure 9 Percentage of gross domestic expenditure on R&D financed by the government

In looking into clusters, the public R&D expenditure consists of the federal/national government's funding and their own funding. Table 19 shows the funding source and amount in each cluster. Allocation of the national funding to each region was not available in Japan. Though the total funding by the national funding is less in Japan, the funding by local government is larger. However, it is also reported that universities and colleges received $4.2 billion in total in FY2017.[48] This is partly because the survey includes the expenditure of state government departments, agencies, public authorities, institutions, and other dependent entities, but doesn't include direct appropriation from state legislatures to universities, colleges, and private organizations. In addition, there might be a difference in the definition of R&D spending between the U.S. and Japan. Thus, it is difficult to conclude the significance in Japanese local governments' priorities, but the expenditure from the local governments cannot be ignored both in the U.S. and Japan.

Table 19 Funding on R&D by federal/national government and local governments[10]

(million $)	US (FY2016)	Massachusetts	Boston/Cambridge	California	Bay Area	Japan (FY2017)	Kanto	Tokyo	Kinnki	Kyoto	Osaka
National R&D funding	111,123	5,525	ND	15,714	ND	31,988	ND	ND	ND	ND	ND
Local gov. R&D funding	2,317.13	23.43	ND	573.99	ND	4,521.13	752.48	358.73	690.59	168.61	190.17

Another measure to compare R&D activity is the number of researchers.

Figure 10 shows the number of researchers per 1000 employed. As it shows researchers are more available in Japan than in the U.S. and China. However, the number is not changed in these 10 years in Japan in contrast to other countries in which the number has been increasing.

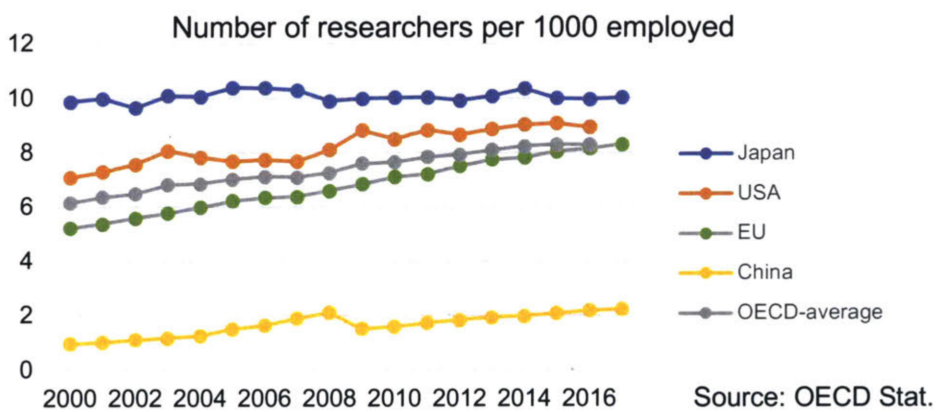


Figure 10 Number of researchers per 1000 employed

Same as the expenditure of R&D, the researchers are also distributed to academia and the private sector. In Japan, 57.3% of researchers are in business enterprises and 38.2% are in universities and colleges.[49] The mobility of researchers between universities and industry is quite low in Japan and it is less than 0.5% of researchers in these sections.[49] On the contrast, 73.4% of researchers belonged to the private sector in the U.S. (latest available data:1999). There is no data about the mobility of

[10] The data source is noted in Chapter 11.

researchers among sectors, but it is estimated to be higher in the U.S. than Japan. These difference in researchers' allocation and mobility might be considered especially for the knowledge transfer in the ecosystem.

7. Comparison of Stakeholders in the U.S. and Japanese Ecosystem

In this section, we'll analyze the stakeholders in each region which we identified above following the metrics we discussed in Chapter 5.

7.1 Analysis and Comparison of Stakeholders

In this subsection, we firstly identify and compare the six stakeholders in each cluster following the definition in Table 7, then compare the structure of stakeholders.

(1) Government: promoting side

Other than the Bayh-Dole Act, the political instruments which aim to promote R&D are mainly categorized into two; funding and tax incentives. These policy instruments give incentive to researchers and industries to promote a specific R&D field and are executed in all the government level, that is Federal/National government level, State/Prefecture government level, and City government level. From the view of regional clusters, policies in all these levels affect the economics and R&D in a cluster. Thus, we explore the governments' policies in promoting biotech industries in each cluster in the following part.

(a) United States (Federal government)

(i) NIH grant

In the U.S., the largest funding to biomedical research field comes from National Institute of Health (NIH)[11] which invests more than $32 billion in a year. 80% of the funding is awarded to almost 50,000 competitive grants to more than 300,000 researchers at more than 2,500 universities, medical schools, and other research institutes and 10% supports projects conducted by NIH's laboratories. [50] The top 5 states which are awarded from NIH grant are shown in Table 20.

---

[11] https://www.nih.gov

Table 20 Top 5 States awarded by NIH funding in FY2018[12]

Ranking	Location	Awards	Funding (million $)	Population (million)	Funding per capita ($)
1	California	8362	$4,243.4	39.6	107.27
2	Massachusetts	5367	$2,887.1	6.9	418.30
3	New York	5448	$2,632.7	19.5	134.72
4	Pennsylvania	3747	$1,810.2	12.8	141.35
5	Maryland	2508	$1,531.6	6.0	253.47

California is ranked 1st place in the funding amount and Massachusetts follows. However, in the aspect of the funding per capita, Massachusetts is far more than other states, it overs $400. In the top 70 organizations which are awarded more than $100 million in 2018 from NIH, 11 organizations are listed from Massachusetts and 10 of them are located in Boston/Cambridge. In California, 9 organizations were awarded more than $100M in 2018, but only 3 (UC San Francisco, Stanford, and UC Berkeley) are in top 70.

(ii) NSF funding

The National Science Foundation (NSF)[13] funding is another funding resource for academic researchers including life sciences. Its total budget for was $5,650 million and $672 million (12%) was allocated to life sciences in FY2017.[51]

NSF supports not only academic research but also creation of innovation. Innovation Corps (I-Corps)[14] is the funding program launched in 2011 by the federal government to prepare scientists and engineers to extend their focus beyond the university laboratory in order to accelerate the economic and social benefits of the basic-research projects. In this program, teams are provided the seven-weeks curriculum to learn how to transform innovation to successful products and services. They also provide the supplement funding (up to $55,000) to cover the cost during the program.

---

[12] The data source is noted in Chapter 11
[13] https://www.nsf.gov
[14] https://www.nsf.gov/news/special_reports/i-corps/index.jsp

I-Corps at NIH[15] is the I-Corps program organized in NIH. In this program, teams are provided curricula specifically tailored to life sciences, such as therapeutics, diagnostic and e-health, and medical devices.

(iii) Small Business Innovation Research (SBIR) and Small Technology Transfer Research (STTR)

Small Business Innovation Research (SBIR) and Small Technology Transfer Research (STTR)[16] are the programs provided by Office of Investment and Innovation (OII) in the Small Business Administration (SBA) of the federal government. These programs help research-intensive small businesses in the U.S. with the potential for commercialization. Federal agencies with extramural R&D budgets that exceed $100 million are required to allocate 3.2% (FY2017) of their R&D budget to SBIR programs, and 11 agencies participate in the program in 2017. In addition, the percentage for budget allocation has been increasing since 2011. As similar, Federal agencies with an extramural R&D budget that exceed $1 billion are required to reserve 0.45% of the extramural research budget for STTR awards to small business, and 4 agencies correspond in 2017. California and Massachusetts are top 2 awarded states for SBIR and STTR and one-third of awards and obligations are allocated to these two states; $ 10.4 billion to California and $ 6.6 billion to Massachusetts.

(b) United States - Massachusetts

In addition to the federal grants, Massachusetts states also provide other incentives to biotech industries. In 2008, the state made a $1billion, ten-year commitment to the life sciences industries.[52] This is known as the Massachusetts Life Sciences Initiative (MLSI). The Massachusetts Life Sciences Center (MLSC) was created to charge in carrying out the initiative. There are three major initiatives:

---

[15] https://sbir.cancer.gov/programseducation/icorps

[16] https://www.sbir.gov

- $250 million in funding for discretionary investments, including grants for Massachusetts-based researchers
- $500 million in capital investments for life sciences infrastructure in Massachusetts
- $250 million in tax incentives provided to certified life sciences companies

In addition, $20 million was funded to MLSC in 2010 for:

- Stimulate Massachusetts' platform for life sciences research and development, encouraging companies to locate and grow here
- Accelerate the commercialization of ground-breaking new therapies and technologies
- Invite and match private investment to leverage public funds to best support economic development
- Promote workforce programs that train or retain Massachusetts workers to compete and succeed in this thriving sector
- Encourage students to pursue careers in the life sciences

According to MLSC's 2018 Impact Report, life sciences employment in Massachusetts increased 28,000 and 6th place to 2nd in the U.S., following California from 2003 to 2016. In addition, average expenditures of industrial R&D in life sciences grew in 16.7% (CAGR) on contrast that the U.S. average is 2.8%.[53]

After the 10 years has passed, Massachusetts extends MLSI for another 5 years and $623 million (including $150 million tax credits) in funding for education, R&D and workforce training for the industry.[54] This is known as the Life Science 2.0.

(c) United States - California

In contrast to Massachusetts, California does not have a statewide bioscience-specific strategy or targeted industry focus.[17] They have the tax incentives for general

[17] https://www.phrma.org/resources/state-map

manufacturing companies including the R&D tax credit. Instead of the state government, the regional organizations and the industry associations play a major role. These organizations will be investigated in the later section ((9) Supporters).

Apart from the state funding system, the California Institute for Regenerative Medicine (CIRM), which was created by voter approval in 2004, fund stem cell research at institutions across California. The referendum authorized $3 billion in this funding. Other funding programs including education programs are also provided by the regional organizations and the industry associations.

(d) Japan (national government)

(i) Act on Promotion of Healthcare

In Japan, the Act on Promotion of Healthcare Policy was approved in 2014. This policy not only supports R&D in medical research filed but also encourage the development of business related to healthcare and medicine. Supporting of biotech startups is one of the topics in the policy underpinned by increasing demand from biotech industries to startups and cutting-edge technologies in universities.[55] For this purpose, new grants for funding biotech startups and collaborative research between academia and industry have been started from FY2017 in AMED and METI published a report to promote the connection between biotech startups and investors for the purpose of offering solutions to challenges facing emerging markets from the perspective of R&D-oriented firms in the fields of biotech.[56], [57]

(ii) Funding programs by AMED

In Japan, most of the funding to biomedical research is provide by AMED.[18] In FY2017, AMED provides $1.23 billion (138 billion JPY) as almost 2,400 competitive grants.[58] The top 10 universities awarded by AMED is shown in Table 21.

[18] https://www.amed.go.jp/en/index.html

Table 21 Top10 universities funded by AMED in FY2017

	Organization	Prefecture (Region)	Awards	Funding (million $)	Funding (million ¥)
1	The University of Tokyo	Tokyo (Kanto)	211	123.4	13,842
2	Tohoku University	Miyagi (Tohoku)	84	92.5	10,374
3	Kyoto University	Kyoto (Kinki)	142	90.4	10,139
4	Osaka University	Osaka (Kinki)	142	75.9	8,509
5	National Cancer Center Japan	Tokyo (Kanto)	121	68.1	7,642
6	Keio University	Tokyo (Kanto)	78	55.5	6,220
7	Riken	Saitama (Kanto)[19]	64	47.0	5,272
8	Kyusyu University	Fukuoka (Kyusyu)	71	30.8	3,458
9	National Institute of Infectious Diseases	Tokyo (Kanto)	72	25.9	2,910
10	National Center for Global Health and Medicine	Tokyo (Kanto)	26	21.9	2,453

Source: AMED find[20]

5 of 10 organizations are located in Tokyo, including the University of Tokyo and Keio University. Kyoto University and Osaka University are the top 2 organization funded by AMED in Kinki area.

The funding of AMED focuses on leading-edge medical innovation mainly in 9 areas; Drug discovery and development, medical device development, translational and clinical research, regenerative medicine, genomic medicine, cancer research, psychiatric and neurological disorders, emerging/re-emerging infectious disease, rare/intractable disease. In addition to the research grants for these areas, AMED provides subsidies for collaborative research among academia and industry and also for startups in biotech and medical field. Cyclic Innovation for Clinical Empowerment (CiCLE)[21] is the program for collaborative research and the support for translational

[19] Riken has several institutes all over Japan, including Wako research institute (Saitama, Kanto), Yokohama research institute (Kanagawa, Kanto), and Kobe research institute (Kobe, Kinki). However, their main office is located at Wako (Saitama) and the dataset didn't distinguish their research center, thus here we allocated all the awards to Riken to Riken's main office.
[20] https://amedfind.amed.go.jp/amed/index.html
[21] https://www.amed.go.jp/en/program/list/07/01/001.html

research platform and Venture Innovation for Clinical Empowerment (ViCLE)[22] is the program for small startups before IPO. The total budget for CiCLE is $773 million (85 billion JPY).

(iii) Kakenhi (Grants-in-Aid for Scientific Research)

In addition to AMED, most of the basic research in life sciences and medical research is funded by Grants-in-Aid for Scientific Research (Kakenhi).[23] Within $545 million[24] (5.99 billion JPY), 40.4% ($220 million, approx.10,500 awards) was newly awarded to life sciences research in FY2017[25]. Table 22 shows the top 11 universities funded by Kakenhi (in a total of all fields). Regions, where universities are located, are more diverse than funding from AMED. However, the University of Tokyo, Kyoto University, Osaka University, and Keio University are also ranked high in 1313 organizations which were funded in FY2017.

Table 22 Top 11 universities funded by Kakenhi in FY2017

Rank	Organization	Prefecture (Region)	Awards	Funding (million $)	Funding[26] (million ¥)
1	The University of Tokyo	Tokyo (Kanto)	3,787	150.3	16,853.9
2	Kyoto University	Kyoto (Kinki)	2,948	92.5	10,377.9
3	Osaka University	Osaka (Kinki)	2,511	73.6	8,260.3
4	Tohoku University	Miyagi (Tohoku)	2,428	67.2	7,536.8
5	Kyusyu University	Fukuoka (Kyusyu)	1,908	50.1	5,620.6
6	Nagoya University	Aichi (Chubu)	1,773	50.6	5,674.9
7	Hokkaido University	Hokkaido (Hokkaido)	1,649	42.4	4,757.4
8	University of Tsukuba	Ibaraki (Kanto)	1,248	28.3	3,170.4
9	Kobe University	Hyogo (Kinki)	1,145	20.8	2,332.9
10	Hiroshima University	Hiroshima (Chugoku)	1,105	18.2	2,042.7
11	Keio University	Tokyo (Kanto)	1,040	24.1	2,705.2

Source: Allocation of Grants-in-Aid for Scientific Research in FY2017, MEXT[59]

[22] https://www.amed.go.jp/pr/2017_seikasyu_04-04.html
[23] https://www.jsps.go.jp/english/e-grants/
[24] Direct expense on R&D. In Japan, almost 30% of the government's grant is paid to an institute as associated cost. Direct expense on R&D means the amount of funding which subtract the associated cost from the total funding.
[25] http://www.mext.go.jp/a_menu/shinkou/hojyo/__icsFiles/afieldfile/2017/10/10/1396984_01_1.pdf
[26] Direct expense on R&D. Ibid.

(iv) Government grants for fostering an innovation ecosystem

In addition to providing R&D funding grants in academia, the governments have been providing grants to foster innovation ecosystem in Japan, such as funding for collaborative research, providing risk capital, supporting entrepreneurship programs and providing supports to startups. This is because of the increasing demand on innovation and smooth introduction of academic research's results to industries. As mentioned above, AMED provides programs for supporting R&D projects focusing on the medical field and in this stage, but other ministries and agencies also support R&D projects in this stage regardless of the research and industry field.

Table 23 is the list for the government's main funding programs and other policies (except investment for risk capitals) for fostering innovation ecosystem. The programs listed here are categorized into 6; Entrepreneurship education, funding for establishing the system for supporting collaborative research and startups, funding for collaborative research between academia and industry, funding for entrepreneurs and startups, awards and other programs and tax incentive.

Major funding sources are MEXT, Japan Science and Technology Agency (JST), which is the subsidiary agency of MEXT, and New Energy and Industrial Technology Development Organization (NEDO), which is the subsidiary agency of METI. METI also promote the innovation by technology-based startup and the open innovation for the purpose of boosting Japanese economy thorough its belonging agencies (NEDO, Japan External Trade Organization (JETRO) and The Small and Medium Enterprise Agency (SME)) and its own program.

Table 23 List of the government funding programs and other policies for fostering innovation ecosystem

Program	Budget FY2018 (million $ (million JPY))	Description	Ministry /Agency
Entrepreneurship Education			
EDGE-NEXT program	3.23 (357)	Funding for 5 major universities to develop a program for establishing entrepreneurship education.	JST
Technology Commercialization Program (TCP)	ND	Training and opportunity for entrepreneurs to learn the commercialization of their technology	NEDO
NEDO Entrepreneurs Program (NEP)	ND	Support for entrepreneurs in starting their business	NEDO
NEDO Technology Startup Supporters Academy (SSA)	ND	Program for educating professionals who support and take a lead in creating technology-based startups	NEDO
Funding for organization supporting collaborative research and startups			
Formation of the open innovation	12.8 (1408)	Funding for establishing management system for open innovation in universities by allocating the professionals who can coordinate the cross-sectional collaboration.	MEXT
Program on Open Innovation Platform with Enterprises, Research Institute and Academia (OPERA)	16.4 (1811)	Funding for collaborative research among academia and industry, especially focusing on human resource development and improvement of collaborating system in universities.	JST
Program for establishing open innovation hub (iHub)	11.1 (1224)	Funding for creating a hub for the collaboration among academia, industry and governments.	JST
Program for establishing local innovation ecosystem	28.0 (3093)	Funding for establishing a team for accomplishing local academia and industry collaboration based on the strength in the region.	MEXT
Funding for collaborative research between academia and industry			
Adaptable and Seamless Technology transfer Program through target driven R&D (A-STEP)	69.5 (7674)	Funding for R&D project which aim to get the proof of concept collaborating with industry	JST
Program for creating startups from advanced research and technology (START)	16.2 (1784)	Funding for promoters who support teams planning to start a business in establishing business model, patent strategy and marketing.	JST
Funding for startups and entrepreneurs			
Subsidies for Seed-stage Technology Based Starutp	ND	Subsidies for seed stage and technology based startups which are invested by nominated VCs.	NEDO
Subsidies for promoting application by collaboration with research institute	ND	Subsidies for startups which play role in technology transfer to the industry by collaboration with research institute	NEDO
Subsidies for Startups in Corporate Alliance	ND	Subsidies for startups to execute collaborative R&D with industries	NEDO

Awards and other			
Award for Academic Startups	ND	Award for startups spin-out from universities based on technology. Started in 2014.	JST
The Nippon Venture Award	ND	Award to startups and entrepreneurs who can be role models for young entrepreneurs. Started in 2015.	Prime Minister METI MAFF
J-Startups	ND	Providing priorities in supporting by the government and private sector for nominated startups. Started in 2018.	METI JETRO NEDO
Tax Incentives			
Tax Deduction for Angel Investors	-	Tax deduction for income and capital gain in the investment to private investors who invest to startups or venture capitals	SME

Source: the program information on each ministry/agency

In addition to the funding program, Japanese government awards prizes to startups as shown in Table 23, Awards for Academic Startups and the Nippon Venture Award. This is because that recognition and impression on startups are not good compared with other established company in Japan and because Japanese government encourages people to be entrepreneurial and supportive to entrepreneurs through these awards.

J-Startup is the recently started project. It is the awarded name for selected startups which are recognized their excellence and achievements. Once a startup is awarded as J-Startup, a company not only can use the name of "J-Startup", but also has priority in the supports from the government and industry, such as subsidies, opportunities to present their business, appearance in public relations, connection to the network, mentoring and acceleration programs. JETRO also help them in expanding their business to abroad by mentoring and supporting in exhibiting in large conferences, such as South by Southwest (SXSW) and Consumer Electronics Showcase (CES) in the U.S.. The program started in June 2018, 92 startups has been awarded until the end of March 2019 and their area is quite diverse; Artificial Intelligence (AI), service platforms, robotics, space industry, material science and medicine.

Tax incentive is given to private investors to increase the risk capital. In this tax deduction, a private investor, not a corporate investor, is given the tax deduction for income and capital gain from invested startup when they invest to startup companies which are within 3 years (or 10 years) after its foundation.

(v) Risk capital provided by the national government

One of the noteworthy points about investment in Japan is a significant amount of risk capital is provided by the government. As mentioned above, not only the local government but also the national government provide risk capital. This policy is based on the recognition that the risk capital especially in the early stage is not provided enough from the private sector. CiCLE and ViCLE in AMED is one type of the risk capital provided as subsidies. Another type of risk capital from the national government is provided as an investment. There are mainly two investment types in risk capital from the government. On is Innovation Network Corporation of Japan (INCJ)[27], which was founded by METI, and another one is the government's funding to JST and some universities for the purpose of investing through a venture capital affiliated with each entity.

INCJ is now a part of Japan Investment Capital (JIC),[28] which have just established September 2018. INCJ itself is an investment company founded by the Japanese government and private companies. In the establishment of INCJ in 2009, the government invested $2.6 billion (286 billion JPY) and the private companies invested $127 million (14 billion JPY). INCJ invests in various type of companies which contribute to creating industries which support next-generation by open innovation. Its fund supply risk capital to venture firms and revitalization or reorganization of existing companies. Until FY2018, INCJ invests 137 deals and provide $10 billion risk capital. 80% of deals are for venture firms (24% in the capital). 19% of deals are for life sciences field (17% in the capital).

---

[27] https://www.incj.co.jp/english/
[28] https://www.j-ic.co.jp/en/

MEXT also provides risk capitals to startups via JST and universities. Funded by the supplementary budget in FY2012, $1.5 billion (120 billion yen) was provided to four universities (University of Tokyo ($523 million), Kyoto University ($366 million), Osaka University ($208 million) and Tohoku University ($157 million)) and $752 million (60 billion yen) was to JST in order to promote the R&D cooperated by academia and industry.[29] Based on this fund, each university established the venture capital to invest startups spin-out from own university.

JST's investment program is called Support program of Capital Contribution to Early-Stage Companies (SUCCESS) which invest startups founded based on science and technology. Different from other funding programs, JST takes equity of startups in the investment using SUCCESS. Since the beginning of the program in 2014, JST has invested in 24 startups until the end of March 2019.[30]

(e) Japan – Tokyo (Kanto)

In Tokyo, Tokyo Metropolitan Government funds Tokyo Metropolitan Institute of Medical Science[31], but the amount of competitive grants for R&D are quite limited.[32] However, the government commits to develop Tokyo as a global business center and to foster the innovation ecosystem in Tokyo based on "Invest Tokyo" policy[33] benefited by the national strategic special zone where regulations are mitigated or tax incentives are given.[34]

---

29 http://www.mext.go.jp/component/a_menu/science/detail/__icsFiles/afieldfile/2013/03/25/1322146_09_1.pdf

30 https://www.jst.go.jp/entre/result.html

31 http://www.igakuken.or.jp/english/

32 http://www.zaimu.metro.tokyo.jp/syukei1/zaisei/20190125_heisei31nendo_tokyotoyosanangaiyou/30jigyouhyoka.pdf

33 http://www.seisakukikaku.metro.tokyo.jp/tokku/english/

34 https://www.kantei.go.jp/jp/headline/kokkasenryaku_tokku2013.html

Based on this policy, the government has been executing several programs which support entrepreneurs and startups. For example, they opened Tokyo One-Stop Business Establishment Center (TOSBEC) where an entrepreneur can ask and be supported in starting a business in the administrative process in multi lingual. It also supports non-Japanese entrepreneurs not only in business and visa but also in life in Tokyo. TOKYO Entrepreneur Station is another facility to provide the human network, office space and information to entrepreneurs and potential entrepreneurs.

In addition, the metropolitan government provides several accelerator programs and platforms in the general tech, the fintech, the blockchain technology, the automobiles and the biopharmaceuticals.

"Blockbuster TOKYO"[35] is an acceleration program funded by Tokyo Metropolitan Government focusing on biopharmaceutical startups. This program started in 2018 and provides seminars, advice from specialists, such as R&D, marketing, patent, business development and fundraising. Almost 130 teams are supported by the program and 30 of them are intensively supported and benefited from additional services, such as mentoring, the introduction of a management board and matching with business partners including investors.

Other than Tokyo, several cities in the Kanto area focus on R&D in the general field or R&D in the life sciences field. Tsukuba city in Ibaraki prefecture, 35 miles (56 km) from Tokyo, is a traditionally developed as the science city from the 1960s and now the city where more than 30 public and private research institute and 20,000 researchers are accumulated.[36] Derived from the excellent research and educational institutions, the city has been cultivating innovation and making social contributions. For example, the city was designated the comprehensive special zone for

[35] https://www.blockbuster.tokyo
[36] http://www.tsukubainfo.jp/tsukuba/

international competitiveness development by the Japanese government[37] and have been trying to promote a project which leads the creation of innovation by making the best use of science technology and human resources accumulate in the city.

Kawasaki city in Kanagawa prefecture is another area where the city government strategically supports the life science industry. The city is known as the industrial city benefited from the closeness to Tokyo. It owns a vast reclaimed land in its waterfront and develops that area. One of the projects is Tonomachi King Skyfront which is a center for open innovation in life sciences and environmental sciences. In this area, many biotech companies and R&D facilities are accumulating, including Life Innovation Center (LIC) which is established by Kanagawa prefecture and focuses on the application of regenerative medicine.[38] The city is also a part of the comprehensive special zone for international competitiveness, called the life science innovation special zone in Keihin-waterfront and supported by the prefecture government and national government. They give tax incentives for biotech research institutes and companies, invite several public research institutions and emphasize the closeness to the Haneda International Airport, across the river, and to Tokyo.

(f) Japan – Kyoto (Kinki)

Kinki area is also designated as the comprehensive special zone for international competitiveness, called Kinki innovation special zone. This zone consists of Kyoto Prefecture, Kyoto City, Osaka Prefecture, Osaka City, Hyogo Prefecture and Kobe City. All these three cities have renown universities or research institute in life sciences, thus the special zone mainly focus on life sciences. Though the funding for R&D from the local governments are small compared with the national governments, research institutes and companies in this zone have a priority in funding and tax incentives if their project is authorized as contributing the purpose of the zone.

[37] http://www.tsukubainfo.jp/tsukuba/tsukuba.html
[38] http://www.pref.kanagawa.jp/docs/mv4/cnt/f531405/

Among those three cities, Kobe City is unique in architecting the city as a medical industry city, called KOBE Biomedical Innovation Cluster (KIBIC).[39] This project is started by Kobe City for the purpose of the revival of Kobe's economy damaged by the Great Hanshin-Awaji Earthquake in 1995. With cooperation among academia, industry and government, they established the center for advanced medicine and accumulate the industry related to medicine. As a result, 350 research institutes (as of the beginning of 2019), hospitals and companies are located in Kobe's Port Island, which is a refilled land in the Kobe port. KIBIC has strength in the access to/from the Kobe Airport, the interaction with great technologies and talents in RIKEN Kobe institute and universities where accelerate, the research environments in supporting clinical research and drug discovery and other supports in business and accelerating R&D.

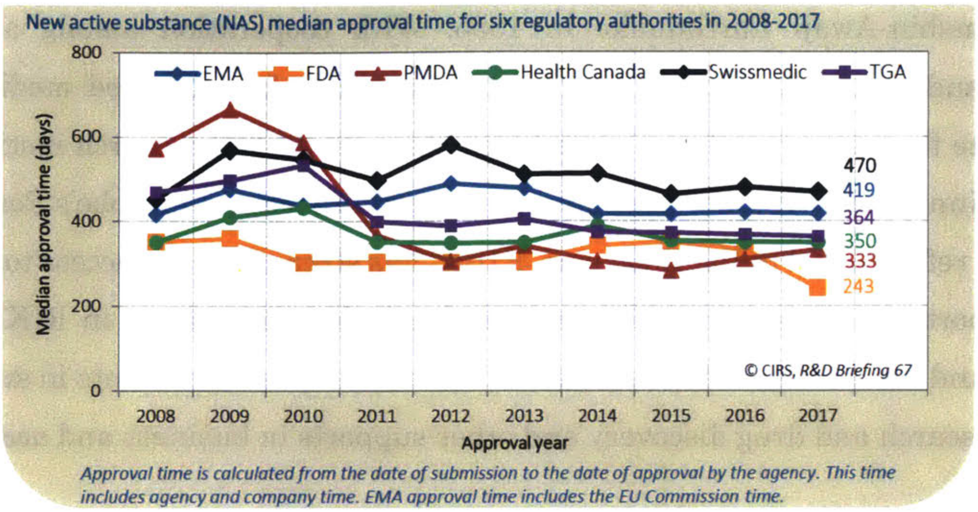
(2) Government: regulatory side

The approval process is almost the same in the major countries including the U.S. and Japan. However, the duration for the approval process affects the overall time for R&D, thus the duration affects the strategy of a company and/or researcher in applying the examination.

Figure 11 shows the median approval time for six regulatory authorities in the world, including FDA and the Japan Pharmaceuticals and Medical Devices Agency (PMDA). Until 2010, there was approximately 300 days gap between the approval by FDA and PMDA for a new active substance. This lag is recognized as a big issue for improving medicine in Japan. To eliminate the gap, PMDA has been increasing the number of examining officers and started another expedited approval process ("Sakigake" designation scheme)[40] in 2015, as well as the prior-assessment consultations approximately 6 months before submission of a new drug application.[60] As a result,

[39] https://www.fbri-kobe.org/kbic/
[40] https://www.jstage.jst.go.jp/article/rsmp/6/2/6_197/_pdf/-char/ja

the lag is almost resolved after 2011. Therefore, the duration for the approval from the regulatory authority is almost the same in the U.S. and Japan.



Source: Center for Innovation in Regulatory Science, R&D Briefing 67 (2018)[60]

Figure 11 New Active Substance (NAS) Median Approval Time for 6 Regulatory Authorities in 2008-2017[41]

(3) Corporate: Pharmaceutical companies

Pharmaceutical companies are important players in the ecosystem in creating demands for new technologies and human resources and providing money for startups and universities for R&D. For example, Massachusetts in 2017 was ranked second among states for biotechnology research and development jobs. California, the first place, has 39,203 such jobs.[6]

Looking at the top 50 global pharmaceutical companies by prescription sales and R&D spending in 2017,[61] 16 companies are from the U.S., 16 are from Europe and 10 are from Japan (Table 24). However, in the top 20 ranking, the number of Japanese companies are far behind the U.S. and only one company is nominated (Table 24).

[41] European Medicines Agency (EMA), the US Food and Drug Administration (FDA), the Japan Pharmaceuticals and Medical Devices Agency (PMDA), Health Canada, Swissmedic and the Australian Therapeutic Goods Administration (TGA)

Table 24 Number of Companies in Top 50 and Top 20 pharmaceutical companies by countries[42]

Country	Top 50			Top 20		
	Number of companies	Total sales (billion $)	Total R&D (billion $)	Number of companies	Total sales (billion $)	Total R&D (billion $)
United States	16	290.56	57.54	9	242.02	48.23
Japan	10	55.91	13.15	1	13.58	2.94
Germany	5	45.10	8.68	2	31.80	6.33
Ireland	3	21.06	2.07	1	14.45	1.57
United Kingdom	2	48.45	10.39	2	48.45	10.39
Switzerland	2	83.61	17.00	2	83.61	17.00
France	2	38.65	7.33	1	34.08	6.18
India	2	6.49	0.63	0	0	0
(Europe in total)	(16)	(265.39)	(49.13)	(8)	(229.36)	(43.6)

Source: Statista[61]

Table 25 shows the location of headquarters and existing business units in the clusters we are focusing on. At least 12 of 20 companies locate their R&D facilities in Boston/Cambridge area and 10 locate in San Francisco Bay Area. On the contrast, most companies locate their business units in the clusters in Japan and only two company owns their R&D Facility in Kinki cluster. However, this top 20 ranking doesn't cover Japanese pharmaceutical companies.

Table 25 Location and the type of facilities in the clusters by top 20 companies[43]

Rank	Company name	Base country	Location of Headquarter	Existing business units			
				Boston /Cambridge	San Francisco Bay Area	Kanto	Kinki
1	Pfizer	U.S.	NY	R&D	R&D	Business	-
2	Novartis	Switzerland	Basel	R&D	R&D	Business	Business
3	Roche	Switzerland	Basel	R&D	Business, R&D	Business	Business
4	Merck & Co.	U.S.	NJ	R&D	R&D (open 2019)	Business	Business
5	Johnson & Johnson	U.S.	NJ	Innovation Facilities	Innovation Facilities	Business	Business
6	Sanofi	France	Paris (US: NJ)	R&D	Office	Business	Business
7	GlaxoSmithKline	UK	London	R&D	-	Business	Business
8	AbbVie	U.S.	IL	R&D	R&D	Business & R&D	-

[42] Countries which has only 1 company in the list was omitted
[43] The data source is noted in Chapter 11.

9	Gilead Sciences	U.S.	Foster City, CA	-	HQ and R&D	Office	-
10	Amgen	U.S.	Thousand Oaks, CA	R&D	R&D	-	-
11	AstraZeneca	UK	Cambridge (UK)	R&D	R&D	Office	Office
12	Bristol-Myers Squibb	U.S.	NY	R&D (open in 2018)	R&D	Business & R&D	-
13	Eli Lilly	U.S.	IL	Innovation Facilities	-	Office	Business
14	Teva Pharmaceutical Industries	Israel	Israel (US: PA)	ND	ND	Office	-
15	Bayer	Germany	Leverkusen (Germany)	Innovation Facilities	Innovation Facilities and R&D	Business	Business
16	Novo Nordisk	Denmark	Bagsvard (Denmark)	-	-	Office	Office
17	Allergan	U.S.	Dublin (Ireland)	-	-	Office	-
18	Shire	Ireland	Lexington, MA	R&D	NA	NA	NA
19	Boehringer Ingelheim	Germany	Ingelheim am Rhein (Germany)	-	Office	Business	R&D
20	Takeda	Japan	Tokyo (Japan)	US HQ, R&D	-	Business	Business

* Office: No information about the type of facilities
* NA: No information was available.

The location of headquarters and R&D facilities in the top 10 Japanese pharmaceutical companies are shown in Table 26. All 10 companies locate their R&D facilities in Kanto and/or Kinki. However, their locations are peripheral region in Kanto and Kinki, only three companies locate in Tokyo, and 5 are in Kyoto or Osaka. Thus, considering the area size of clusters, the density of R&D facilities in Japanese clusters are relatively low compared with Boston/Cambridge and San Francisco Bay Area. On the other hand, Table 25 and Table 26 also shows there are high accumulation of the business offices of pharmaceutical companies in Tokyo and Osaka rather than two clusters in the U.S..

Table 26 Location of Headquarters and R&D facilities of top 10 Japanese pharmaceutical companies[44]

Rank (world)	Company Name	HQ or Main Business Office		R&D Facilities		
		Kanto	Kinki	Kanto	Kinki	Other
20	Takeda Pharmaceutical Company Ltd	Tokyo	Osaka	Kanagawa	Osaka (will close)	
23	Astellas Pharma Inc,	Tokyo	-	Ibaraki	Kyoto	Shizuoka
26	Daiichi-Sankyo Co., Ltd.	Tokyo	-	Tokyo		
28	Otsuka Holdings	Tokyo	Osaka	Ibaraki, Saitama	Hyogo, Shiga	Tokushima, Saga
32	Eisai Co., Ltd.	Tokyo	-	Ibaraki		
38	Chugai Pharmaceutical Co., Ltd.	Tokyo	-	Tokyo, Kanagawa		Shizuoka
40	Sumitomo Dainippon Pharma Co., Ltd.	Tokyo	Osaka		Osaka, Hyogo	
45	Mitsubishi Tanabe Pharma Co., Ltd.	Tokyo	Osaka	Saitama, Kanagawa	Osaka	
46	Ono Pharmaceutical Co., Ltd.	Tokyo	Osaka	Ibaraki	Osaka	Fukui
49	Kyowa Hakko Kirin Co., Ltd.	Tokyo	-	Tokyo, Ibaraki, Gunma		Shizuoka, Yamaguchi

We also need to consider the current trend of pharmaceutical companies. As mentioned in Chapter 4, pharmaceutical companies have been changing their R&D strategy and shifting to the open innovation style. In addition, Japanese pharmaceutical companies have been restructuring their organization for catching up with the change in pharmaceutical industry and some companies (Takeda and Mitsubishi Tanabe) recently decided to close their R&D facilities in Japan as a part of the restructuring process. The firing of researchers is also started (Takeda and Astellas). Thus, the pharmaceutical industry and market would be changed.

Another point we need to consider for pharmaceutical companies is that they also behave like supporters in the ecosystem especially in the U.S.. In the line of collaboration with academia or open innovation, pharmaceutical companies

[44] The data source is noted in Chapter 11.

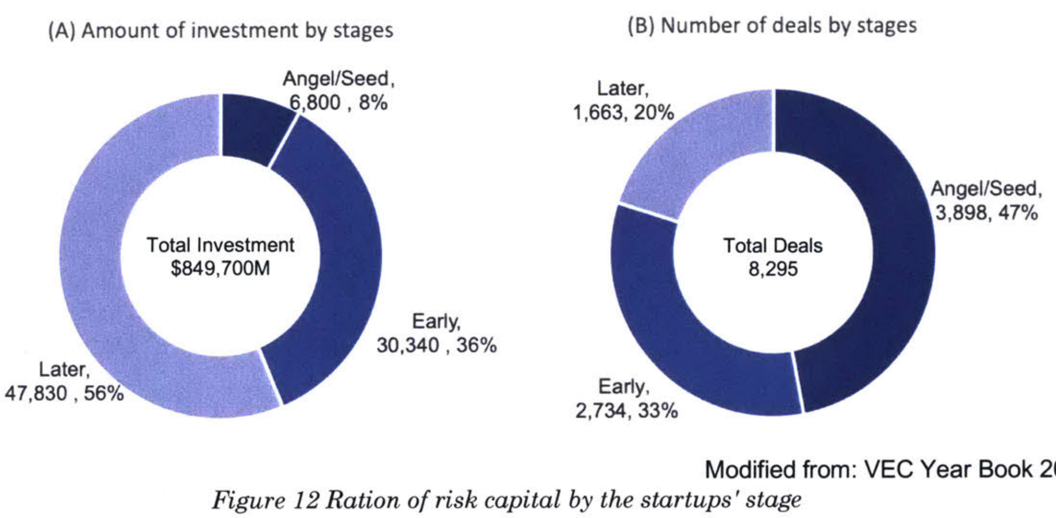
frequently organize pitch events. This activity works for fostering entrepreneurship and giving connection among stakeholders.

(4) Risk capital: Venture capitals

The total amount of the risk capital, the invested money to startups, $85 billion in the U.S. and $1.8 billion in Japan in 2017.[62] As a percentage of GDP, the venture capital investment is 0.4% in the U.S. and 0.03% in Japan.[63] Although total risk capital has been increasing in Japan from 2009 (just after the financial crisis), the amount is far behind from the U.S.[62] In this section, we analyze the risk capital in the clusters separately because we need to consider the total amount noted above and because the risk capital is tightly connected to startup's business, thus their location.

(a) United States

In the U.S., the total bioscience venture capital investments in 2014-2017 was $66.2 billion, and 23% was to Massachusetts and 43.1% was to California.[64] The ratio by the startups' stage is shown in Figure 12. According to Figure 12, the risk capital per deal is $1.7 million in the seed stage, $11 million in the early stage (Series A) and $28.8 million in the late stage. Of course, the risk capital per deal should be much huger in life science industries than other fields, but it suggests there are many seed investment opportunities in the U.S.[62]



Modified from: VEC Year Book 2018[62]

Figure 12 Ration of risk capital by the startups' stage

About the type of venture capital, 20% of investing money (14% of startups) is CVC (Corporate Venture Capital) in biopharma venture investment and its ratio has been increasing.[65]

Boston/Cambridge

In Massachusetts, the venture capital investment to biopharma has been increasing since 2012 and it was $3.1 billion in 2017, tripled from 2012[6]. In addition, Massachusetts biopharma companies raised $2.7 billion in the first two quarters of 2018. In 2017, 60% of the investment into Massachusetts is from the U.S.-based investors outside of Massachusetts[6].

Among the invested companies, 62% of all biotech venture in the state was received by Cambridge-based companies and the deal was $1,835M. Boston is the next and the amount was $320M[6]. This shows that the high concentration of risk capital to Cambridge in Massachusetts.

San Francisco Bay Area

In California, life sciences VC investment was $6.1 billion in 2017, and it is estimated that it will be $7.6 billion in 2018. The regional base amount of investment, 51% was to San Francisco (North Bay Area) and 22% was to Silicon Valley (South Bay Area), thus almost 70% of investment in California was invested to San Francisco Bay Area[66], [67].

A noteworthy point about California is that the huge amount of investment money in all field. For example, 48% of the total the U.S. venture capital investment came to California in 2017[67].

(b) Japan

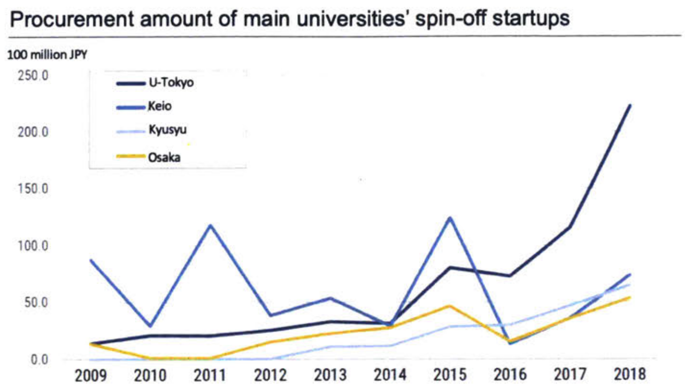
As mentioned above, the total risk capital in Japan is 2% of the U.S. The small size of the investment money is not only in the total amount but also the amount for each deal. The presence of CVC is also small. In 2017, 95% of investment money was from VCs and 5% was from CVCs (91% of deals are by VCs and 9% are by CVC).[45] However, 42% of investing money is not from VCs or CVCs, but from business firms.[62]

In the aspect of the investment stage, 14.7% was in seed stage and 46.7% was early stage.[62] This suggests that the risk capital in Japan is more focused on the seed/early stage (total 61.4%) than in the U.S. (45%). The percentage in Japan excludes the investment from INCJ which operates a larger investment, but 72% of investment by INCJ was to seed or early stage.[46] Thus, the tendency seems to be maintained even if the investment by INCJ was included. The risk capital per deal is \$0.5 million in the seed stage, \$0.8 million in early stage (Series A), \$0.9 million in expanding stage and \$1.0 million in the late stage. Thus, the risk capital per deal is smaller in all stage than the U.S.

From the recipient side, startups affiliated to universities are received \$ 625 million in total (2018).[68] Among universities, startups affiliated to the University of Tokyo occupies almost 30% and Keio University follows as shown in Figure 13.

---

[45] Calculated from the survey of trends in VC's investment by Venture Enterprise Center (VEC)
[46] https://www.meti.go.jp/shingikai/economy/jic/pdf/002_06_00.pdf



Modified from: entrepedia (2019.2.21) [68]

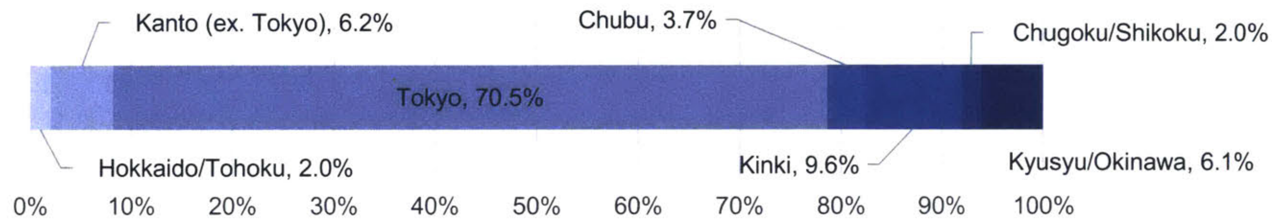
Figure 13 Trends in investment of university affiliated startups

Among the investment to life sciences, 18.4% of risk capital was invested to biotech, medical and healthcare field in 2017. In addition, the average risk capital per deal in the biotechnology field was $1.0 million[62].

In addition to the amount of risk capital, the specialty of the venture capitalist is also important in biotech business because of the high risk in this field. It is pointed out that the specialty of venture capitalist is not enough in Japan compared with the U.S. where they secure human resources who have MD and/or Ph.D.[57].

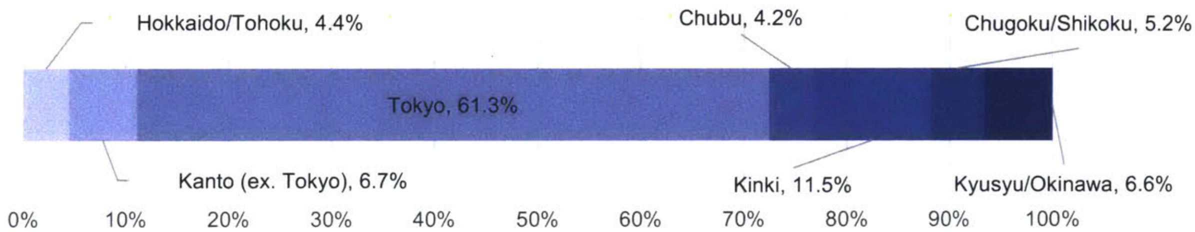
Tokyo (Kanto)

Figure 14 and Figure 15 shows the allocation of risk capital by region. Tokyo occupies 70.5% of risk capital and 61.3% of deals and the rest of Kanto area occupies 6.2% and 6.7%. Thus, most of the risk capital is accumulated in Tokyo and the Kanto area. There should be several reasons which explain this bias, and one of them is that the location of startups. The same research says that 61.2% of startups are located in Tokyo. It is difficult to say which is chicken and egg, but both the risk capital and startups are accumulated in Tokyo.



Modified from: VEC Year Book 2018[62]

Figure 14 Allocation of risk capital by region 2017 (ratio in the amount of risk capital)



Modified from: VEC Year Book 2018[62]

Figure 15 Allocation of risk capital by region 2017 (ration in the number of deals)

For the purpose of promoting the investment to startups, Tokyo Metropolitan Government funds risk capitals to support startups.[47] In 2013, the first fund was created with $18 million (2 billion JPY) by the government and $27 million from the private sector. This fund was focused on manufacturing. In addition, another fund was established in 2017, with $9 million from the government and $82 million from the private sector.

Kyoto (Kinki)

Kinki area is the second place in the amount of risk capital and deals following to Kanto area, but its ratio is 9.6% in risk capital and 11.5 % in deals.

In the Kinki area, the prefecture governments and the city governments funds technology-oriented startups[48]. For example, Kyoto City has just started its fund with

[47] http://www.sangyo-rodo.metro.tokyo.jp/chushou/kinyu/fund/

[48] http://www.kouiki-kansai.jp/koikirengo/jisijimu/sanshin/fund_info/fund.html

$0.1 million, Osaka Prefecture government funds $0.2 million to Osaka Bio Fund, which focuses on biotechnology and healthcare with $10 million risk capital and Osaka City funds $4.5 million to Hack Venture's fund with $44 million. All these funds are partly or fully funded by each government to encourage the involvement of the private sector.

(5) University

(a) The worldwide position of universities and academic research in the U.S. and Japan

The university ranking is one of the indicators which tells the position of a university in the world. In THE (Times Higher Education) World University Ranking, 24 universities are nominated in top 50 from the U.S., but only 1 from Japan (Table 27). Table 28 shows the ranking of universities we analyze here. The only one Japanese university in the top 50 is University Tokyo (ranked 42). Kyoto University is ranked 65, but others (Keio University and Osaka University) are below 250. All the universities we analyze in this research are ranked within 15. There are discussions to use this indicator for comparing universities in different countries and the ranking include both education and academic activity, but this ranking could be a good indicator for compare universities in a certain country. As the percentile of GDP, the number of top 500 universities are less than OECD average in Japan, though the U.S. is almost at the average, in OECD's analysis in 2012.[14]

Table 27 Number of universities in top 50 in THE World University Ranking 2019 by country

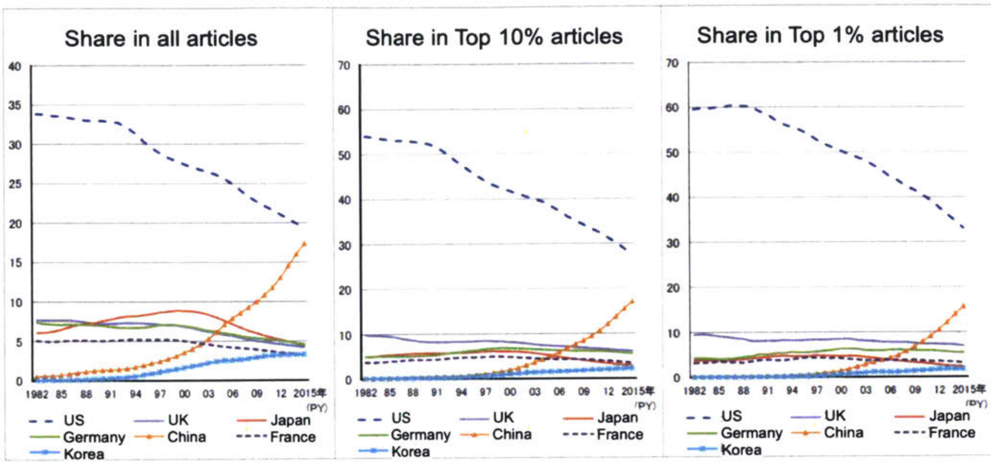
Country	Number of universities
United States	24
United Kingdom	7
Germany	3
Canada	3
China	2
Hong Kong	2

Switzerland	2
Australia	2
Japan and other 4 countries	1

Table 28 Ranking of universities in this research

Ranking	Name of university
3	Stanford University
4	Massachusetts Institute of Technology
6	Harvard University
15	University of California, Berkeley
42	University of Tokyo
65	Kyoto University
251-300	Osaka University
601-800	Keio University

To evaluate the activity and quality of the academic side, the number of scientific papers is one form of R&D output. The U.S. is ranked 1st in the share of papers of all fields in the total number of papers, in the top 10% papers and in the top 1% papers (Figure 16). Japan was ranked 2nd in the share of papers in the total number of papers from the 90s to 2005, but the percent has been decreasing. As to the number of adjusted top 10% papers (All fields), Japan is 9th in all countries.[69] Limited to the papers in clinical research and basic life science research field, the share of papers in total and top 10% papers are both behind the U.S., China, and main European countries (Table 29)



Source: NISTEP "Japanese Science and Technology Indicators 2018"[69]

Figure 16 World share of papers in major 7 countries (All fields, in total numbers, top 10% papers and top1% papers)[49]

Table 29 Share of papers in clinical research and basic life science (in total number of papers and top 10% papers (based on the fractional counting method))

(A) Clinical research and medicine

		World share of article (%)	World share of top10% article(%)
1	US	26.1	36.9
2	China	10.4	7.6
3	UK	5.5	7.7
4	Japan	5.3	3.5
5	Germany	5.0	5.3
6	Korea	3.5	1.6
7	France	3.1	3.6

(B) Basic life sciences

		World share of article (%)	World share of top10% article (%)
1	US	22.1	32.0
2	China	13.6	10.5
3	Germany	4.7	6.1
4	Japan	4.6	2.7
5	UK	4.2	6.8
6	France	3.0	3.7
7	Korea	2.8	1.6

Source: NISTEP "Japanese Science and Technology Indicators 2018"[69]

Another indicator for evaluating the quality of academic research is the number of highly cited articles/researchers presented by Clarivate Analytics. In this analysis, the top 1% articles in the number of citations are classified as the highly cited article and the highly cited researchers (HCR) are selected based on this category. The United States is ranked as no.1 with 2,639 HCR and Japan is raked as 12[5],[70].

[49] Based on the fractional counting method, 3 years moving average in all scientific field.

In another study in OECD, the publications in the top-quartile journals per GDP in Japan is less than the average of OECD countries, and it is almost on average in the U.S. It is also said that these numbers in Japan are also well below what might be expected given public spending on R&D. [14]

Although the data above shows the less competitiveness of Japanese academic research than other countries including the U.S., the number of Nobel prize laureates is the next position following the U.S. in Japan as shown in Table 30. Thus, the strength of academic research in Japan seems to be lower than the U.S., but it still competitive with other counties.

Table 30 Number of Nobel prize laureates in natural sciences by country

	~2000	2001~2010	2011~2017
US	195	38	28
Japan	6	9	7
UK	68	8	3
Germany	63	5	1
France	25	4	3

Source: MEXT "Science and Technology Directory 2018"[49]

(b) Demographics of clusters

Table 31 shows the demographics of clusters related to universities; the number of universities, graduate students in science and engineering (S&E) recipients of Ph.D. degree. By adjusting with the population, the number of universities is relatively low in Japan, but the number of graduate students and doctorate recipients in S&E is almost similar in the U.S. and Japan. Especially in Tokyo and Kyoto, the number is higher than California and comparable to Massachusetts. However, the number of enrollments to Ph.D. course has been decreasing recently in Japan, because of the fear for employment after finishing Ph.D. and the financial issue.[69],[71]

Table 31 Number of universities, graduate students in S&E and doctorate recipients in S&E by clusters[50]

	US (2016)			Japan* (2018)					
		MA	CA		Kanto		Kinki		
						Tokyo		Kyoto	Osaka
# of universities	9,437	261	1,246	782	256	138	155	34	55
(per 1000 people)	0.0288	0.0378	0.0315	0.0062	0.0059	0.0101	0.0077	0.0131	0.0062
Graduate students in S&E	609,420	32,436	60,903	162,096	68,676	45,415	32,806	11,029	11,426
(per 1000 people)	1.86	4.70	1.54	1.28	1.59	3.31	1.63	4.24	1.30
Doctorate recipients in S&E	41,324	2,353	4,954	11,203	4,497	3,004	3,232	901	845
(per 1000 people)	0.126	0.341	0.125	0.089	0.104	0.219	0.161	0.347	0.096

*graduate student in S&E and Doctorate recipients in S&E in local level is estimated from the ration of students in S&E courses in masters and Ph.D. in national level.

(c) Demographics of Universities

The financial and administrative demographics of universities are summarized in Table 32. The budget size and the number of gifts and donation are relatively smaller in Japanese universities than US universities. Also, Japanese four universities' revenue mainly depends on the subsidies from the government (exclude R&D grants) and tuition.

Table 32 Financial and administrative demographics of universities[51]

	US (AY2018)				Japan (AY2018)			
	Harvard	MIT	UC Berkeley	Stanford	U-Tokyo	Keio	Kyoto	Osaka
Established year	1636	1861	1868	1885	1877	1858	1897	1931
Finance								
Total Budget (million $)	5,000	3,578	2,800	6,500	2,344	2,092	1,498	1,332
Gifts/Donation* (million $)	1,418	737	ND	1,100	84	62	80	ND
% of tuition in revenue	21%	10%	ND	15.0%	7.3%	23.4%	7.3%	8.5%
% of subsidies from gov.	-	-	14.0%	-	31.5%	3.9%	33.5%	30.9%

[50] The data source is noted in Chapter 11.
[51] The data source is noted in Chapter 11.

Students and Faculties								
# of undergraduate	6,699	4,602	30,853	7,083	14,024	28,712	13,222	15,250
# of graduate	13,120	6,972	11,666	9,473	13,630	4,917	8,573	8,054
# of Ph.D. recipients	683	621	799	758	1,219	278	777	645
# of faculties	2,400	1,967	2,447	2,240	10,772**	2,300	2,699	3541
Ratio								
% of Ph.D. recipients per graduate students	5.21%	8.91%	6.85%	8.00%	8.94%	5.65%	9.06%	8.01%
Student per faculty	8.26	5.88	17.38	7.39	2.57**	14.62	8.08	6.58
budget per student ($)	252,283	309,124	65,853	392,607	84,758	62,204	68,735	57,168
budget per faculty (thousands $)	2,083	1,818	1,144	2,902	218**	910	555	376

* newly gifted/donated in AY2018

**Including the number of staffs

In the aspect of the number of students and faculties, there is a greater number of graduate students in the most of universities in the U.S., but the percentage of Ph.D. students in the graduate students is almost similar among eight universities (5-9%). The student-faculty ratio varies among universities, but there is no significant difference in the trend of the U.S. and Japanese universities.

However, the budget per student and faculty shows some difference between the U.S. and Japan. Except for UC Berkeley, the budget per student is 3-5 times higher in US universities than Japanese universities. This difference might come from the difference between the public school and the private school, but Keio University (the private school) shows a similar ratio as three national universities here. The budget per faculty is also higher in US universities than in Japanese universities.

(d) Academic activity of universities

Academic research activity can be measured by the expenditure on R&D (input), the number and the quality of researchers and the impact of the research (output). The latter part (output) is difficult to measure, but the number of high impact articles, awards and patents are generally used. The amount of funding in R&D of each universities are shown in Table 33. The total funding includes the funding from federal/national governments, local governments, non-profitable organizations, industries, and other organizations to R&D. As the table shows, the total R&D expenditure is low in Japanese universities, but the ratio of industry-sponsored research funding is almost higher in Japanese universities than in US universities, except for MIT. This point will be discussed in (f).

Table 33 Research funding by universities[52]

	US				Japan			
(million $)	**Harvard**	**MIT**	**UC Berkeley**	**Stanford**	**U-Tokyo**	**Keio**	**Kyoto**	**Osaka**
Total Research Funding	1077.25	946.16	708.50	1066.27	602.08	182.28	390.95	315.63
industry sponsored (number of deals)	50.65 (-)	158.45 (-)	65.60 (-)	99.47 (-)	66.84 (1,979)	26.87 (793)	47.31 (1,053)	64.67 (1,269)
% of industry sponsored	4.70%	16.75%	9.26%	9.33%	11.10%	14.74%	12.10%	20.49%

The number and quality of researchers is the variable in converting R&D funding to actual research. The number of researchers/post-doctoral fellows and awarded researchers are shown in Table 34. There are not enough comparable data about the number of researchers and post-doctoral fellows. The data in MIT somehow suggests that there is not a huge difference among universities (Keio University is slightly lower), though there might be a difference in the definition of the researcher. The number of Nobel laureates are quite high in US universities, but this number is the accumulative number and doesn't reflect the actual current quality.

[52] The data source is noted in Chapter 11.

Table 34 Number of researchers and awards[53]

	US				Japan			
	Harvard	**MIT**	**UC Berkeley**	**Stanford**	**U-Tokyo**	**Keio**	**Kyoto**	**Osaka**
researchers	ND	3,760	ND	ND	6,595	2,716	5,030	3,249
post-doctoral fellow	5,674	1,493	1,184	2,264	ND	ND	ND	ND
National Academy Membership	382	267	230	340	-	-	-	-
# of Nobel laureate	48	90	22 faculties 30 alumni	17	10	0	9	1

The quality of the researcher is also evaluated by the impact of researchers. The analysis of highly cited articles by Clarivate Analytics also provides the ranking and number of High Cited Researchers (HCR) by universities. The ranking and the number of HCR of these universities are listed in Table 35. As the table shows, the number of researchers is counted by institutes, thus some of the research institute in MIT and affiliated hospitals of Harvard Medical Schools are counted separately from universities. Anyway, the number of HCR is far less in Japanese universities than US universities.

Table 35 Number of HCR of universities

Ranking	University	Number of HCRs
1	Harvard University	186
3	Stanford University	100
6	UC Berkeley	64
12	MIT	45
13	Broad Institute (MIT)	44
44	Brigham & Women's Hospital (Harvard)	38
-	University of Tokyo	10
-	Massachusetts General Hospital (Harvard)	8
-	Kyoto University	7
-	Osaka University	6
-	Beth Israel Deaconess Medical Center (Harvard)	6
-	Keio University	1

Source: Highly Cited Researchers 2018, Clarivate Analytics[5]

[53] The data source is noted in Chapter 11.

(e) Patents of universities

The number of patents is one of the measures to evaluate the impact of research executed in a university as mentioned above. Table 36 summarize the number of applied and issued patents for each university and also shows the total revenue from patents. For the number of patents, the number of international patents issued in University of Tokyo and Kyoto University overs Harvard and Stanford issued in the U.S.

From the aspects of patents' licensing, we don't have comparable numbers, but the licensing activity (newly licensed patents in the U.S. universities vs the increasing of licensed patents in Japanese universities) is almost comparable, or rather active in Japanese universities. However, the total revenue from patents is quite low in Japanese universities compared with Harvard and Stanford (and MIT also (estimation)). Royalty fee from the patents is strongly affected by a blockbuster patents, but Harvard University and Stanford University always keep the revenue more than $40 million,[54] though the Japanese universities have never overs $10 million. [72]

Table 36 Number of patents and the total revenue from patents by universities[55]

<table>
<tr><th rowspan="2"></th><th colspan="4">US</th><th colspan="4">Japan</th></tr>
<tr><th>Harvard</th><th>MIT</th><th>UC Berkeley</th><th>Stanford</th><th>U-Tokyo</th><th>Keio</th><th>Kyoto</th><th>Osaka</th></tr>
<tr><td>New patent application (domestic*)</td><td>ND</td><td>ND</td><td>188</td><td>ND</td><td>471</td><td>146</td><td>230</td><td rowspan="2">612</td></tr>
<tr><td>New patent application (international**)</td><td>ND</td><td>ND</td><td>ND</td><td>ND</td><td>90</td><td>83</td><td>380</td></tr>
<tr><td>New patent filed/issued (domestic)</td><td>234</td><td>361</td><td>71</td><td>214</td><td>195</td><td>57</td><td>137</td><td>128</td></tr>
<tr><td>New patent filed/issued (international)</td><td>ND</td><td>ND</td><td>ND</td><td>ND</td><td>245</td><td>55</td><td>277</td><td>184</td></tr>
<tr><td>Newly Licensed patents</td><td>51</td><td>123</td><td>53</td><td>150</td><td>ND</td><td>ND</td><td>ND</td><td>ND</td></tr>
</table>

[54] Annual data from the website of Harvard University and Stanford University.
[55] The data source is noted in Chapter 11.

Total Licensed patents in 2017(difference from 2016)	ND	ND	ND	ND	1394 (+369)	136 (+55)	683 (+113)	464 (+168)
Total revenue from patents (million $)	54.10	ND	4.33	40.96	7.29	0.47	5.80	0.85

* For US universities, domestic is US patents. For Japanese universities, domestic means Japanese patents.
** Including the number of PTC application.

(f) Collaborative research and sponsored projects with industries

Collaborative research and sponsored project with industries is another way to transfer the knowledge in academia to industry. As shown in Table 33, the ratio of industry-sponsored research funding is higher in Japanese universities. However, the total budget of sponsored research of each cluster (summed up the amount of two each university) is almost half in Japanese two clusters compared with Boston/Cambridge, though we don't include the amount of other universities existing in the cluster. On the other hand, the total spending on R&D by industry was $ 375 billion in the U.S. and $122 billion (~30% of the U.S.) in Japan (2016). [1] Thus, if we estimate that the percentage allocated to sponsored research in the industry is the same or less in Japanese industries, the amount of sponsored research might be less in Japan as a total.

(6) Hospitals

In the biotech startup ecosystem, hospitals are the place where clinical research is executed. Therefore, hospitals are essential stakeholder in the process of application and the accessibility to hospitals is important in a smooth transition to clinical research. In that sense, Boston/Cambridge area has quite good access to the research hospitals because there 5 of top 6 hospitals receiving NIH funding as independent hospitals in the U.S.; Massachusetts General Hospital, Brigham and Women's Hospital, Boston Children's Hospital, Dana-Farber Cancer Institute, and Beth Israel Deaconess Medical Center.[6] All of these five hospitals are affiliated to Harvard Medical school. MIT doesn't have the medical school, but they are benefited from these hospitals, same as startups and companies in this area. On the other hand, Stanford and UC Berkeley have the medical school and also UC San Francisco has the medical school in San Francisco Bay Area.

In the case of Japan, twelve Core Clinical Research Hospitals[56] are nominated and funded by MHLW to establish the core center for clinical research in order to overcome the weakness in the transition to clinical research and the response to the need for establishing the system for providing high-quality clinical. In these centers, the organization and human resources including the clinical research coordinators are prepared. Most of twelve hospitals are established in the medical school of a university including University of Tokyo, Keio University, Kyoto University, and Osaka University.

The existence of the place for clinical research might not matter for the clinical research itself because the clinical research is highly protocoled research and sometimes hospitals all over the U.S. are needed to participate to fulfill the number of required patients. However, the existence of doctors who have the needs for new diagnosis or treatment and know the process of clinical research might help the ecosystem from the knowledge side.

(7) Entrepreneur

(a) Entrepreneurial attitude

Entrepreneurial attitude is one of the ways to evaluate the strength of entrepreneurship. *The Global Entrepreneurial Monitor (GEM)* monitors the state of entrepreneurship in their nations from many aspects, such as self-perception about entrepreneurship and the social value about the entrepreneurship.[73] The E-Cap metrics monitored here are summarized in Table 37. The ranking includes the most of Europe, North American and South American countries, several Middle East and African countries and also some East and South Asian country, such as China, Korea,

[56] https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/tyukaku.html

India, Thailand, Indonesia, and Taiwan, in addition to Japan. Among these countries, Japanese ranking both in the self-perception and the societal value about the entrepreneurship is almost lowest in most of the values. (High ranking in fear of failure negatively affects entrepreneurship, thus ranked high in this metrics is low in the meaning of entrepreneurship.) On the other hand, the U.S. is ranked rather higher or middle in all values.

Table 37 Self-perception and the societal value about entrepreneurship

	US		Japan	
	Value	**Rank**	**Value**	**Rank**
Self-Perception About Entrepreneurship				
Perceived opportunities	69.8	5/49	8.1	49/49
Perceived capabilities	55.6	13/49	10.1	49/49
Fear of Failure	35.2	23/49	46.4	9T/49
Entrepreneurial intentions	12.2	35/48	5.0	46/48
Societal Value About Entrepreneurship				
High status to entrepreneurs	78.7	9/47	51.5	42/47
Entrepreneurship a good career choice	62.7	25/47	22.8	46/47

Source: The Global Entrepreneurial Monitor 2018-2019 Global Report [73]

Another research shows Japanese people are less interested in business startups compared with other nations including the U.S., though the proportion of prospective entrepreneurs who engage in entrepreneurial activity is almost same in Japan (19%) and the U.S. (20%).[74]

However, the result above is a comprehensive analysis of people and it is possible that entrepreneurship is different in age group and a certain background. For example, "Survey on starting business and entrepreneurship" (Development Bank of Japan, 2019) shows that younger people (under 29) has more interest in starting a business than other age groups. Also, entrepreneurial awareness among students is steadily growing.[74] Especially in the University of Tokyo, it is reported that the number of students who attend to the entrepreneurship class, "Entrepreneur Dojo", and also the number of the affiliated startups have been increasing.[75] The same tendency is also observed in other universities about the number of startups. Thus, the entrepreneurial attitude is higher especially in universities than other environments in Japan.

(b) Entrepreneurial activities

GEM also develops the metrics for measuring entrepreneurial ship activity; Total Early-Stage Entrepreneurial Activity (TEA). In this measurement, the percentage of people who are engaged at the beginning of the startup business.[73] As shown in Figure 17, TEA is constantly low in Japan (5.3 and ranked 44th in 2018) compared with the U.S. (15.6 and ranked 13th) and UK (8.2 and ranked 34th). However, the Japanese ranking becomes slightly higher in younger age, 39th in 18-24 years and 38th in 25-34 years.

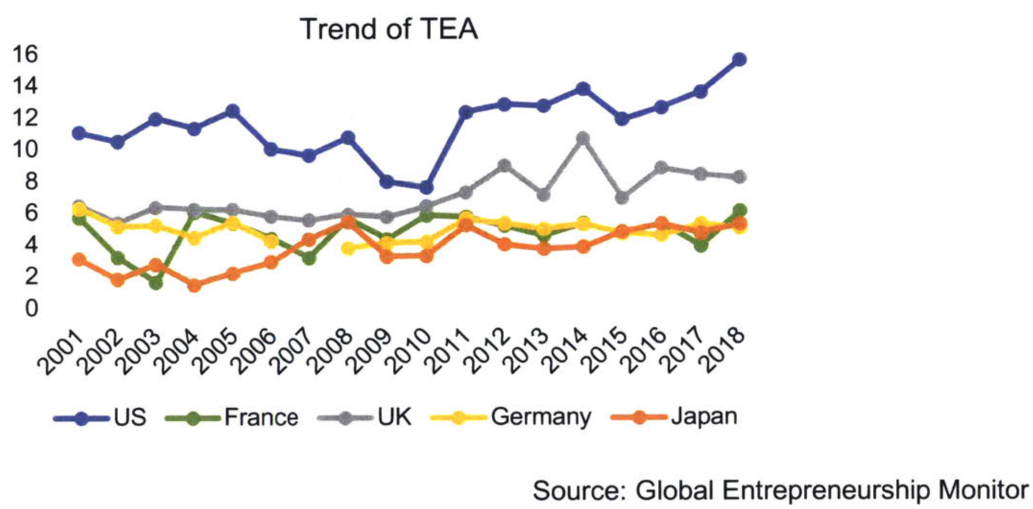
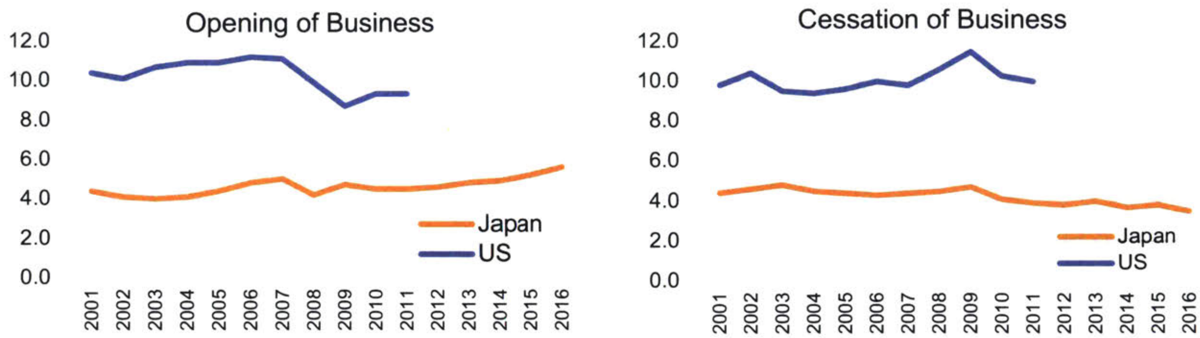


Figure 17 Trend of TEA in five major countries

Another barometer for evaluating entrepreneurial activity is numbers related to starting a business. Figure 18 shows the opening and cessation of business rate in Japan and the U.S. As it shows, the opening/cessation rate is lower in Japan. This suggests, opening a company is relatively rare in Japan. Thus, it might reflect low entrepreneurship in Japan.



Modified from: NISTEP "Japanese Science and Technology Indicators 2018"[69]

Figure 18 Percentage of opening or cessation of business

Table 38 shows the number of university-affiliated startups in the U.S. and Japan. The criteria for counting the number is different; a startup which raised more than $1million during 8/1/2017 ~ 8/22/2018 is counted in the U.S. dataset and all the startups existing is counted in Japan. In addition, the definition of affiliation is different. From the difference in the criteria and the number, it suggests that the number of startups in Japanese university is less than in the U.S. In the survey, it was also shown that startups formed was 11 in UC Berkley, 29 in University of Tokyo and 43 in Kyoto University in 2017. In another survey at MIT, 12.0% of alumni are estimated to participate in entrepreneurship within 3 years post-graduation in 2000s and 1,300 firms were founded each year by MIT alumni during the 2000s.[76] All these data suggest that entrepreneurship activity in the U.S. universities is higher than in Japan, though the entrepreneurship in Japanese universities has been increasing.

Table 38 Number of university-affiliated startups[57]

A. Number of startups raising more than $1M in a year.

Ranking in the U.S.	University Name	Number of $1M raised Startups*
1	Stanford	303
2	MIT	198
3	Harvard	186
4	UC Berkeley	138

*Affiliation to a university is defined by founder. Only a startup raised more than $1M in 8/1/2017~8/22/2018 was counted.

B. Number of existing startups.

Ranking in Japan	University Name	Number of Existing Startups**
1	University of Tokyo	245
2	Kyoto University	140
4	Osaka University	93
11	Keio University	51

**Affiliation to a university is defined by relationship (founder, licensing, investment, etc.).

(8) Supporters: Organizations of supporters

In establishing a startup, an entrepreneur needs many additional resources both in the business side and R&D side in addition to its core technology as mentioned above. Usually, he or she doesn't have such additional capability or knowledge unless he/she is a serial entrepreneur. Or, even if he/she has such capability and knowledge, it could be more efficient to outsource some of the works. Table 39 is the list of supporting organizations and their providing services.

Table 39 List of supporting organizations and their services

Type of firms	Providing service
Law firm	Filing company, patenting
Accounting firm	Accounting
Consulting firm	Business development/strategy
HR firm	Coordinating/consulting human resources (building team)
Business incubator / Startup accelerator	office and/or laboratory space, connections, mentorship, educational components and demo day
R&D outsourcing firm	Executing manualized experiments

All the firms and services generally exist both in the US and Japan. Among these firms, business incubators and/or startup accelerator play an important role in

[57] The data source is noted in Chapter 11.

developing startups. Thus, in the following section, we explore the incubator and accelerator in each cluster.

United States

The first startup accelerator program was started by Y Combinator in 2005 at Cambridge, Massachusetts (moved to Silicon Valley in 2009[58]).[77] Also, TechStars, which is another top accelerator in the U.S., was founded in 2007. After that, accelerator programs' role in the startup ecosystem has been increasing and one-third of U.S. startups that raised a Series A in 2015 went through an accelerator and 579 accelerator programs exist all over the world by Global Accelerator Report 2016.[78],[79] At the same time, getting into some of the well-known accelerator program is very difficult and its acceptance rate is as low as 1.5%.[80]

Some acceleration programs specifically focus on biotech startups. IndieBio is the first accelerator focusing on life sciences.[81] In this program, each startup receives $250 thousand seed funding, laboratory and co-working space, dedicated mentorship and become part of a network of IndieBio alumni, investors, biotech entrepreneurs, investors, press, corporate partners, and so on. The program is completed for 4 months and organized twice a year. In each batch, fifteen early stage biology companies move to downtown San Francisco and reside their facilities. In exchange for the program and the initial funding, IndieBio receives 8% equity at $3 imllion valuation cap.[59]

IndieBio is backed by venture capital, but some accelerators come out of the government, academic institutions and big pharmaceutical companies. Johnson & Johnson Innovation manages JLABS which locate 12 cities all over the world, including Boston/Cambridge and South San Francisco. Bayer, AstraZeneca, and Illumina operate accelerator programs linked with their business.[82]

---

[58] http://old.ycombinator.com/ycca.html
[59] https://indiebio.co

In addition to acceleration programs, incubation facilities become popular. Different from other technology areas, R&D in biotechnology can't be executed in the "garage". They need special laboratories which met the criteria of the regulation for biological and/or chemical experiments. Building this type of facilities by themselves is tough work for young startups, thus startups have to execute their experiments in universities or pharmaceutical companies with whom they can collaborate and this was a gap between academic research to industry. To solve this problem, co-working space equipped with wet-lab (laboratory space for biological experiments) have been increasing the number.

In the Greater Boston area, there are nearly 50 startup accelerators, incubators, and similar support programs.[83] MassChallenge[60] is the representative one which is originally started with backing from the City of Boston and Massachusetts state governments. 39 startups succeeded in exit their business until August 2018. This number is ranked 5th among the major accelerator programs in the U.S. In addition, there are also organizations who provide networking opportunities for stakeholders in the ecosystem, such as Venture Café[61] and LaunchBio[62]. These two non-profit organization also have many sites other than Boston/Cambridge (LaunchBio has one in San Francisco) and expanding their network.

There are many incubating facilities in Boston/Cambridge. Among them, LabCentral[63] is well known in the U.S. for providing working space for biotech startups and connection to the stakeholders in the ecosystem. LabCentral is supported by the Massachusetts government in founding, setting up their facilities, based on the state's Life Science Initiative in 2013. It offers fully equipped laboratories and office spaces to 60 startups and networking opportunity for

[60] https://masschallenge.org
[61] https://venturecafefoundation.org
[62] https://www.launchbio.org
[63] https://labcentral.org

residences with more than 150 events per year. In 2017, 10% ($267 million) of U.S. Series A biopharma investment was to LabCentral resident and alumni companies. Its acceptance rate to have a bench is less than 20%. Because of this low acceptance rate (companies are well-selected) and the success of graduating companies, LabCentral is well-known in biotech industries and catches the eye of VCs and pharmaceutical companies. In addition to LabCentral, many incubation facilities exist and ahave been opening in Boston/Cambridge, such as Alexandria LaunchLabs[64].

San Francisco Bay area is the base of Y Combinator and IndieBio, but also 500 Startups, TechStars and Plug and Play, which are all famous accelerators, locates run their program in there. There are also incubation facilities focusing on life sciences, such as MBC BioLabs. In addition, there are 25 lab space/incubators in California and 5 lab space brokers, i.e. real estate company focusing for life science lab space.[65]

Japan

The pioneer of the accelerator program in Japan is Open Network Lab (Onlab)[66] founded in 2010 by Mr. Hayashi and Mr. Joy Ito in Media Lab, MIT. After that, the number of accelerator programs has been increasing both the one backed by big cooperates and by venture capitals, and more than 50 programs were operated by big companies in 2016.[84] In addition, worldwide accelerators have started programs in Japan. In 2017, Plug and Play opened their branch in Shibuya (Tokyo).

As for the incubation facilities focusing on life sciences, there are 44 facilities in Kinki area (Kyoto: 10, Osaka: 13, Hyogo: 14) and most of them are established in public/private R&D facilities or business incubation facilities.[67] In Kanto area, a

[64] https://www.alexandrialaunchlabs.com/
[65] CLSI website: http://califesciencesinstitute.org/entrepreneurship/lab-space-incubator/
[66] https://onlab.jp
[67] https://www.kansai.meti.go.jp/2-4bio/ac_data/incubation_site.html

sharing wet-lab facility, "Beyond Biolab", was opened by a venture capital (Beyond Next Ventures) in 2018 and a rental laboratory is also opened in Kawasaki by a biotech equipment company in 2017. However, there is a demand for incubation facilities focusing on biotech startups, thus the number of these facilities is estimated to be increased.

There is also strong support from the policy side. Tokyo Metropolitan Governments have started "Blockbuster Tokyo", which is an accelerator program specialize for biopharmaceutical startups, in 2018.[68] Osaka city opened Osaka Innovation Hub in 2013. It arranges more than 200 events including Hackathon and pitch events and also operates seed acceleration programs (OSAP). Kobe-City also started the acceleration program collaborating with 500 Startups science 2017 and opened the life science incubation facilities, "CoLaborator Kobe", collaborating with Bayer in 2018.[69]

In addition, Takeda opened the incubation facility, called Shonan Health Innovation Park (Shonan iPark)[70], in 2018. Before that, this facility was the R&D division of Takeda, but they renovated it as the open innovation facilities after they closed the R&D division there. They equip the mentoring services, the consulting services in intellectual property and pharmaceutical affairs, the supporting in pre-clinical research, and consulting in drug discovery in addition to holding networking events and pitch events. It locates 27.5 miles (44 km) from Tokyo, 19.5 miles (31 km) from Tonomachi King Skyfront in Kawasaki and 212 miles (341 km) from Kyoto. In addition, there is no universities having strong R&D schools and no R&D facilities of other pharmaceutical companies. To overcome these disadvantages, iPark collaborates with Center for iPS Cell Research and Application (CiRA) in Kyoto University and Life Innovation Center (LIC) in Tonomach King Skyfront. Also, other

[68] https://www.blockbuster.tokyo
[69] https://www.colaborator.jp
[70] https://www.shonan-health-innovation-park.com/en/

pharmaceutical companies (Mitsubishi Tanabe Pharma, Asuka Pharma) and the research institutes (National Cancer Center) have settled part of the R&D group. Thus, the network among stakeholders including the startups settling in iPark has started to be formed.

(9) Supporters: Association of all stakeholders

Association of all stakeholders plays an important role in making all stakeholders get together. The way to make it happen has several variations, such as, networking or meet-up events, pitch competition, studying lecture series and conferences. Biotechnology Innovation Organization (BIO) [71] is the world's largest trade association representing biotechnology companies, academic institutions, states' biotechnology centers, and related organizations across the United States and in more than 30 other nations, including Japan. BIO produces the BIO International Convention, which is the world's largest gathering of the biotech industry, as the opportunity for networking and partnership among the members.

United States

In addition to the worldwide stakeholders' association like BIO, Massachusetts Biotechnology Council (Mass Bio) works as the network of stakeholders in the ecosystem in Massachusetts. Mass Bio is founded in 1985 as a not-for-profit organization and more than 1,100 biotechnology companies, academic institutions, disease foundations and other organizations involved in life sciences and healthcare join. It organizes networking and educational events, savings through the purchasing consortium, business development and entrepreneurial support programs, public policy and advocacy engagement and economic developments support.[72]

[71] https://www.bio.org
[72] https://www.massbio.org

California Life Sciences Association (CLSA)[73] is the largest stakeholders' association in California state. Before 2015, it was two association depending on region; the Bay Area Bioscience Association (BayBio) and the California Healthcare Institute (CHI). Its members are the scientist, inventors, entrepreneurs and leaders in the industry over 750 organizations. It provides group purchasing savings, networking opportunities through meeting and events and advocacy to public policy. In addition, CLSA operates California Life Sciences Institute (CLSI)[74] to maintain California's leadership in life science innovation by supporting entrepreneurship, education, and career development. For this purpose, CLSI provides entrepreneurship programs for connecting startups with resources and expertise, such as educational workshops, research database access, and peer and executive networking, STEM education in Northern California and career development workshops.

Japan

In Japan, there are two major cross-country organizations for biotech industry. One is Japan Bioindustry Association (JBA)[75], which was founded in 1942. It was started as the association for fermentation industries, such as alcohol, and changed its name as JBA and its function along with the changing technology. Its purpose is promoting biotech industries by the collaboration among industry, academia, and government. For this purpose, it organizes public policy advocacy activity, studying seminars, partnering events, and networking with foreign countries. 381 organizations including startups, companies, academia and public entities are the members of JBA. However, events which give startups to make connections with other stakeholders are limited almost only BioJapan (the largest matching event between startups and investor).

[73] https://califesciences.org
[74] http://califesciencesinstitute.org
[75] https://www.jba.or.jp

LINK-J[76] is another cross-country stakeholders' association and more focusing on incubating startups. It was founded in 2016, backed by a real estate company (Mitsui Fudosan, Inc) and some academic researchers in order to promote the open innovation by the collaboration among industry, academia, and governments in the life science area.[85] LINK-J's office locates at Nihonbashi in Tokyo, where most of pharmaceutical companies locate traditionally. It organizes networking events for entrepreneurs and studying seminars and supports the activity of accelerating programs. It also rents their supports to the member organizations to organize events or seminars. More than 240 organizations are the member or tenant of Link-J and some members, such as branch offices in universities including four universities we analyzed here, use these opportunities as a showcase for their startups. Benefitted from its location and contents, entrepreneur and investors have a chance to meet in their space. In addition, the incubating facility mentioned above (Beyond Biolab) also locates the same building. Thus, this area has the potential to be a center of a biotech cluster in Tokyo.

In the local level, some cities have stakeholders' association if we ignore their function in the ecosystem. For example, Tsukuba City has Tsukuba Life Sciences Promoting Committee[77], which members are more than 40 organization including big pharmaceutical or biotech companies, academia, research institute, and the government, but their activity is far different from such a cross stakeholder organization like in the U.S. Their focus is more on R&D collaboration and not on the business side, such as networking and meeting up or developing startups. Kobe City also has Foundation for Biomedical Research and Innovation at Kobe (BRI)[78] for the purpose of promoting the collaboration among corporate, scientific, academic, and medical institutions located at the Kobe Biomedical Innovation Cluster. Its member is widely from industry related to biomedical and life sciences area, academic

---

[76] https://www.link-j.org
[77] http://tsukuba-gi.jp/lifescience/
[78] https://www.fbri-kobe.org/english/

research institute and government. However, their focus is also on R&D collaboration and not on entrepreneurs.

(10) Summary and conclusion

(a) Summary of stakeholder's measurements

Table 40 is the summary of stakeholders analyzed above. As it shows, there is no missing part in the stakeholders in the organization level, though there are quantitative differences between Japan and the U.S. In addition, we cannot find the difference in the base structure of stakeholders between the U.S. and Japan. To figure out the difference of the ecosystem, we analyze the difference of stakeholders' feature in the next part.

Table 40 Summary of the six stake holders in clusters

Stakeholder Category	Organization		United States: Boston, Cambridge	United States: San Francisco Bay Area	Japan: Tokyo	Japan: Kinki (Kyoto, Osaka)
Government	Government		Federal (Several Ministries and agencies including NIH) *NIH funding: $32B (FY2018) ($2.9B for MA, $4.2B for CA) *NSF funding: $672M to life sciences (FY2017) *Supports for small businesses (SBIR, STTR)		National (several Ministstries and Agencies including AMED) *AMED funding: $1.25B (FY2017) *KAKENHI: $545M to life sciences (FY2017) *Supports for cllaborative research and sumall businesses *Awards for startups	
		State/Prefecture	Massachusetts *$623M for life sciences (5years)	No obvious support from State/City government	Tokyo Metropolitan Government *Block Buster Tokyo	Kyoto, Osaka
		City	Boston, Cambridge		Kawasaki-city, Tsukuva-City	Kyoto, Osaka, Kobe
	Regulatory Agency		FDA		PMDA	
Corporate	Pharmaceutical Company		R&D budgets of Top 50 pharmaceutical companies: $57.54B (16 companies) R&D budget of top 20 pharmaceutical companies: $48.23B (9 companies)		R&D budgets of Top 50 pharmaceutical companies: $13.15B (10 companies) R&D budget of top 20 pharmaceutical companies: $2.94B (1 company)	
			- 15 of top 20 global pharmaceutical companies locat office inluding R&D facilities	- 13 of top 20 global pharmaceutical companies locat e office including R&D facilities	- 18 of top 20 globarl pharmaceutical companies locates office (mainly business) - 10 of top 10 Japanese pharmaceutical cmpanies locate business base - 3 of top 10 Japaese pharma locate R&D facilities	- 12 of top global pharma locate its offices (mainly business office) - 5 of top 10 Japanese pharmaceutical cmpanies locate business base - 5 of top 10 Japanese pharma locate R&D facilities
Risk Capital	Venture Capital		$3.6B in Life Science (2017)	$6.1B in Life Science (CA, 2017)	$210M in bio/medical/healthcare (FY2017, 18.4% of total)	
					$637M (all fields,FY2017)	$86M (all fields, FY2017)
University	University		48 universities (including MIT and Harvard, 2018)	50 universities (including Stanford and UC Berkeley, 2018)	138 universities (including U-Tokyo and Keio U, 2018)	34 universities in Kyoto, 55 unversities in Osaka (including Kyoto U and Osaka U, 2018)
		Academic reputation	MIT: ranked 4th, 90 Nobel laureates Harvard: ranked 6th, 48 Nobel laureates	Stanford: ranked 3rd, 17 Nobel laureates UC Berkeley: ranked 15th, 22 faculties and 30 alumni for Nobel laureates	U-Tokyo: ranked 45th, 10 Nobel laureates	Kyoto-U: ranked 65th, 9 Nobel laureates Osaka-U: 1 Nobel laureates
		Number of highly cited researchers (HCR)	MIT: 99 (MIT, Broad Institute) Harvard: 186 (exclude affiliated hospitas)	Stanford: 100 UC Berkeley: 64	U-Tokyo: 10 Keio: 1	Kyoto: 7 Osaka: 6
		Startups	*raised more than $1M in FY2017 MIT: 198 Harvard: 186	*raised more than $1M in FY2017 Stanford: 303 UC Berkeley: 138	*existing startups U-Tokyo: 245 Keio: 51	*existing startups Kyoto: 140 Osaka: 93
		Royality revenue	MIT: $54.1M	Stanford: $41.0M UC Berkeley: $4.3M	U-Tokyo: $7.3M Keio: $0.5M	Kyoto: $5.8M Osaka: $0.9M
	Hospital		5 of top 6 hospitals in the US. (5 are affiliated to Harvard Medical School)	Medical schools in Stanford, UCB and UCSF	3 of 12 Core Clinical Research Hospitals (including the medical shools in U-Tokyo and Keio U)	2 of 12 Core Clinical Research Hospitals (the medical schools of Kyoto-U and Osaka-U)
Entrepreneur	Startup		500+ biotech companies including startups (2018)	3418 biotech companies including startup (CA, 2018)	577 startups (all field, 2017)	138 startups in Osaka, 135 startups in Kyto (all field, 2017)
			13 biotech IPO (2018 Jan-Jun, Massachusetts)	9 biotech IPO (2018 Jan-June)		
Supporters	Organizations of supporters		exists many	exists many	exists many	exists many
		Incubators/Accelerators	LabCentral, LaunchBio, etc.	IndieBio, MLC BioLabs, LaunchBio, etc.	Onlab, Plug and Play, Beyond BioLab, etc.	44 incubation facilities for life sciences
	Association of all stakeholders		MassBio	CLSA	JBA, LINK-J	

(b) Features of Stakeholders

We summarize the difference of stakeholders' feature found by the analysis above.

(i) Government

The roles of nationals and local governments are summarized in Table 41. Both the U.S. federal government and Japanese national government provide funding on R&D in academic research (NSF and NIH funding vs KAKENHI and AMED funding), public/private sector partnership and innovative firms (SBIR and STTR vs A-STEP and START). The Japanese government also provide risk capital in addition to R&D grants. On the other hand, incentives for industries and support for startups are provided by local governments' level in both countries. This observation might reflect the orientation of industry is mostly given by the local level.

Table 41 Roles of the national/local governments in the biotech startup ecosystem

	Clusters			
	Boston /Cambridge	**San Francisco Bay Area**	**Kanto (Tokyo)**	**Kinki (Kyoto, Osaka)**
Dominant R&D budget	Federal	Federal	National	National
Tax incentive (Life science)	State	-	City	-
Other incentives	-	-	City	Prefecture, City
Risk capital for startups	-	-	National, Prefecture	National, Prefecture, City
Supports to entrepreneurs and startups	State	-	Prefecture	Prefecture, City

Though the volume of funding by the government in the U.S. is much higher than Japan both in the size ($54 billion vs $14 billion (all field), $32 billion (NIH) vs $1.25 billion (AMED)), it's comparable as percentage in GDP (0.31% vs 0.28%). In addition, the Japanese government established a strong policy for promoting medical R&D and also the policy for promoting investment.

In the local government level, their role is different among clusters. In Massachusetts State, there is a strong push from the government side as a policy including funding, tax incentives, and entrepreneurial education. In Tokyo and Kinki area, the governments also boost the life sciences industry, but their main policy instruments are supporting programs for entrepreneurs and startups including incubation facilities. The R&D budget mainly depends on the national government in Japan. In contrast, California state doesn't have specialized policy for life science field, though the state spends a significant amount on R&D. This difference suggests, the component missing in California is provided by other stakeholders.

On the other hand, there is almost no difference in the U.S. and Japan in the regulation side. This is the result of the efforts by the Japanese government to reduce the lag from the U.S.

Advantage of Japan: Strong boost from the government(s)
Challenge in Japan: Less amount of R&D funding

(ii) Corporate
Looking around the world, there is a comparable number of big pharmaceutical companies in the top 50 in Japan, but the number becomes quite less in the top 20. R&D spending of these companies are relatively small in Japanese pharmaceutical companies.

The functions of the department which are located in these clusters show some specificity. In Boston/Cambridge and San Francisco Bay Area, most of the top pharmaceutical companies allocate R&D facilities, but not in Tokyo (Kanto) and Kyoto/Osaka (Kinki). Also, Japanese pharmaceutical companies, R&D facilities are located a little bit far from the center or universities of Tokyo, Kyoto or Osaka. However, the business offices are accumulated in Tokyo (Kanto) and Kyoto/Osaka

(Kinki), including the world top pharmaceutical companies. Especially in Nihonbashi area, their offices are accumulated almost like R&D facilities in Boston/Cambridge.

Advantage of Japan: High accumulation of headquarters (or business base) in Tokyo (Nihonbashi Area)
Challenge in Japan: Small R&D spending. The physical distance between R&D facilities of pharmaceutical companies and universities.

(iii) Risk Capital

Not only the size of risk capital (far smaller in total amount and amount per deal in Japan than the U.S.), but also the feature of venture capitals is also different.

The biggest difference is the specialty of a person in the VC side and specialty of a company. In Japan, the number of MBA and/or Ph.D. holders in VCs are lower than other countries, and the number of VC which focuses on biotechnology area is also lower. These suggest that the significant lack of specialty in the investment side. This causes problems not only in validating a startup but also in supporting (incubating) startups during investing. In addition, supports from VC to entrepreneurs/startups, such as mentoring and suggestions both in R&D and business, are less in Japan because of this problem. However, the specialty of venture capitalist in pharmaceutical companies' CVC is estimated to be enough.

Advantage in Japan: Growing in investing market
Challenge in Japan: Small amount of investing money. Investor's specialty in biotechnology and/or finance.

(iv) University

As a system of the university, the accessibility of universities and Ph.D. recipients are not different in Japan and the U.S., though the number of Ph.D. candidate has been decreasing in Japan. And the student-faculty ratio is almost comparable.

However, the budget per faculty or student is less in four Japanese universities than in four US universities, though the percentage of income from industry is much more in Japan than in the U.S.

In the aspect of the quality of research, the position of four Japanese universities is lower than four US universities in the world university ranking and the ranking of the highly cited researchers. Also, the rate of highly cited articles is far less in Japan than in the U.S., though Japan is still comparable to other major countries, like France.

The number of patent applications is not different among universities in the U.S. and Japan. This suggests, Japanese universities also have the same motivation for applying patents. This is might be because of the Japanese government's policy to give incentive to the researcher for it. However, the royalty which each university earns is less in Japan. This suggests there might be a challenge in transferring technology from academia to industry. We will explore this part in the following sections.

> Advantage of Japan: Comparative accessibility to universities and researchers in the cluster.
> Challenge in Japan: Small amount of funding on R&D per researcher. Decreasing of the rankings evaluating research impact and the number of Ph.D. student. Challenge in transferring knowledge from academia to industry.

(v) Entrepreneurs

The number of entrepreneurs is far smaller in Japanese clusters than in the U.S.'s clusters, but the number of startups has been increasing in Japan. The entrepreneurial attitude is still lower in Japan and the opportunity where students (people) can meet entrepreneurs are quite limited or almost nothing. Lack of a role model as an entrepreneur contributes to the small number of entrepreneurs and fear to be an entrepreneur in Japan. In addition, the small number of entrepreneurs means low demands for the support and/or services to entrepreneurs.

> Advantage in Japan: High potential in fostering entrepreneurship (growing in the interest in entrepreneurship and startups in younger people.)
> Challenge in Japan: Low entrepreneurship, Small number of entrepreneurs (a role model as an entrepreneur), deficient of supports to entrepreneurs/startups,

(vi) Supporters

Because of the accumulated knowledge and history, there are many supporting organizations who can provide service to startups especially accelerators and incubators in the U.S. where are many incubators and accelerators including programs specifically targeting biotech startups. Also, there are law firms and consultants who have high expertise in biotech. However, in Japan, they now try to transplant these systems and some activities seem to be successful, but it has just started and the availability of these activities are restricted depending on the localization. In Tokyo, there have been many companies and they have started to realize the needs of startups and started the business, but less in local cities. Thus, there might be many isolated startups in Japan.

For the association of all stakeholders, this movement also has just started in Japan, especially in Tokyo. Thus, the supporting activity to entrepreneurs and the ecosystem is still week in Japan, thought the demand looks increasing.

> Advantage in Japan: Potential supporters exist, demand for supporters are increasing
> Challenge in Japan: Deficient number of supporters and activities. Immaturity in supporting entrepreneurs/startups.

(c) Conclusion

In comparing the ecosystem in the U.S. and Japan, all stakeholders exist in all clusters. However, there are some differences in the activity, quantity, and quality. For example, the size of governments' and universities' funding, R&D budgets of pharmaceutical companies and risk capital is one of the differences. Also, R&D facilities are accumulated at Boston/Cambridge and San Francisco Bay Area, but not in Japanese clusters.

Also, the activity in entrepreneurship and supporting activities for startups are different and less in Japanese clusters, though these activities have been increasing in Japan.

From the aspect of knowledge transfer from academia to industry via startups, the system equipped with universities seems to be less functional in Japanese universities estimated from the comparison of the number of patents and the R&D budget.

Thus, we explore the effect of these difference in the activity, quantity, and quality to the ecosystem in the following sections.

7.2 Analysis of stakeholders' network in the U.S. and Japanese clusters

In this subsection, we'll analyze the stakeholder's network in Boston/Cambridge as the best case based on the information in Chapter 7. Then, we'll analyze the case in Japan and figure out the difference in the stakeholder's network.

(1) Stakeholder's Network in the Boston/Cambridge Cluster

In the successful biotech ecosystem, the transaction of technology from academia to industry is efficiently executed. Thus, figure out the important pathway in successful technology transaction from academia to industry is important in analyzing the ecosystem.

Based on the original stakeholder's value network in Figure 6 and the analysis above, the stakeholder value network in Boston/Cambridge is drawn in Figure 19. In this figure, knowledge transfer without contracts is omitted. As shown in Figure 6 and Figure 19, technology, human resource and money are the major factors exchanged among the stakeholders. The intermediators which deliver these factors are patent, human capital, and contract (a formal way of transacting knowledge and money). In the aspect of knowledge transfer without contracts, it delivered via human's mouth, thus, it is an informal way of transacting knowledge.

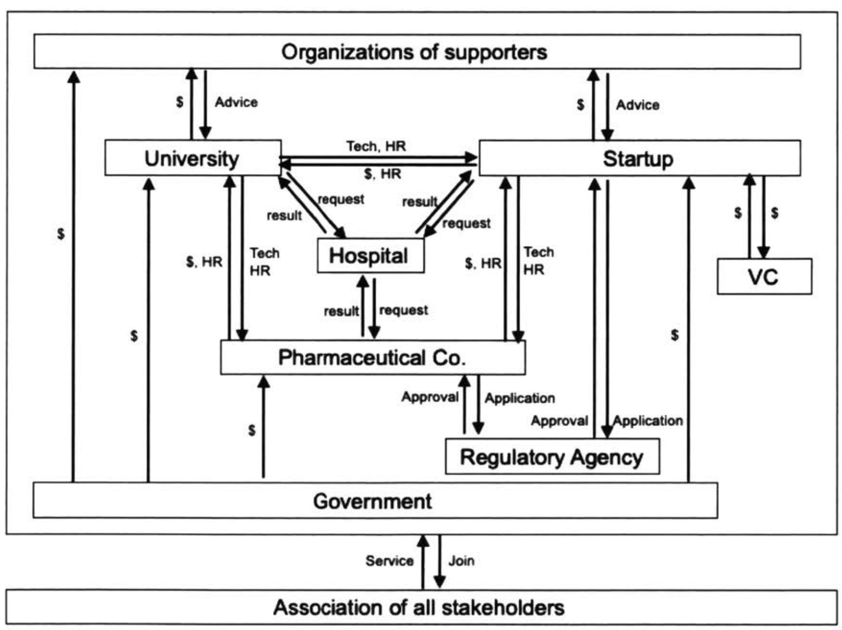


Figure 19 Stakeholder Value Network in the biotech startup ecosystem

In order to compare the relationships among stakeholders in the clusters, the Design Structure Matrixes (DSM) are created for each cluster. In this time, we focused on the promotion side of the R&D (thus we omit the regulatory agency and hospitals from the matrix) and four types of deliverables; 1) technology (delivered by patent),

2) knowledge (delivered by human resource), 3) money (delivered by contract), 4) knowledge (delivered by word of mouth).

Figure 20 shows the relationship among stakeholders in Boston/Cambridge cluster by using DSM. As the figure shows, technology (patent) is generated in university and hand over to startups and pharmaceutical companies. In addition, knowledge transaction without human resource (thus by word of mouth) occurs almost all interactions among stakeholders.

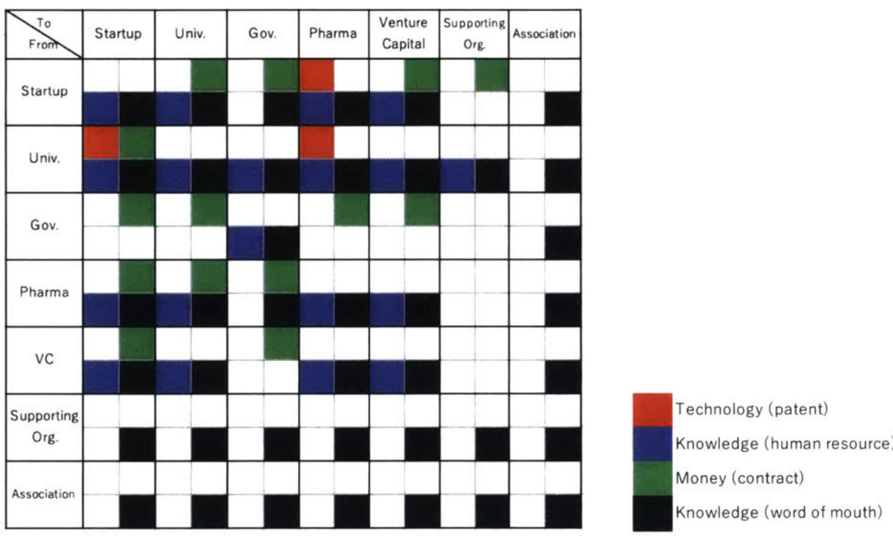


Figure 20 DSM for stakeholders in Boston/Cambridge cluster

This result comes up with the hypothesis that a university's function in conveying knowledge from academia to industry is weaker in Japan and that the knowledge spill-over from each organization is less in Japan.

(2) Environment surrounding entrepreneurs in the Boston/Cambridge Cluster

Environment surrounding entrepreneurs is also important in the startup ecosystem. As in Figure 4, there are many required steps in managing a startup not only in R&D but also in the business side. An entrepreneur or a small team of a new startup usually don't have capability or knowledge in all the skills and knowledge required in establishing a startup. Thus, the environment where enables them to be supported is an important factor in the ecosystem.

The providers of measures to accomplish the tasks for a biotech startup (Table 5) in the case of Boston/Cambridge is summarized in Table 42. As the table suggests, the availability of measures to accomplish tasks for biotech startups are underpinned by the number of opportunities, the high mobility of human resources and the word of mouth (spilled-out knowledge) and some part of these are provided by universities which support entrepreneurs, tries to connect academic resource to industry and provides supports required for execute its function. In addition, most of the stakeholders, pharmaceutical companies, VCs, supporting organizations (especially accelerator and incubator) and the association of all stakeholders provide the opportunity for entrepreneurs to accomplish each task. The network among the stakeholders becomes tighter by these opportunities by stakeholders and participation of stakeholders to the ecosystem ant the network strongly supports entrepreneurs in Boston/Cambridge.

Table 42 Required task and availability for a biotech startup in Boston/Cambridge cluster

	Type of task	Specific tasks	measure to accomplish	availability
Business Side	Funding	Grant application Applying business competitions Fund raising from VC	- meeting with VC or pharmaceutical companies - attending pitch competition - apply grant	plenty of opportunities in making appointment and pitching
	Human Resource	Recruiting	- recruiting in meet-up or events - using consultant focusing on HR	plenty of human resource who want to join a startup
	Establishing company	Filing the business Finding Advisory Board	- find an appropriate corporate which can support by word of mouth	easy to obtain information about who should ask first

	Company exit	preparing for IPO	- using the support programs provided by universities	
		negotiation for M&A or licensing		
	Patent	Patenting		
		IP licensing		
R&D Side	R&D	for patenting	- recruiting researchers - gathering enough R&D budget	plenty of opportunity both in HR and budget
		for IND		
	Managing clinical trials	coordinating clinical trials	- recruiting appropriate person - raising enough budget	plenty of opportunity both in HR and budget
		analyzing the data		

Not mentioned in Table 42, but the shared knowledge among researchers in academia and industry is also important for startups in promoting their R&D. This happens not only by published journals but also by word of mouth. Thus, the network among the people who are involved in R&D regardless of the belonging organization is also important in the ecosystem.

Geographical proximity among stakeholders might contribute to the closeness in the communication in Boston/Cambridge and the accelerate the network effect by accidental meetings and the physical accessibility to others. However, this point should be investigated more because there is not such geographical proximity of stakeholders in San Francisco Bay Area.

(3) Stakeholders' network and the environment surrounding entrepreneurs in Japan

In order to examine the strength of connection among stakeholders in four transferred values, technology, knowledge with human resource, money, and knowledge without human resource, firstly we evaluate the status of each value one by one and estimate the percentage of each activity compared with Boston/Cambridge cluster.

- Technology transfer

Technology transfer is executed by patent licensing and the collaborative or sponsored research between academia and industries. There is no big difference in the number of patents transferred from a university to industries in two Japanese clusters and Boston/Cambridge cluster. For the number of collaborative or sponsored research with academia, we don't have data of the U.S. cases. Therefore, we estimate the number form the amount of funding from industry. The amount of collaborative or sponsored research in universities analyzed here is almost half in two Japanese clusters compared with Boston/Cambridge cluster. Of course, we don't include the number of other universities, but we estimate the transfer efficiency from university to startup/corporate is 75% of Boston/Cambridge in Japan.

- Money transfer (funding, investment)

The money provided from the government, pharma, and VC to universities, startups, and pharma is mainly the R&D funding. As discussed above, the government spending on R&D per GDP is almost the same in Japan and the U.S. However, the amount of sponsored research with industry and the investing money to startups in Japan is half in the sponsored research and one-tenth in the investing money. In addition, funding from universities to startups is less in Japan.

Some of the money transfer is via tax or tax incentives (Startup/Pharma/VC to Government, Government to Startup/Pharma/VC). We estimate there is no difference in this aspect.

- Knowledge transfer with human resource mobility

The human resource mobility from universities to other sectors basically depends on the hiring process. Considering the relatively low entrepreneurship in Japan, the transfer from university to startups should be less.

Another path for human resource mobility, such as mobility among pharmaceutical companies, VCs, and startups, depends on a job change. Japanese employment and salary are based on lifelong employment seniority ranking, therefore, the incentive for changing the job is low and the human resource mobility is said to be less compared with other nations. Thus, human resource mobility among pharmaceutical companies, VCs and startups are estimated to be low in Japan without exception.

- *Knowledge transfer via word of mouth*

It is difficult to measure the quantity of knowledge transfer via word of mouth because it depends on the frequency of contacts among peoples and contains both public and private channels. Thus, we estimate the quantity by the number of networking events the number of organizations which hold such events. In that sense, there is less opportunity for networking in Japan because the associations of stakeholders have organized or started the networking events recently and other stakeholders rarely have a culture to organize such events, as mentioned above. Thus, it is estimated that the activity on knowledge transfer via word of mouth is generally low in the Japanese ecosystem. In addition, the activity of supporting organization is estimated to be less because the small needs from startups depending on the small number of startups.

Based on these discussions, DSM for stakeholders in Japanese clusters is created as shown in Figure 21. The numbers in the cell are the percentage of activity/quantity of each interaction compared with the case in Boston/Cambridge. If there is no quantitative data, it is estimated 100 in the case there is no significant difference and 50 in the case the activity/quantity is estimated less. The intensity of colors reflects the percentage. The matrix suggests the interaction among stakeholders, thus the network of the ecosystem, is weaker in the Japanese ecosystem compared with Boston/Cambridge cluster, Figure 20. The DSM also suggests that universities' contribution to the human resource is limited in the recruitment and the feedback about industrial knowledge to universities is limited. This limited opportunity in knowledge transfer suggests that the knowledge of each stakeholder accumulates only in own organization and not shared among stakeholders.

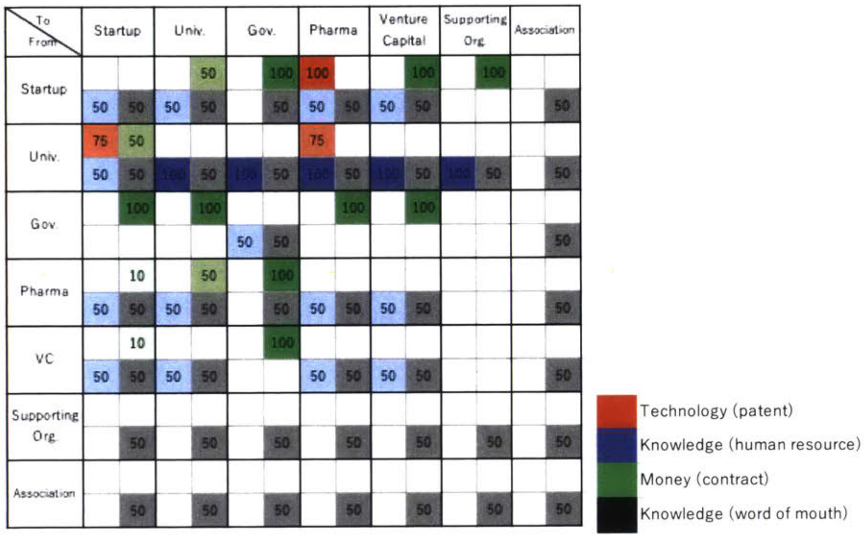


Figure 21 DSM for stakeholders in Japanese clusters

Assumed from the observation above, the environment surrounding entrepreneurs in Japan might be more severe than in the U.S. This is because most of the measures to accomplish the task of startups shown in Table 42 are more difficult and smaller to be available based on the estimation from Figure 21.

(4) Difference between the U.S. and Japanese clusters in technology transfer and knowledge transfer

The analysis above shows that the ecosystem delivers technology as the tangible asset and knowledge as the intangible asset, and that money is consideration of these assets. Thus, analyzing the ecosystem separately for these two assets might give us insights for understanding the difference of ecosystems.

The stakeholder's value network and DSM above suggest that the core value of the ecosystem is technology exchanged among universities, startups and pharmaceutical companies, also shown in Figure 6. Precise deliverables focusing on technology transfer is shown in Figure 22. In referencing the flow of technology shown in Figure 22 and values shown in DSM analysis above (Figure 20 and Figure 21), the output from universities is clogged in Japan, though we don't have the data about M&A and licensing from startup to pharmaceutical companies. Though it's less efficient in Japan, the efficiency is around 75% of the U.S. from the numbers and estimation above.

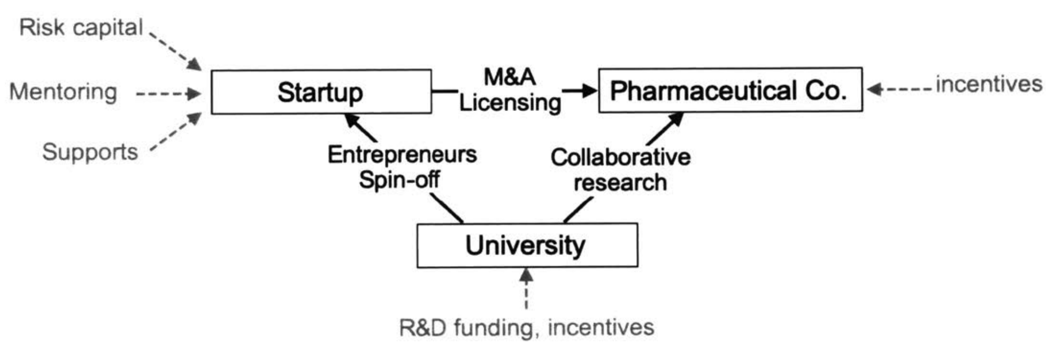


Figure 22 Stakeholders network in the technology transfer

On the other hand, DSM analysis in Figure 20 and Figure 21 also suggests that knowledge transfer is much less happens than technology transfer in Japan. It is less than in the U.S.

These two results suggest that the Japanese ecosystem is much weaker in the knowledge transfer than technology transfer. Our stakeholder analysis shows that this is because of the limited opportunity of meeting up with people who belong to other stakeholder categories.

(5) Conclusion

The analysis and comparison of the stakeholders' network in the U.S. and Japan suggest that the basic structure of the stakeholders is the same, though the network among stakeholder is rather weak in Japan. The weakness mainly comes from the less knowledge transaction among stakeholders both via human resource mobility and via word of mouth and also from the low activity of supporting organizations and the association of stakeholders. However, these reasons are partly because the ecosystem in Japan is still in the developing stage and less established than the U.S. clusters.

Technology transfer is the core value delivered in the ecosystem. The efficiency for delivering it is not such a severe situation in Japan in comparing with the U.S., but we don't have enough data to make this result decisive. The result shows that technology tends to be clogged within universities in Japan compared with the U.S. In addition, the weakness of the knowledge transfer suggests that the knowledge also tend to be accumulated only within each organization and not shared in the network in Japanese clusters. Thus, considering that the latest academic knowledge is generated in universities, the path to share this knowledge in the ecosystem is important especially in knowledge dependent industry, such as biotech industries.

In the aspect of the funding, it seems to have stronger connections than others in Japan, but this is partly because the number is adjusted by GDP. GDP in the U.S. is 3.6 times of Japanese GDP. Therefore, there is a substantial difference in this aspect and the connection via the funding process might be less in Japan.

8. Function and Comparison of Universities in the Ecosystem

As mentioned above, universities are the source of technology, knowledge and human talents and also equip the function to transfer those to the industry. In this section, we'll discuss the function of universities in the biotech startup ecosystem and compare their role in the ecosystem in the clusters of the U.S. and Japan.

8.1 Overview of universities' function in the ecosystem

(1) Types of universities' function in the ecosystem

As noted in the literature review, a university is an instrument of knowledge transfer from academia to industry, also they generate new academic knowledge at the same time. There are several pathways in the transaction; knowledge spillover via human resource mobility, collaborating research, patent licensing, published articles, face to face communication including advising, and so on.

The analysis in Chapter 5 revealed that there are 4 types of supply from universities to ecosystem; technology, knowledge (human resource), knowledge (word of mouth), and money. Thus, the function of a university in the ecosystem is basically the provider of these resources. However, the forms and values of the resources are different in the type of recipients (mainly startups, pharmaceutical companies, and VCs).

Table 43 summarizes the actual resources from universities to three stakeholders in the ecosystem; startups, pharmaceutical companies, and VCs. It shows that the resources require from other stakeholders (recipients) depend on the type of resources. To meet these requirements from the stakeholders, universities need to equip several systems to foster and deliver the resources.

Table 43 Resources from universities to the ecosystem

Types of resources provided by universities		Recipient of resources		
		Startups	**Pharma**	**VCs**
Knowledge	Human Resource	Entrepreneur	Researcher	Specialist
	Word of Mouth	Advice in R&D / Business	Advice in R&D	Advice in investment
Technology		Patent licensing	Patent licensing	-
Money		Funding	-	-

(2) Organization and system supporting the functions

To make the transfer smooth and systematically, most of the universities equip responding organizations or systems for each purpose. The typical list is shown in Table 44. Education and recruiting system for providing pharmaceutical companies and VCs is the rather generally equipped system in a university. Therefore, there are five types of organizations and systems which support the function of universities in the ecosystem; 1) Entrepreneurship education system, 2) Entrepreneurs' platform, 3) Technology transfer, 4) Funding opportunity and 5) Industry-university relationship management.

Table 44 Organizations and systems responding transfers from universities to the ecosystem

Types of resources provided by universities		Recipient of resources		
		Startups	**Pharma**	**VCs**
Knowledge	Human Resource	Entrepreneurship education system	Education and Recruiting	
	Word of Mouth	Entrepreneurs' platform	Industry-University relationship management	
Technology		Technology transfer		-
Money		Funding program	-	-

8.2 Functions of universities in the U.S. ecosystem.

In this subsection, we will analyze the organizations and systems which are responsible for transferring the knowledge from universities to industries in each university and cluster based on the analysis before, focusing on five functions. Then, we'll explore the key feature of each organization and system in the successful ecosystem.

(1) Organizations providing five functions

Table 45 summarizes the organizations which provide five functions mentioned above. All four universities, MIT, Harvard University, UC Berkeley and Stanford, provide more than 20 classes in a year to students including both undergraduates and graduates. MIT and UC Berkeley install major or minor course related to entrepreneur. These classes are provided not only by the business schools and also by the engineering school. Also, students have many opportunities to register classes held in other schools to which they don't belong. Thus, collaborative culture among cross-fields and the network for sharing knowledge might be fostered. In addition, universities also provide entrepreneurial education to society by online certificate courses.

The network for entrepreneurs is also formed by platforms provided by the universities' system. Each university equips a kind of entrepreneurship center which provides networking opportunities, programs, and services for entrepreneurs within a business or engineering school or as a cross-sectional organization, and sometimes a university has several centers at the same time. Establishing centers in each school seems redundant, but it possible work effective for entrepreneurs because it is sometimes a psychological barrier visiting an office in a different organization. Among the programs provided by universities, the business supporting programs, such as mentoring services legal supports, are noteworthy. This is because these supports are essential especially for young startups founded by non-experienced entrepreneurs.

Table 45 Entrepreneurship Opportunity in universities

Functions		MIT	Harvard Univrsity	UC Berkeley	Stanford Universty
Education	Classes	- 64 graduates' subjects from by busines school and other schoolds	- 50+ graduates' subjects by the business school and other schools	- 16 graduates' subjects and 5 undergraduates' subjects by the L&S Entrepreneurship Initiative and Berkeley Haas Entrepreneurship Program	- 150+ graduates' and undergraduates' subjects by the business school and other schools including d.school
	Degree	- Entrepreneurship and Innovtion Minor (undergraduate)	- Innovation and Entrepreneurship Certificate (online)	- Berkeley Management, Entrepreneurship, & Technology (M.E.T.) (undergraduate)	- Innovation and Entrepreneurship Certificate (online)
Platform	Entrepreneurs' Platform	- MIT Innovation Initiative - Martin Trust Center for MIT Entrepreneurship - Venture Mentoring Service	- Technology and Entrepreneur Center at Harvard (TECH) - Arther Rock Center for Entrepreneurship Harvard Innovation Labs	- The Berkeley Gateway to Innovation (BEGIN) - L&S Entrepreneurship Initiative - Berkeley Haas Entrepreneurship Program - Berkeley Postdoctoral Entrepreneur Program (BPEP) - Sutardja Center for Entrepreneurship & Technology - CITRIS Invention Lab - Startup@BerkeleyLaw	- Stanford Entrepreneur Network - The Entrepreneurship Center at Stanford Engineering - Center for Entrepreneurial Studies - Center for Social Innovation - Stanford Venture Studio - Startup Garage
	Biotech specific	- The MIT-HMS Healthcare Innovation Bootcamp			- SPARK program - Biodesign
	Incubatiion Faciities/ Accelerators	(Incubation facility) - MIT The Engine (Accelerator) - MIT delta v	(Incubation facility) - Harvard i-labs (Accelerator) - Launch Lab X - Phisycal Sciences & Engineering Accelerator	(Incubation facility) - SkyDeck (Accelerator) - SkyDeck - CITRIS Foundry - LAUNCH	(Incubation facility) - Start X (Accelerator) - Start X - Launchpad - Cardinal Ventures
	Biotech specific		- The Pagliuca Harvard Life Lab (Incubation facility) - Blavatnik Bomedical Accelerator	- QB3 Garage@Berkeley (Incubation facility)	- StartX/QB3 Lab (Incubation facility) - StartX Med (Accelerator)
Funding	Funding Grant	(8 programs in total) - MIT Sandbox innovation Fund Program - Deshpande Center - MIT Legatum Center	- Xfund Entrepreneurship Venture Capital Fund - Pilot Fund	- Berkeley-Haas Dean's Startup Seed Fund - CITRIS Tech for Social Good Program - Student Technology Fund	- Stanford-StartX Fund
	Prize, Competition Hackathon	- MIT $100K (6 prizes and competitions in total) - Hack MIT (6 hackathons in total)	- thePresident's Innovation Challenge - HIVE Pitch Competition - New Venture Competition	(total 7 competitions) - Big Ideas@Berkeley - Venture Capital Investment Competition - Pear's The Berkeley Challenge	- BASES (Business Association of Stanford Entrepreneurial Students) Challenge
Industry-university relationship management		- Industrial Liaison Program - Office of Resource Development - Office of Sponsored Program	- Office of Technology Development	- The Sponsored Projects Office - The Office of Foundation Relations & Corporate Philanthropy - Intellectual Property & Industry Research Alliances (IPIRA)	- Office of Technology Licensing - University Corporate and Foundation Relations - Industrial Contracts Office - Office of Sponsored Research - Office of Research Administration - Sponspred Receivables Management
Technology Transfer		- Technology Tansfer Office	- Office of Technology Development	- IPIRA	- Office of Technology Licensing

One of the famous programs which focus on biopharmaceutical technology is Stanford University's SPARK program.[79] SPARK program was established in 2006 to advance academic biomedical research discoveries into promising new treatments for patients by bridging the gap between academia and industry and especially by educating students and researchers. It provides access to specialized knowledge and technical expertise regarding drug and diagnostic development, dedicated core laboratory facilities, and source of funding to support translational efforts to participants, including professors, clinicians, postdoctoral scholars, and graduate students. This program is introduced to other countries and SPARK currently supports and partnered with 65 universities/schools in 22 countries, including 10 Japanese universities.[80]

Other instruments equipped to universities are incubating facilities and accelerators which are often specialized to biotechnology. The function of these instruments is the same as generally established in the ecosystem, but they sometimes have the restriction in the affiliation of the technology and/or companies to the university. However, SkyDeck in UC Berkeley also opens a door to whom don't have any affiliation to the university and is from abroad (Global Acceleration Program), though this program is extremely competitive (2% acceptance rate). In addition to the incubating and accelerating function, these facilities also work as a platform for networking. For example, the demo day of acceleration programs is the opportunity for appealing their business in front of the future investor or partners and the facility often organize networking events for the resident companies.

Funding is also important for entrepreneurs, especially who have just come up with the idea and need to prototype it. In these cases, not a huge grant but a small amount of money is needed. Thus, this type of funding enables them to try and error with

---

[79] https://sparkmed.stanford.edu

[80] Chiba University Hospital, Hiroshima University, Kitasato Institute, Kyoto University, Nagoya University, Oita University, Osaka University, University of Tokyo, University of Tsukuba, University of Yamanashi

their idea. Universities explored here provide this type of funding as a grant and/or a prize for a competition. MIT $100K is one of the representatives of these type of prize, it is the series of three contest organized by students and bring together students and researchers from across MIT and the Grater Boston. $100K the grand prize for the winner in MIT Launch, one of the three contests, and more than $300K in non-dilutive funding is awarded to new ventures which won the prize in three competitions.

Relationship with industry including technology transfer (licensing of patents) and exchanging or exploring of the knowledge is broad and the responding office sometimes also support entrepreneurs in universities in making business. In MIT, the office managing patent and the office managing other relationships are separated, but these two functions are managed unitedly by one administrative office in other universities. In the next section, we explore the functions required for the relationship with industries father.

Another finding is that these organizations or programs are sometimes managed by student groups, such as MIT $100K, LAUNCH, and BASES Challenge. This suggests that students learn in universities not only about entrepreneurship but also about how to support entrepreneurs.

(2) Management of relationship with industries

Even though the name and the basic function of the office which manages the interface between a university and industries look same, the actual services and the way to manage is possible to be different. Table 46 summarize the function of offices which manages the industrial relationship including the technology transfer. As a total function of offices which manages the academia-industry intermediate affairs, All university provides at least four services to a client company: 1) the navigation to a proper office in a university, 2) the navigation to a university's resource (patents and faculties/researchers), 3) the patent licensing and 4) arrange and administrate company sponsored researches. On the faculties/researcher's side, their general services are: 1) the advice on patent filing, 2) provide industry funding research opportunity, and 3) the administrative work in the corporate-sponsored research. In addition to these, some offices provide industries to connect their startups (MIT, UC Berkeley), and some offices support their researchers/faculties in starting or developing a startup company (MIT, Harvard, UC Berkeley).

Table 46 Function of industry related offices in four US universities

		providing service															
		to Industry						to researcher/entrepreneur						Other			
University	Office name	patent licencing	navigatng the university's resource	access to other resource in univ.	access to faculties, labs	access to startups	access to research, patents,	support for patent filing	acceleration /incubation	access to companies	industry funding	industry information	venture support	conference, showcase, networking	fund-raising	administrative work in collaborative research	number of officers
MIT	Industrial Liaison Program		x	x	x	x	x		x	x	x	x		x	x	x	56
	Technology Licensing Office	x			x		x	x									37
	Office of Resource Development														x		ND
	Office of Sponsored programs															x	ND
Harvard	Office of Technology Development	x			x		x	x	x		x		x				48
UC Berkele	Intellectual Property & Industry Research Alliances																4
	Industry Alliances Office							x			x		x			x	7
	Office of Technology Licensing	x			x	x	x										9
	The Sponsored Projects Office										x					x	26
	The Office of Foundation Relations & Corporate Philanthropy		x								x				x		ND
Stanford	Office of Technology Licensing	x			x		x	x									29
	Industrial Contracts Office															x	8
	University Corporate and Foundation Relations		x		x						x				x		ND
	Office of Sponsored Research															x	ND
	Office of Research Administration															x	9

Among these organizations, MIT Industrial Liaison Program (ILP) is exceptionally expanding their function. In addition to matching industries' and researchers' demand/supply, they proactively working both with MIT faculties and the client companies in order to create and strengthen mutually beneficial relationships between MIT and corporations worldwide.

ILP is the fee-paying corporate membership program that was established in 1948. They have face-to-face meetings with MIT faculties and researchers to know their research and demands and with companies also to know their needs and resource. Based on this knowledge, the officers match a faculty/researcher and a client company. Thus, the officers strongly commit not only on the client companies but also on the faculties and researchers. This also appears in the number of officers in ILP. It's larger than the numbers of other intermediate offices in four universities including MIT TLO.

(3) Opportunity for students

Universities also provide opportunities involved in the industrial R&D to students. For example, in MIT, some classes assign students to work with a sponsoring company and to create products or business plan as the class project. In this type of class, there are typically mentors who bridge or interpret students and industry in addition to the mentors from a company.

In addition to the opportunities provided by universities, students' extra curriculum activities play some roles in universities. There are many student clubs or organizations related to entrepreneurship and startups and some of them focus on biotech and/or healthcare. Table 47 is the list of student clubs in four universities. Some clubs are affiliated to the specific school (especially to the business school), but there also clubs open to all students (and affiliated people) in a university.

The purpose of these clubs is mainly in bridging the gap between the academic research and business side and provide networking events, seminars, lectures, and conferences. They sometimes actual support programs to entrepreneurs, such as accelerator programs. These opportunities not only work as recruiting opportunities but also develop skills for supporting entrepreneurs. In addition, most of them are sponsored not only by the university but also by specific companies related to the biotech industry including big pharmaceutical companies, VCs and startups. Therefore, these clubs also work as the platform for networking and connecting people in academia and industry.

Table 47 List of student clubs

University	Club	affiliation to the specific school
MIT	MIT Biotech Club	
	MIT Sloan Healthcare Club	the business school
	18+ student clubs related to entrepreneurship	
Harvard	Harvard Biotech Club	
	Healthcare Club	the business school
	At least 2 student clubs related to entrepreneurship	
UC Berkley	Biomedical Engineering Society	undergraduates
	Phoenix Consulting Group	
	HAAS Healthcare Association	the business school
	20+ student clubs related to entrepreneurship	
Stanford	Stanford Biotechnology Club	graduate students
	Stanford GSB Health Care Club	the business school
	14+ student clubs related to entrepreneurship	

(4) Key features of universities in the ecosystem

The fundamental functions of universities are educating students and generate new knowledge. In addition to these functions, the universities play following roles in the startup ecosystem as following;

- Entrepreneurship education
- Contact window for researchers to industries
- Contact window for industries to researchers
- Platform for networking and exchanging knowledge
- Platform for supporting entrepreneurs

These functions result in lowering the barrier for starting a company (show entrepreneurship) and the risk of failure for entrepreneurs and also in giving industries the opportunity to immerse and engage in universities. In addition, academic researchers become to know and understand how industrial research is and where is the opportunity for business through these connections. As a result, the gap between academia and industries are filled-in by collaborative research, knowledge exchange, human resource exchange, and startups.

8.3 Performance of Japanese universities in the ecosystem

In this subsection, we will analyze the comparable organizations and systems which we analyzed above in Japanese universities.

(1) Overview of the system of Japanese universities in the ecosystem

Organizations manage entrepreneurial activity and academia-industry intersections are listed in Table 48 based on the five functions we discussed above.

Three national universities, University of Tokyo, Kyoto University, and Osaka University, have a similar organizational structure, that is the office of industry-academia (-government) collaboration manages the most of affairs related to the academia-industry relationship. It offers entrepreneurship classes or students and/or programs for entrepreneurs, incubation facilities, administrative processes in technology transfer and supports for researchers/faculties in patent filing and starting company. The universities equip the affiliated venture capital and sometimes their technology licensing offices are also managed by the affiliated organization.

Keio University, the private school, have a little different structure because it has several campuses and their campuses are more independent, but the basic is the same. There is the headquarters of academia-industry relationship (Office for Open Innovation), the VC (Keio Innovation Initiative and SFC Forum) and TLO (Section for Intellectual Property).

Table 48 Entrepreneurship opportunities in Japanese universities

		University of Tokyo	Keio University	Kyoto University	Osaka University
Entrepreneurship education		- 5 classes by Entreprenurship Dojo (undergrads, engineering school)	- 7 classes in the business school and engineering school - Entrepreneur Laboratory (Sytem Design Management)	- 4 classes by Office of Society Academia Collaboration for Innovation - 1 class in the business school	- 2 classes for graduates by Co-Creation Bureau
Platform	**Entrepreneurs platform**	- Divison of University Corporate Relations - Innovation Platform for The Uniersity of Tokyo	- Office for Open Innovation	- Office of Society Academia Collaboration forInnovation - Kyoto University Original Co.,	- Co-Creation breau - Osaka Univ. Innovators Club - Strategic Grobal Partnership & Cross-Innovation Intiative, Medical School
	incubation facilities	- 5 incubation facilities including biology labortoy equipment.	- Keio Fuisawa Innovation Village	- KUViC	- 2 innovation facilities
	Acceleration program	- Todai IPC 1stRound		- Kyoto University Venture Incubation and Capital Investment	
Funding	**Venture Capital**	- The University f Tokyo Edge Capital - Innovation Platform for The University of Tokyo	- Keio Innovation Initiative - SFC Forum	- Kyoto University Innovation Capital - Kyoto University Venture Incubation and Capital Investment	- Osaka University Venture Capital
	Funding Grant	- Utokyo Gap fund program	- Subsidies for entrepreneur	- GAP fund	- Osaka Univ. Innovation Bridge Grant
	Prize	UTokyo 1000k			
Industry-university relationship management		- Office of Innovation and Entrepreneurship, Divison of University Corporate Relations - Innovation Platform for The University of Tokyo	- Office for Open Innovation - Headquaters for Research Coordination and Administration - Research administration office of each school	- Office of Society Academia Collaboration for Innovation (SACI)	- Office for Industry-Uniersity, Co-Creation Bureau
Technology Transfer Office		- Todai TLO - Office of Intellectual Property, Divison of University Corporate Relations	- Section for Intellectual Property, Headquaters for Research Coordination and Administration	- Office of Society Academia Collaboration for Innovation (SACI) - Kansai Technology Licensing Ortanization	- Technology Transfer Division, Co-Creation Bureau - Medical/Health Intellectual Property Strategy Office, Strategic Grobal Partnership & Cross-Innovation Initiative - Intellectual Property Strategy Team, Research Support Department, The Center of Medical Innovation and Translational Reserch

In all four cases, almost all the activity related to entrepreneurial activities and industry-academia collaborations is organized belong to the headquarters of industry-academia(-government) relationships. They also manage the incubation facilities in the campus. VCs and TLOs are sometimes managed by affiliated organizations which closely work with the universities' headquarters because they require a different type of skill which doesn't exist general administration office within universities.

Entrepreneurial educations are also controlled mainly by the headquarters (and sometimes with the engineering school), not by the business school. This is partly because some university (University of Tokyo and Osaka University) don't have the business school and partly because of the difficulty in cross-registration of classes beyond schools and departments. However, there are several crowned class or organization sponsored by companies. In this case, classes or research meet the requirement from the sponsoring company.

In addition to the organizations established in the universities, there are some students' organizations related to entrepreneurship. Table 49 is the list of major student's organization related to entrepreneurial activities. Not focusing on the biotech industry, but they organize the networking opportunity, the business contests, and the education programs. TNK, The University of Tokyo's Entrepreneurs Society, open to other universities, significantly contribute to entrepreneurial activities among students. More than 50 startups are established by students or graduates who have been a member of TNK, and some of them successfully exist their business (IPO or M&A).[86]

Table 49 Student organization related to entrepreneurial activity in Japanese universities

University	Name of organization
University of Tokyo	TNK, The University of Tokyo's Entrepreneurs Society[81]
Keio University	Keio Business Club (KBC)[82]
Kyoto University	Techno Plat Executive committee (TPEC)[83]
Osaka University	-

Overall, though the scale of entrepreneurial opportunities is less in Japanese universities than in the U.S.'s, most of the organizations are covered in Japanese universities. We'll explore the activity of these organization in the following part.

(2) Management of relationship with industries

Table 50 summarize the function of offices which manages the industrial relationship including the technology transfer. The basic functions are executed a certain office in a university, same as in the U.S. Different from the universities in the U.S., the administrative office in each department plays a role in the industry-academia collaboration especially in administrative works (i.e. contract). In addition, because of the systematic and centralized operation in the academia-industry(-government) collaboration, these offices have a function in supporting startups which are limited in the industry-academia related offices in US universities. (In the U.S., this function is covered by other offices or organizations.)

[81] http://www.venture-tnk.com
[82] http://circle-square.sfc.keio.ac.jp/kbc
[83] https://tpeckyoto.wixsite.com/tpec

Table 50 Function of industry related offices in four Japanese universities

University	Office name	providing service															number of officers
		to Industry						to researcher/entrepreneur						Other			
		patent licencing	navigating the university's resource	access to other resource in univ.	access to faculties, labs	access to startups	access to research, patents,	support for patent filing	acceleration /incubation	access to companies	industry funding	industry information	venture support	conference, showcase, networking	fund-raising	administrative work in collaborative research	
Univeiristy of Tokyo	Division of University Corporate Relations																ND
	Office of Innovation and Entrepreneurship, Divison of University Corporate Relations				x		x	x	x				x	x			14
	Office of Intellectual Property, Divison of University Corporate Relations								x								ND
	Administrative office in each depertment				x						x					x	ND
	Innovation Platform for The University of Tokyo					x			x	x			x				6
	Todai TLO	x			x		x	x									28
Keio University	Office for Open Innovation	x						x	x				x				ND
	Headquaters for Research Coordination and Administration		x														ND
	Section for Intellectual Property	x					x	x		x	x		x			x	ND
	Administration office of each school				x											x	ND
Kyoto University	Office of Society Academia Collaboration for Innovation (SACI)				x			x	x	x	x		x				ND
	Kansai Technology Licensing Ortanization	x					x	x		x							ND
Osaka University	Co-Creation Bereau																ND
	Office for Industry-Uniersity		x		x		x			x	x						6
	Technology Transfer Division	x						x									14
	Strategic Grobal Partnership & Cross-Innovation Initiative (Medical School)																ND
	Medical/Health Intellectual Property Strategy Office													x			10
	Intellectual Property Strategy Team, Research Support Department							x									1

Among there organization Innovation Platform for The University of Tokyo, Co. (U Tokyo IPC)[84], which is founded in 2016, has a unique function in the ecosystem. They equip most of the service needed by startups, such as funding, incubation and acceleration and matching up with companies. The University of Tokyo Edge Capital (UTEC) also works as the VC affiliated to U-Tokyo, but U-Tokyo IPC additional supporting programs other than funding. In their acceleration program, startups admitted are provided funding, partnership with companies, services required for operating business, networking opportunity with other entrepreneurs, companies and faculties/researchers and office spaces. These supports make maximum use of the resource which can be obtained by the strong affiliation to the University of Tokyo and its community. In addition, they also support companies which need innovation

[84] https://www.utokyo-ipc.co.jp/en/

and seek the new business by supporting their innovative business and provide the industry to match up with portfolio startups. Through these activities, U-Tokyo IPC aims to expand the innovation ecosystem in the University of Tokyo.

(3) Funding to entrepreneurs and startups

As shown in Table 48, all four universities here affiliate with their venture capitals. The VCs of three national universities fund startups also in seed stage, even before establishing a company based on the purpose of the VCs funded by the national program. In addition, these university affiliated VCs mostly invest in the startups which utilize the result of R&D in the university.

Other than VCs, some universities also have the small fund (the gap fund) which supports the seed stage startups to fill the gap between the academic research funded by the government grant and the stage where they are funded by private venture capital firms. For example, the gap fund is provided by all these four universities. In addition, this stage is supported by the acceleration program and prize money, such as U-Tokyo 1000k prize. However, the number of competition and prize which awards small size of capitals as a winner's reward is limited in the universities. Only the U-Tokyo 1000k is the one among these 4 universities. The small number of competitions means the startups don't have an opportunity not only which receive small rewards but also which talk their idea to many possible business partners.

8.4 Comparison of functions of universities in the U.S. and Japan

In this subsection, we will compare and analyze the entrepreneurship opportunities and the system of industry-academia collaboration in the U.S. and Japanese universities.

(1) Comparison of the system's structure

In the aspect of organizations, universities both in the U.S. and Japan equip enough offices which cover the functions required for supporting the startup ecosystem from universities' side. However, the structure of organizations is quite limited. In the U.S., many offices are redundantly and independently existing but collaborate with each other in need. On the other hand, Japanese universities have well organized system which the headquarters of industry-academia(-government) collaboration manages the offices which cover each function required for supporting ecosystem, such as collaborative research, incubation, and acceleration of startups, the technology transfer, and supporting researchers in a patent filing. Also, they collaborate with other affiliated companies, VCs and TLOs.

The well-organized system in Japan is mainly a result of government policy. In addition, this system includes both functions required for supporting industry-academia collaboration and for supporting startups. These two pathways in transferring knowledge from university to industry are important for knowledge-based technology, especially biotechnology. Thus, fundamentally the system is reasonable for supporting the knowledge transfer.

Also, this difference in redundancy vs systematic structure also appears in the funding system to entrepreneurs/startups. The redundancy in the U.S. may give entrepreneurs and startups many opportunities and choice. On the other hand, entrepreneurs and startups don't need to wonder where to access in Japan because its system is clear and easy to understand.

The entrepreneurship education system is different in the two nations. In the U.S., the classes are opened in many departments and some of them are organized by the business schools. Students are able to register classes held by not only the department where one belongs but also other departments and schools. On the other hands, in Japanese universities, most of the classes are organized by the part of the industry-academia(-government) collaboration office or the affiliated office of these offices, thus classes are usually organized by a certain school or department unless business school. Part of this reason is that it is difficult to register officially these classes for students unless the cross-sectional office offers and because some universities don't have the business school. This difference in the education system might affect the immersion and accessibility of classes to the students.

In addition to classes, students in the U.S. have more opportunities to join the ecosystem. Students clubs and projects provide students to work with stakeholders in the ecosystem and students sometimes work as one of the stakeholders, such as entrepreneurs and supporters. Thus, students can learn entrepreneurship not only in classes but also in the actual situation. On the other hand, these opportunities are quite limited in Japanese universities partly because the activity of students' clubs are low.

Of course, these differences mentioned above are derived from the mass of entrepreneurs, startups and surrounding organizations. Therefore, we'll analyze the differences quantitatively in the next.

(2) Quantitative comparison of the system

To compare the system of entrepreneurial opportunities, we firstly analyzed the number of researchers per industry-academia management officer and the number of entrepreneurship classes per graduate students. Table 51 shows the number of researchers per industry-academia management officers based on the numbers in Table 46 and Table 50. As we analyzed above, the range of duties for the industry-academia related administrations and technology transferring is different among universities.

Therefore, we define the industry-academia officers based on the Japanese system. That is, the officers in the industry-academia(-government) collaboration office which include the technology licensing, the patent filing, and sponsored research but not include the administrative work related to sponsored research. As Table 51 shows, there are no big difference in the average among universities in the U.S. and Japan, rather the availability of officers is slightly higher in Japan. University of Tokyo, Kyoto University, Osaka University show a similar number with MIT. Therefore, the supporting system for entrepreneurs looks similar in these universities in using these metrics.

Table 51 Number of researchers per industry-academia management officer by universities[85]

Universities in US

	MIT	**Harvard**	**UC Berkeley**	**Stanford**	
# of faculty (a)	1056	2480	2912	2240	
# of academic/research staff (b)	6161	2857	3286	ND	
total researcher (c = a+b)	7217	5337	6198	2240	
officers in industry-academia relations (d)	93	48	20	37	average
researcher per officer (c/d)	77.6	111.2	309.9	60.5	139.8

Universities in Japan

	U-Tokyo	**Keio**	**Kyoto**	**Osaka**	
# of faculty (a)	(10722)	(2639)	(7242)	(3249)	
# of academic/research staff (b)	ND	ND	ND	ND	
total researcher (c = a+b)	6702	3293	5087	4784	
officers in industry-academia relations (d)	57 (91)	22	67	69	average
researcher per officer (c/d)	117.6 (73.6)	149.7	75.9	69.3	103.1 (92.1)

For the availability of entrepreneurship, there is a huge difference as shown in Table 52. Not only the number of classes, but the number of classes per graduate student is one-tenth in Japanese universities compared with universities in the U.S. This means

[85] The data source is noted in Chapter 11.

that Japanese graduate students have less opportunity to feel entrepreneurship through official classes.

Table 52 Entrepreneurial classes per student by universities

Universities in US (AY2018)

	MIT	Harvard	UC Berkeley	Stanford	average
# of classes (a)	64	50	16	150	
# of graduate students (b)	6972	13551	11501	9437	
availability (a/b)	0.0092	0.0037	0.0014	0.0159	0.0075

Universities in Japan (AY2018)

	U-Tokyo	Keio	Kyoto	Osaka	average
# of classes (a)	5	7	5	2	
# of graduate students (b)	12796	5783	8573	8054	
availability (a/b)	0.00039	0.00121	0.00058	0.00025	0.00061

In addition to the entrepreneurial education and environment mentioned above, there is a limited number of competition and prizes in Japanese universities, though there are non-university affiliated competitions. Competition is a type of showcase of entrepreneurs and role models. Limited activity of students' clubs and organization also affects the environment (Table 47 and Table 49). Therefore, Japanese graduate students don't have enough opportunities to be involved in entrepreneurship and to have a network with startups/industries in order to be the same as the graduate students in the U.S.

(3) Qualitative comparison of the system

Above section mentions the system of supporting entrepreneurs are not different in the U.S. and Japan in the number. Thus, the next question is the quality of the system.

The analysis above suggests that there is no big difference in the availability of the industry-academia collaboration office in the universities. However, the action of these offices might cause the difference of entrepreneurship and/or the activity of industry-collaboration in the universities.

Most of the offices equip the contact window for industries and faculties/researchers and the professionals who have some specialty in the industry. Thus, the quality which we should compare is the type of activity imposed upon officers. From the description on each website or brochure, we find the Industry Liaison Program (ILP) in MIT has unique activity among these.

ILP is established in 1948 and work to create and strengthen a mutually beneficial relationship between MIT and corporations.[86] The program is fee-paying corporate membership and more than 200 of the world's leading companies partner with ILP in 2015. ILP has a unique system for accomplishing its purpose. Each officer is assigned to the liaison to a company and faculty in the area of his/her technical backgrounds.

As a company liaison, an officer creates a company's action plan based on the discussion and the deep understanding of its interest and needs with his/her knowledge and understanding of the industry area. At the same time, as a faculty liaison, an officer works proactively on understanding the research in MIT and often have meetings with faculty and research for that purpose. As a result, officers can provide more tailor-made service with a deep understanding of the interest area and also the faculties are educated on how to work with industry and the possibility of their research in the industry. In addition, ILP provides some incentives for faculties to participate in the activity of ILP's program for partner companies, such as research funding.[87]

The tailor-made type of supports to companies are also equipped in other universities, not as an independent organization's function but as a part of a program offered by

[86] http://ilp.mit.edu
[87] MIT ILP Guide for Faculty and Staff

offices. For example, the University of Tokyo has started a similar program as MIT ILP, called Proprius 21 in 2004.[88] Like MIT's ILP program, a program officer coordinates the tailor-made support to a company, for example supporting to find a partner, to find new technology and to collect and analyze the information and program based on the company's strategy. This program has started firstly to increase the collaborative research with much bigger budget because the funding size of a sponsored project is small in Japan even though companies fund much more budget on the sponsored project with universities in the U.S. or Europe.[89] After its start, the program produced many successful collaborative researches and it is still continued as "Proprius 21 Plus".

Though ILP's activity functions as educating faculties and researchers and Proprius 21 doesn't, the example of ILP in MIT and Proprius 21 in the University of Tokyo gives us the idea that the collaborative or sponsored research sometimes started in the stage that a company doesn't have concrete image of a project. Thus, the support of officers who know well both about the university's resource and the company's need enables to connect a certain company to a certain faculty and to start the collaborative or sponsored research.

However, the strategic immersion to faculties is not mentioned in other universities' organization. This might affect the attitude of faculties/researchers in a university in facing or seeking the opportunity in the industry. First is because that the face-to-face meeting between ILP's officer and a faculty notice a faculty an unaware possibility of his/her research in industries, though the excavation of the technological seed within a university is possible by searching the directory of faculties and researchers. Another reason is that an officer can obtain the newest information or on-going idea which are not available from the published information by the face-to-face meeting.

[88] https://www.ducr.u-tokyo.ac.jp/organization/history.html
[89] https://www.jreast.co.jp/development/tech/pdf_19/Tech-19-02-09.pdf

In addition to the quality of activity provided by universities, the quality of student activity might different. For the activities of the students' clubs in four US universities, industries usually sponsor them and connected to students. For example, MIT Biotech Group is sponsored not only by the departments and centers in MIT but also by Mass Bio and consulting companies. They organize events which provide students opportunities to meet entrepreneurs and peoples in VCs, pharmaceutical companies and consulting firms, such as networking events and career fairs. In addition, they also organize the lecture series to learn how to develop drugs, thus actual business, from the view of startups, VCs, and pharmaceutical companies. Harvard Biotech Club is also sponsored by many private companies including pharmaceutical companies and organize events including lecture series and career fairs. Therefore, the activity of these clubs is well connected to industries and provide the opportunity to learn entrepreneurship and business and create own network in biopharmaceutical industries.

On the other hand, Japanese students' clubs are isolated from industries compared with students' clubs in MIT and Harvard. For example, their activity is rarely sponsored by a specific company. In addition, there is less opportunity in networking with entrepreneurs and people working in a industry. Overall, the gap between students and the ecosystem is not filled in by these activities.

The difference in the quality of students' activity is mainly derived from the cultural aspect, students are generally less active in extra-curricular activities and industries are less active in sponsoring students' activities in Japan. In addition, the recruiting activity is strictly restricted by the Business Federation and the rule makes people hesitate to have opportunities which might be suspected as recruiting activity. As a result, companies don't have an incentive in sponsoring students' activities.

(4) Conclusion

Universities provide entrepreneurial opportunity through classes and offices managing industry-academia(-government) collaboration. This system is almost the same in the U.S. and Japan, but the quantity and quality are different.

The type of offices and the numbers of officers per faculties are similar among the universities, though the whole structure of offices is different. Japanese universities have well organized structure and it enables them to provide their faculties and students strategic opportunities for entrepreneurial activities and collaboration with industries. The structure of offices in the U.S. is less structure and related offices exist separately, but they collaborate with each other. The independence of offices in the U.S. might contribute to develop their role farther and to make more effective services for faculties, researchers and entrepreneurs. In the case of Japan, most of the activities are part of the organization, the industry-academia(-government) collaboration office, thus the allocation of resources and decision making for each program might become less weighted by the head of the office.

Most of the offices work with faculties/researchers based on appointment, thus wait for the action from faculties/researcher and companies, but ILP office in MIT works more proactively. The officers not only work with companies with a understanding of what they need but also understand and educate faculties/researchers for collaborative opportunities. The University of Tokyo runs a similar program, Proprius 21 (now called Proprius 21 Plus), in the sense of deeper understanding of the client's needs. However, it has not gotten the point where the officers educate faculties and researchers. The case of ILP in MIT suggests the possibility that the university's office can change the mind of faculties and researchers through its activity.

Education is another system where the universities can provide an entrepreneurial opportunity. In the four universities in the U.S., there are plenty of opportunities for students learning entrepreneurship through classes regardless of which department a student belongs. This is not only because of the number of classes but because of the department which open the classes and the system enables the cross-registration beyond schools and departments. On the contrary, Japanese students only have one-tenth of opportunities in the number of classes. In addition, the classes are generally operated by the office of industry-academia collaboration office or a certain department, and the registration system itself makes it difficult for students to register classes managed by other departments. Also, the lack or isolation of the business school also contribute to this tendency because the business school is weight is big in the U.S. universities.

In addition, the entrepreneurial opportunity is also provided by student groups in the U.S.. Not only the number of entrepreneurship related student activities, but also the quality, i.e. the connectivity to entrepreneurs and industries, is abundant. This is partly because there are plenty of graduates who work for startups or entrepreneurial activities, such as VCs. However, the entrepreneurial student activity and their achievement have become gathering attention also in Japan, though the total number of activities is still limited.

9. Discussion for Policy Implementation

In this section, findings in previous sections are firstly summarized. In the next, the advantages and challenges of Japanese biotech startup ecosystem will be explored. Then, the policy recommendation for developing the ecosystem is discussed. Finally, we discuss research questions and future works.

9.1 Findings from the stakeholders and its network analysis

In this subsection, major findings from Chapter 7 which compared stakeholders and their network in the biotech startup ecosystem are summarized and discussed.

(1) Structure and feature of stakeholders

As defined in Chapter 5, there are 6 major stakeholders in the biotech startup ecosystem; Government, University, Corporate, Risk capital, Entrepreneurs, and Supporters. We analyzed each stakeholder in 2 clusters in the U.S. (Boston/Cambridge and San Francisco Bay Area) and 2 clusters in Japan (Tokyo (Kanto) and Kyoto (Kinki)).

The results of our analysis suggest that all 6 stakeholders are completed in all 4 clusters we examined here and the structure of stakeholder's networks are also not different. However, the quantity and quality of stakeholders are significantly different in the case of the U.S. and Japan. We suppose that this is partly because of the development stage of the startup ecosystem. Thus, realize differences and implementing proper action are important for the future development of the biotech startup ecosystem in Japan.

The first difference is the size of R&D budget from the governments and in pharmaceutical companies, not in the percent of GPD, but in the face value. The difference of its size might correlate with the size of the project and the possible impact of the results of research, thus the amount of generated knowledge. The biotech industry is highly costing industry and depends on knowledge spillover from academia, thus this tendency might be enhanced by the feature of industry field.

The number of startups (entrepreneurs) and the size of risk capital are also small in Japan compared with the U.S. The relationship of these two is demand and supply, thus it is possible that the small amount of the risk capital is caused by the limited number of startups. However, the data suggest that the size of investment per deal is smaller in Japan than in the U.S. This tendency might affect negatively to the number of startups and entrepreneurs in addition to the cultural refrains from risk in Japan.

Supporters are important for efficient development of startups and entrepreneurs. The U.S. clusters are the origin of hands-on VCs, incubators, and accelerators, and equips a big network of involving people, i.e. stakeholders. On the other hands, these supporting system and network are not enough in Japan and the network might be small, though many incubation and acceleration programs and forming of stakeholders' associations have just boosted recently.

In the aspect of quality, there are several differences. For example, the percentage of the biotech startup's CEO who has a Ph.D. or MD or MBA or having experience working in a pharmaceutical company lower in Japan than the U.S. The same situation supposed to happen in VCs especially if VC is a CVC of a non-pharmaceutical company. In addition, skills and knowledge in entrepreneurs supposed to be not enough in Japan because there are not enough education opportunity and the network of entrepreneurs.

In addition, expertise in the biotech industry or biotech startups is not well accumulated in the supporters in Japan. This is partly because the Japanese ecosystem is developing stage and everyone doesn't have enough experience in this area, and because experienced people in this field typically belongs to pharmaceutical companies. For example, a man who knows drug development and IP strategy in the field is in a pharmaceutical company and rarely in a law firm or a patent firm. In the case of the U.S., the high mobility of human resources in the ecosystem and the demand from startups seem to increase the accumulation of required expertise.

The analysis also suggests the difference in the quality of universities in the aspect of contribution to the startup ecosystem. Though the strength in academic research in Japan is not far behind from the U.S., Japanese universities have some difficulty in transferring knowledge to industry. Details will be discussed in the next subsection.

Despite these disadvantages in the Japanese biotech startup ecosystem, one good point is the strong push on medical research and startup business including the supply of risk capital from the national government. Some local cities already have started trying to foster a biotech startup ecosystem with the maximum usage of this government policy. Looking back the case of Boston/Cambridge cluster, the policy of Massachusetts state supposed to contribute in accumulating industries and forming ecosystem on the top of existing excellent universities. Thus, how the local governments' make maximum use of the national government's policy (funding, tax incentives, and other special supports) and figure out the best policy to form the biotech startup ecosystem with considering their existing resources, such as universities and industries, is quite important.

(2) Network of stakeholders

The basic network of stakeholders is also not different in all 4 clusters as shown in Figure 19. However, the connection among stakeholders are weak in Japan (Figure 20 and Figure 21). This is because of weakness in knowledge transfer among stakeholders both on human resource mobility and network effect (word of mouth).

Compared with the U.S., Japanese human resource market's mobility is low and traditionally life-long employment is the standard in major companies including pharmaceutical companies. In addition, it is rare that academic researchers move out from academia to industry as a researcher or non-researching position especially when one stays in academia several years after he/she finished a Ph.D. degree. In addition, the small number of university spin-off startup suggests that the creation of startups by researchers and faculties are also rare, though the total number of cases have been increasing and successful cases appear, such as Pepti Dream.

In addition to knowledge transfer depending on human resource mobility, knowledge transfer depending on word of mouth is also less in Japan. This is partly because of the weak connection among the people who belong to different organizations and because of the limited opportunity to meet people who belong to different opportunities. Of course, there might be a mental hurdle and cultural custom to work with other organizations especially in universities.

Geographical condition might need to consider in discussing the networking among people. In Boston/Cambridge cluster, universities, startups, VCs and pharmaceutical companies located within walkable distance. This proximity lowers the hurdle to meet or join events held in other entities and enables accidental encounter around the area. However, the proximity might not be essential because the distance among stakeholders in San Francisco is not such proximity as Boston/Cambridge. The distance of Tokyo ~ Tsukuba or Kyoto ~ Osaka cluster is almost the same as Stanford ~ UC Berkeley. Thus, the opportunity for establishing a network, such as meet-up events and personal introductions, might be much more important.

In that sense, events ,where many stakeholders get together, are important to make new connection among them. As mentioned above, the importance of the association was mentioned in Porter, 1998.[21] In addition, this kind of events are organized not only by the stakeholders' association but also by each stakeholder in the U.S. clusters. However, in Japan, events held by a stakeholder are sometimes inner events and other stakeholders are difficult to join, though LINK-J and VCs have been started to operate the U.S. style events mainly in Tokyo. Possibility of encountering a person and resulting in the formation of network partly depends on the number of such mixers. Thus, increasing of events, incubation facilities and acceleration programs will contribute to establishing the network for entrepreneurs in Japan. Thus, the formation of the network can be improved soon for developing the ecosystem in Japan.

(3) Key stakeholders and their features in developing the ecosystem,

Understanding how each stakeholder contributes to the ecosystem results in the understanding of the priority in stakeholders in developing the ecosystem to implement the policy. Also, which stakeholder should be the best leader for developing the ecosystem is an interesting question for who try to implement the policy.

Budden and Murray (2019) concluded that universities are the ideal leaders in developing regional innovation ecosystem and found that entrepreneurs, risk capital and government(s) lead innovation ecosystem development in some cases. They also found that a single stakeholder often leads in the early stages and government and other stakeholders might lead jointly at other times. Thus, the development stage of the ecosystem and the key stakeholder(s) have some dependency.[9]

The comparison of Boston/Cambridge cluster and Bay Area cluster suggests that the push, that is the settlement of incentives, from state governments is not essential for establishing the ecosystem because California states policy does not focus on biotech and pharmaceutical industry, though R&D facility of top pharmaceutical companies and the risk money from VCs are accumulated to these clusters. In the case of Massachusetts, the state government established the Life Science Initiative in 1998, but the accumulation of stakeholders already started in the early 80s when Biogen opened their R&D facilities next to MIT. The common points of these two clusters are that both areas are benefitted from the government's policy including Bayh-Dole Act., grants from the federal agencies, such as NIH, NSF and DOE, and SIBR program.

Thus, the effects of the federal government's policy can't be ignored. These cases in the U.S. suggest that the incentive to industry for accumulation can be given not only by the government but also by the government.

Therefore, creation and creator of incentives are important in developing the ecosystem. In the case of the U.S., initial incentives for the accumulation of industry (risk capitals and corporations) were given by universities which have a huge amount of knowledge, technology and human resources including who equips entrepreneurship.

In the case of Japan, incentives from the governments have already implemented, though whether the degree and amount are enough is a discussing point. Large corporates locate their business and development office in the cluster, thought R&D facilities are located a little bit far from the center of the clusters. Risk capitals have been increasing and pharmaceutical companies have been interested in investing in startups and collaborating with universities, though the amount is far smaller than in the U.S. Then, how about universities and entrepreneurs? There are knowledge and human resource in the aspect of science and technology or academic research in Japan. However, the low entrepreneurship and weakness in bridging academia and industries might be the challenge in developing the ecosystem. This means that the incentives for the accumulation of industry including risk capital is not provided enough from universities in Japan.

These challenges have already been mentioned by many stakeholders, and the national government and universities have been trying to overcome the challenges by implementing policy instruments and programs. The current approach and improvements for the future ecosystem will be discussed in the next subsection.

9.2 Functions of a university in a biotech startup ecosystem

In this subsection, major findings from Chapter 8 which analyzed and compared the functions of universities in the biotech startup ecosystem are summarized and discussed.

(1) Overview of the U.S. universities and Japanese universities in the ecosystem

As mentioned in the previous subsection, universities are the ideal leader for developing a regional ecosystem.[9] In the case of the U.S. ecosystem, universities play well in generating new knowledge and human resource and conducts to industry via various channels. The four universities work as the platform for entrepreneurs and startups and bridge academia (including spin-off startups) and industry sometimes in a tailor-made manner. Even though the academic researcher's priority is still publishing academic papers to top journals, many researchers collaborate with companies and work as the advisor for companies including startups and VCs. In addition, these universities publish many articles in the top journals at the same time.

However, there still are huge gaps among universities, industries, and startups in Japan. In the academic side, this is because the reputation for doing both academic research and business at the same time is low and focusing on academic research is encouraged culturally. Thus, there are policy instruments to promote academia-industry collaboration, the progress is slow. Also, the reputation for entrepreneurs is still low as the whole society, though young people's opinion is slightly different.

In Chapter 8 and here, we analyzed and discuss the function of universities in the ecosystem, to explore what causes such a difference mentioned above.

(2) Systems incorporated in a university as a part of the ecosystem

In addition to generating new knowledge and technology, the functions of universities in the startup ecosystem are entrepreneurship education, contact window for researchers to industries, contact window for industries to researchers (a university's resource), and the platform for networking and exchanging knowledge among stakeholders. These fruits are received by all entities in the ecosystem, such as startups, large companies, and VCs.

To implement these functions, each university equips organizations and systems which execute and support required functions. The type of organizations and systems are categorized to five; 1) Entrepreneurship education system, 2) Entrepreneurs' platform (network and support), 3) Technology transfer to industry, 4) Funding opportunity and 5) Industry-university relationship management.

Our analysis suggests, all universities in the U.S. and Japan we analyzed here equip all these five functions and offices which implement them, though there are differences in the structure of offices.

In the case of Japanese universities, all five functions are usually organized under the office of academia-industry(-government), which is independent from any schools and departments and often belongs to the headquarters. On the other hand, each organization are usually independent and well collaborating in US universities. In addition, entrepreneurship classes are held mostly by the office of academia-industry(-government) in Japan, but by each school, such as the business school and the engineering school, in the U.S.

The difference in the organizational structure might affects the quality of their functions. The Japanese system is efficient and well organized, but the decision-making process becomes more complicated and the mission of the office becomes broader. In the case of the U.S, the independence of the offices might contribute in developing their service more precise and efficient for researchers and students with whom they work.

The difference in the education system also might cause the difference in the accessibility for students to entrepreneurship classes, in addition to the difference in the number of classes. In the case of the U.S., the entrepreneurship classes are held by each school, not only by the business school but also by the engineering school. Thus, students in these schools can take the class without cross registration. In Japan, the classes are held by the cross-sectional office, the office of academia-industry(-government), thus independent from schools and sometimes held by the business school. Thus, students in the engineering school need to cross-register. In addition, the weakness of the business school in Japan, some top universities don't have a business school.

The small number of entrepreneurship classes, the low accessibility and the lack of the business school in Japan cause the difficulty not only in developing entrepreneurship of students but also in meeting ups with entrepreneurial people each other, especially meeting with the person in the business side. For startups, a person who has the business mind or skill set is essential in the founders' group. In Japan, such talented people, who sometimes earn an MBA degree in the U.S., are in large companies and not developed in Japanese universities. Thus, developing entrepreneurship in STEM student is important, but the challenge is how to secure the business-side person for startups.

(3) Qualitative and qualitative difference of the U.S. and Japanese universities

In addition to the systematic difference between the U.S. and Japanese universities, there are quantitative and qualitative differences. The most decisive difference is the number of opportunities for students immerging to entrepreneurship. It is difficult to measure how much a student immerses to entrepreneurship, but the number of entrepreneurial classes, competitions, funding programs, and predecessor of entrepreneurs are good measures.

The number of classes, competitions and funding programs for startups or business groups are less in Japan. These points can be improved quickly, but building a network with entrepreneurial predecessor is more important and takes time. For this purpose, the critical mass of entrepreneurs and the place for everyone getting together are important. In the case of the U.S., competitions, funding programs, networking events and student groups function as such a place to meet serial entrepreneurs and learn entrepreneurship and know-hows for starting a business. In Japan, not only the number of classes and programs but also the events and students' groups. Thus, increasing these numbers contribute both for education for entrepreneurship and networking for fostering entrepreneur community.

In terms of quality of universities' organization and system, it is also suggested to be lower in Japan. For startups, Japanese universities sometimes own incubation facilities but not incubation or acceleration programs for startups, though most of the universities in the U.S. not only operate incubation facilities but also run incubation/acceleration programs. Also, each independent organization seems to provide the best service to its customers, such as companies, researchers and faculties, and startups. For example, the case of MIT's ILP is an ideal model because the officers well understand companies and faculties (MIT's resource) and execute their task with more than connecting a company and a researcher. Thus, the efficiency to accomplish the goal of each office suggested to be higher in the U.S. Of course, we need to consider the history of each office in US universities, because most of them have more than 40 years and Japanese ones are just 20 years and reorganize their organizational structure frequently.

Overall, the quantity is one of the challenges in Japanese universities. Increasing the number of entrepreneurship classes, competitions, funding programs, networking events and student groups function is simple and easy to implement in ignoring the budget and regulating factors. However, unless there is a critical mass of entrepreneurs and startups (or business groups), most of them become over demand

and decrease the efficiency of programs or dilute their quality. Therefore, in the case of Japan, where the number of entrepreneurs and startups are small, increasing the quality of offices and grasping latent needs of industries and latent resource of universities are more important in establishing a more tight and effective connection among industries, universities, and entrepreneurs in the ecosystem.

9.3 Advantage and challenge of Japanese biotech startup ecosystem

In this subsection, the advantage and challenge of Japanese biotech startup ecosystem will be discussed based on the analysis in previous subsections.

(1) SWOT analysis of Japanese clusters compared with the U.S.'s clusters

In order to understand the advantages and challenges of Japanese ecosystems, we executed SWOT analysis for each stakeholder and cluster in comparing with the U.S. ecosystem. Table 53 is the result for each stakeholder and Table 54 is for Japanese cluster. We will discuss based on these tables in the following part.

Table 53 SWOT analysis of stakeholders in Japanese ecosystem

Stakeholders	SWOT analysis	
Government	[Strength] - Focusing on medical R&D and startups: incentive for universities, entrepreneurs and corporate	[Opportunity] - Coordination of each policy instruments
	[Weakness] - Small budget size compared with the U.S.	[Threat] - Aging society causes shrinking of economy
University	[Strength] - Academic research quality - Increasing students' entrepreneurship - Increasing interest in collaboration	[Opportunity] - Organized system for academia-industry collaboration and entrepreneurship
	[Weakness] - Small budget size - Limited opportunity for discussing with industry - Low expertise in connecting business (weak supporting system for entrepreneurs and researchers)	[Threat] - Decreasing number of children and Ph.D. candidate

Entrepreneurs	[Strength] - Increasing of support including risk capital	[Opportunity] - Increasing demand and interest in startups
	[Weakness] - weak network and supporting system - small number of serial entrepreneurs	[Threat] - Low entrepreneurship and fear of failure
Corporate	[Strength] - Geographical priority to Japanese universities and market	[Opportunity] - Priority to access resources in Japan
	[Weakness] - Small budget size in R&D - Weaker connection with academia	[Threat] - Global competition
Risk Capital	[Strength] - Incentive from the government	[Opportunity] - Priority to access resources in Japan
	[Weakness] - Small capita size	[Threat] - Low expertise in technology - Global competition
Supporters	[Strength] - All Japan platform (LINK-J, JBA)	[Opportunity] - Increasing interest in the startup ecosystem
	[Weakness] - Low accessibility to whom has expertise	[Threat] - Not enough demands for supporting activities

Table 54 SWOT analysis for Japanese clusters

[Strength] - Support from governments (medical R&D, academia-industry collaboration, startups) - Growing entrepreneurship and growing risk money	[Opportunity] - Well organized system in universities for managing collaboration with industry and supporting startup - Closing of pharmaceutical companies' R&D facilities -> increasing of human resource mobility
[Weakness] - Weak connection among stakeholders - Immature knowledge and skill in startup business and R&D - Small budget size (the government funding, risk capital, R&D in pharmaceutical companies)	[Threat] - Global competition in academia and pharmaceutical industry - Closing of pharmaceutical companies' R&D facilities

(2) Advantage of Japanese biotech startup ecosystem

As mentioned previous parts and Table 53 and Table 54, the advantages of Japanese biotech startup ecosystem are 1) strong boost from the governments (national and local) for R&D in biotech area, the collaboration among academia and industries, and supports to startups, 2) well organized system for supporting academia-industry collaboration and startups in universities also based on the national government's policy.

The target of governments supports covers most of the stakeholders in the ecosystem. Thus, if all stakeholders in a cluster could make maximum use of the policies at the same time, the development of the ecosystem should be boosted.

The well-organized academia-industry collaboration system including the support for startups has potential to coordinate the three important stakeholders, universities, corporate and entrepreneurs, in a seamless way which might be difficult for independent offices in the U.S. universities.

The strength in the academic research and existing risk capitals can underpin the ecosystem although it is difficult to say that their capacity over the U.S.'s one. Especially, increasing of the risk capital (partly provided by the government) and the demand from big pharmaceutical companies which shift to the open innovation model in R&D from traditional in-house R&D model also works positively in future Japanese biotech startup ecosystem.

Another opportunity for the Japanese ecosystem is increasing of human resource mobility. The reason for increase is partly caused by the current tendency of the younger generation but also caused by the closure of several pharmaceutical companies' R&D facilities.[90] This closure has been generated a huge number of free talents, and some of them already founded startups.

Overall, Japan equips the system for fostering the ecosystem, thus it has the potential to develop the competitive biotech startup ecosystem in the future if all pieces combine the suitable way. Also, for entrepreneurs, there is a big opportunity, if one

[90] http://news.livedoor.com/article/detail/16105130/

has enough knowledge, skill, and supports and can make full use of the system provided by other stakeholders.

(3) Challenge of Japanese biotech startup ecosystem

Despite advantages mentioned above, there are many challenges in developing Japanese biotech startup ecosystem. As summarized in Table 53 and Table 54, the small size of the government's budgets, the risk capital, and the corporate's R&D expenditure is one of the challenges. The size of capital is another issue for the ecosystem, but solving this problem is a complicated issue though the lack of pre-seed money, such as prize, can be improved. Thus, we'll discuss the ecosystem in focusing on the quality of the ecosystem, not the quantity, in this research.

Other than the capital size, the analysis above suggests that challenges exist in the root of the ecosystem, for example, low entrepreneurship, weakness of connection among stakeholders and weakness in supporting system for startups.

Low entrepreneurship in Japanese has been pointed out by GEM reports and realized. People fear failure and the entrepreneur is not recognized as a good career choice.[73] In addition to this cultural attitude, opportunities for immersing entrepreneurship might cause low entrepreneurship. For example, even in the top universities we analyzed here, the number of entrepreneurship classes is limited, and the chance to meet the predecessors of entrepreneurs is also limited compared with the U.S. universities we analyzed. This means if we explore all universities including 2nd tier and 3rd tier universities in four clusters, the difference in opportunity between the U.S. and Japan might expand more. Entrepreneurship and entrepreneurs are the sources of startup ecosystems. Therefore, this difference could be the biggest challenge in the Japanese ecosystem.

The reason for low entrepreneurship is not only the number of entrepreneurship classes and the chance to meet entrepreneurs. The weakness of the stakeholders' network based on knowledge transfer might be another reason. For example, the distance between the academia and industries is important in finding an opportunity for business from academic research because faculties and researchers usually can't know the needs and demand of industries only by themselves. In Japan, a weak network among stakeholders caused by low human resource mobility and limited networking opportunity might result in the gap between academia and industry, though the number of collaborative researches has been increasing. In addition, this weakness affects the business of big pharmaceutical companies and VCs who need to know the cutting-edge technology in making their business decision. Thus, the weak network is another challenge for the Japanese ecosystem.

Weakness in supporting system for startups is also challenging point for Japanese clusters. This is partly because the supporting system lowers the risk of startups as mentioned above. For entrepreneurs, lowering risk is important for their business, and for the ecosystem, lowering risk is important for determining their attractiveness for stakeholders. In another aspect, high risk in startups is one of the concerning points for people in considering their job. Thus, the weakness also contributes to lower entrepreneurship and makes people hesitate to join or start a new business.

The closure of several pharmaceutical companies' R&D facilities might give a negative effect to the ecosystem. Though their facilities are far from the center of clusters, the power of development stage research which is different from academic research would decline as a whole. Thus, how we can make use of the skills of fired researchers in the ecosystem is an urgent problem.

To summarize, low entrepreneurship, weak network among stakeholders, and weak system for supporting startups are crucial challenges for developing the Japanese ecosystem.

9.4 Policy recommendations

In this subsection, we'll discuss the policy recommendations for Japan based on the findings from previous parts.

(1) Policies for overcoming the challenges in Japan

To improve the quality of the biotech startup ecosystem in Japan, overcoming the challenges are rather important than boosting the advantages. In this sense, the policies for fostering entrepreneurship, strengthening the network of stakeholders, and improving the support system for startups are required.

For fostering entrepreneurship, the official education by universities is one channel and the mutual development in the entrepreneur's network is another channel. The former channel is simple, but the latter channel is difficult to be managed by the governments' side. In addition, to lower the risk for executing entrepreneurship also could contribute to increasing the number of entrepreneurs as mentioned above. Thus, strengthen the network for entrepreneurs and stakeholders could be the solution for the latter channel.

Also, providing pre-seed money, such as prize and competition, can result in fostering entrepreneurship. As mentioned above, the limited number of such small funding which enables entrepreneurs to produce pilot research or prototype makes people hesitate to go forward because they have to apply bigger grants or funding to go next step and because this step might be a little bit harder for just a trial. Thus, increasing such pre-seed funding and chance might fill the gap between academia and startups.

Both strengthening the network of stakeholders and improving the support system for startups is how to make all stakeholders engage in the ecosystem. In the case of Japan, all stakeholders already exist somehow, thus connecting and engaging them might be effective. To realize this attitude, networking places and events are important. The examples of the U.S. clusters suggest that the stakeholder's network developed in incubation facilities, the cohort of acceleration programs, pitch events, networking events and private connections. Thus, the policy instruments for increasing this kind of programs and events can be the one option. However, considering the gap among stakeholders, such as the gap between academia and industries, a more proactive policy might be needed. In that sense, the organization like MIT's ILP can be a model for proactive bridging between industries and academic researchers by officers' effort. One of the important functions of the ecosystem is transferring the knowledge from academia to industry. Therefore, incorporating the essence of ILP's model to Japanese universities can be a policy for strengthening the relationship among universities and industries.

Incubation facilities and acceleration program occupy an important part of the support system. The number of facilities and programs seems to have been increasing along with increasing demand from startups. This is a good tendency, but the challenge is most people are less experienced in incubating startups. Thus, learning how to develop startups from an experienced people in the U.S. can be a solution for this challenge, and METI already starts "Sido Next Innovation and Hiyaku Next Enterprise" and send selected startups to Silicon Valley or other cities in the world.[91][92]

The support system also requires participation from a different type of specialties, such as lawyers and accountants. Some incubation facilities and universities' programs equip a service to support startups in the aspect of the legal and accounting issues both in the U.S. and Japan. However, the problem is after startups successfully graduate from such facilities and programs. Also, many startups are estimated not to be joining such facilities and programs because the number of them is limited. Thus, how to secure them to access such resources is an important issue. For this purpose, establishing a platform of such services, which provide services in the business side,

[91] https://sido2018.com
[92] https://www.meti.go.jp/policy/newbusiness/kakehashi/kigyo/index.html

is a possible plan to overcome the problem. Another issue for this problem is experts who have such skills and specialty are basically in big companies and not in universities and entrepreneurs can't access to them. Thus, combined with the current policy which encourages people to have second-job might boost them to participate in supporting activity to startups.

To summarize, increasing the opportunity of education for fostering entrepreneurship and establishing the platform fostering the network of entrepreneurs, supporters and other stakeholders are two key policies. In addition, changing the attitude and quality of the office at the intersection of academia and industry is also the key to developing the ecosystem.

(2) Stakeholder who can implement the policy

Another requirement for implement the policy is who should implement it. Referencing the functions of stakeholders, we analyzed above, universities can be the candidate for the implementing body for the policies. Also, they and the office of academia-industry(-government) collaboration partly equip the system we discussed above, though the function and quality are a little bit different.

Japanese universities equip the advantage in the organized system for managing the intersection between academia and industry including the support for startups and the entrepreneurial education. In addition, they have the capacity to organize entrepreneurial classes, though who can teach classes is another problem because of the weakness of the business school in Japan. The limited resource, especially the knowledge related to industry and entrepreneurship, would be the challenge for universities as the implementation body. However, the well-organized system is the advantage of Japanese universities and the implementation of these policies to that system could enhance the effect of the policies.

Another candidate is supporter, such as incubation facilities and the stakeholder's association. They could provide entrepreneurial education, though it is not the official education. They also could form and provide the network for stakeholders and the supporters. However, their challenge is how to bridge the gap between academia and industries. They could involve the academia, but the faculties and researchers who would join their network might be who are interested in the startup ecosystem and have motivations for participating in the ecosystem. Thus, they might be difficult to invoke the potential resource for industries in universities because Japanese universities and faculties are still conservative and might feel the hurdle to access to outsiders of a university.

Comparing the pros and cons for universities and supporters as the implementation body of policies, universities might be the realistic option. This is because we need to invoke the entrepreneurship of faculties and researchers and the resource for starting a business from academic society. In this sense, supporters might have difficulty in accessing such resources in universities. On the other hand, universities have an advantage in contacting with faculties, researchers and students including who doesn't have an in entrepreneurship. This enables them to invoke entrepreneurship more broadly and educate them. In addition, with the benefit in the accessibility to research resource, universities can access the root of business at the beginning and support from that stage. Thus, universities could be the better stakeholder who implements the policies we discussed above.

9.5 Insights for research questions

In this subsection, we will discuss the insights for the research questions in this study set in Chapter 2.

With our analysis and findings through this research, we approach to the questions as follows:

Q1-1: What is the key element in the ecosystem and impactful for the ecosystem?

The stakeholder network analysis suggests that the knowledge transfer via human resource mobility and word of mouth plays an important role in connecting stakeholders in the ecosystem. Comparison of the cases in Boston/Cambridge cluster and Japanese clusters suggests that university and supporter are the candidates for the platform of all stakeholders and that the formal and informal connection among startups, pharmaceutical companies, and VCs is also important. In focusing on technology transfer, the analysis showed that universities, startups and corporates are the main stakeholder in the network and that universities and startups are the supplier of the technology. Thus, in the startup ecosystem, the technology transfer pathway from a university to a corporate via startups is the core of the network.

Q1-2: What is the difference of biotech startup ecosystems in Japan and the U.S.?

We compared the stakeholders and its network in 4 clusters in the U.S. and Japan. The analysis suggests that all stakeholders are completed in all clusters, but the quantity and quality are prior in the U.S. than Japan and the connection among stakeholders are weak in Japanese clusters. For the quantity, the size of governments' budget, risk capital, and R&D investment from pharmaceutical companies are smaller in Japan, and the number of top ranked universities and pharmaceutical companies are also smaller in Japan. Also, the number of entrepreneurs are smaller estimated from the number of startups. However, because of the demand from the governments and industries, the supporting factors for startups including risk capital have been increasing recently. For the quality, the impact of Japanese academic research seems to have been declining, but still comparable with other main countries. However, specialty on biotechnology of VCs and management team of startups might be lower because of the small number of Ph.D. and/or MD and/or MBA holders in Japan.

Q1: What are the weakness and strength of the Japanese ecosystem compared with the successful ecosystem in the U.S.?

The suggestions to two sub questions and above observations reveals that the advantage of the Japanese ecosystem has a strong boost from the government and the growing market in the investment and academia-industry collaboration. Thus, if entrepreneurs or any stakeholder try to make maximum use of the existing system and funding, they have many opportunities to make it successful. On the other hand, weak network among stakeholders, especially the one depending on knowledge transfer via human resource mobility and word of mouth, is the weakness of the Japanese ecosystem. This might make entrepreneurs isolated each other or from supports of other stakeholders and increase the risk of failure.

Q2-1: What are the functions of universities in the ecosystem?

Not only generating new knowledge and human resource, universities play an important role as the intersection between academia and industries. The main two channels connect academia and industries are the collaborative research and the technology transfer via startups. The functions to support these channels are equipped to most of universities we explored here. However, MIT's case shows another function of the university. MIT's ILP office educate researchers and faculties through its activity to know the resource in MIT.

Q2-2: What are differences in universities' function and contribution in the ecosystem between the U.S. and Japan?

We analyzed universities' function in the ecosystem by exploring the system for the intersection between academia and industry in 2 each top university in 4 clusters. The functions of a university can be categorized four; 1) Entrepreneurship education system, 2) Entrepreneurs' platform, 3) Technology transfer, 4) Funding opportunity and 5) Industry-university relationship management. To implement these functions, each university equips the office for managing each function. All the universities have offices managing these five functions, but the organizational structure is quite different in the U.S. and Japan. In all Japanese cases, the offices are organized as belonging to the office of academia-industry(-government) collaboration under the HQ of universities. On contrast, each office is more independent in the U.S. universities. This difference in the independence might affect the depth of officers' work, thus quality and impact to ecosystem, and relationship with faculties and researchers.

Q2: What is the key action (s) for universities in developing the ecosystem in Japan?

Our analysis suggests that fostering entrepreneurship, strengthening the network of stakeholders, and improving the support system for startups are required for developing the startup ecosystem in Japan and that universities could be the best option to implement policies which enables these factors. Japanese universities have an advantage in well-organized administrative offices which manages the intersection between academia and industries including startup. With taking maximum advantage of the system, establishing the platform fostering the network of entrepreneurs, supporters and other stakeholders with more commitment to faculties and researchers by officers would be the key action of universities.

Q: How can we develop a biotech startup ecosystem in Japan?

The stakeholder analysis, its network analysis and universities' function in academia-industry collaboration and supporting entrepreneurs suggests that Japanese clusters and universities equip equivalent entities and functions in the biotech startup ecosystem as same as in the U.S. This suggests that Japanese clusters have a potential to develop a biotech startup ecosystem. Out research suggests that change in universities could boost the ecosystem and make the ecosystem more efficient. However, the quantitative challenge in the budget and bench strength in universities and researchers should be overcome somehow not only by improving the efficiency of the ecosystem.

9.6 Future works

In this study, we analyzed the biotech startup ecosystems in 4 clusters in the U.S. and Japan with a holistic view and focusing on the function of universities in the ecosystem and build a hypothesis for developing the ecosystem in Japan like in the U.S. In this subsection, we'll discuss the future works to understand the ecosystem precisely and to obtain more insights for policy implementation.

(1) Precise analysis of other stakeholders in the ecosystem

We analyzed the advantage and challenge of the Japanese ecosystem from the holistic view in this study, and our study focused on the mechanism of technology transfer via startups and universities as the source and platform of knowledge. During the discussion, we concluded that universities could be the best stakeholder to implement the policy to overcome the major challenges in the Japanese ecosystem. However, each stakeholder and relationships have differences and challenges compared with the U.S. ecosystem. Also, improving universities' system might give more impact to the ecosystem than others do, but the improvement of other stakeholders is also required to enhance the impact. Thus, precise analysis of other stakeholders is required to change each stakeholder for developing the ecosystem.

(2) Causal effects in analyzing the network

Our analysis showed that the set of stakeholders and their network and structure are not different in Japanese clusters from the U.S. clusters and that the relationship among stakeholders is a key for developing the ecosystem in Japan. We also explore the metrics for assessing the ecosystem, stakeholders, and relationships. Our discussions for the policy implementation was based on these numbers, the observation of stakeholders, and the assumption of causalities. To assess the rationality of this study with a more quantitative manner, the analysis of causal effects within the network and building the model would be supported.

(3) Expanding the number of analyzing clusters

We analyzed 2 developed clusters in the U.S., Boston/Cambridge and San Francisco Bay Area, and 2 target clusters in Japan, Tokyo (Kanto) and Kyoto (Kinki). However, there other biopharmaceutical clusters in the U.S. and other countries which are recognized as successful. In addition, each cluster should have some specific features which make them differentiate from others. Thus, exploring such clusters would give us more insights and models for developing the biotech startup ecosystem not only in Tokyo and Kyoto but also in other cities.

(4) Relationship with other policy fields

In this study, we focused on the policy related to innovation and academia-industry intersection. However, the actual is difficult to ignore the effect of other policies in other fields because the stakeholders in the ecosystem might have a stronger relationship with other policy fields. For example, the management of a university is strongly affected by the policy on education and universities, and the strategy of pharmaceutical companies is also impacted by healthcare and medical expenditure. The policy for keeping the competitiveness of academic research in the world cannot be ignored in considering the resource of the ecosystem. Therefore, we need to consider how the change in other policy field affects the ecosystem in developing the ecosystem and to seek the way not to cancel policies with each other.

(5) Application to other fields

The analysis and policy recommendations in this study is mainly based on the biotechnology field, though we adapted the data from whole technology area if the information only for biotechnology is not available. As mentioned above, the knowledge transfer mechanism and industry structure vary across the scientific fields and industry sectors and biotechnology is heavily knowledge dependent among fields. Thus, application to other fields might give us new insights for the ecosystem.

10. Conclusions

In this research, we studied the biotech startup ecosystems in Boston/Cambridge, San Francisco Bay Area, Tokyo (Kanto), and Kyoto (Kinki) and the system for managing the intersection with business in two universities in each area, and addressed two research questions to recommend policies for developing the biotech startup ecosystem in Japanese clusters. The first question concerns the weaknesses and strengths of the Japanese ecosystem compared with the clusters in the U.S. The second concerns the key actions for universities to develop the ecosystem in Japan. To approach these questions, we analyzed the stakeholders in those four regions and also the function of universities there. For this purpose, we set the metrics to evaluate them and analyze the features of stakeholders and their networks. Also, we analyzed the system in universities for managing the intersection of academia and industry. To further analysis for approaching the research question, we implemented the SWOT analysis on the Japanese ecosystem.

The advantages and challenges of the Japanese biotech startup ecosystems we found are summarized below:

Advantages:

(1) Strong support from the governments (national and local) for R&D in the biotech field; the collaboration among academia and industries; and the support for startups.

(2) Well-organized system in universities for supporting academia-industry collaboration and startups based on the national government's policy.

Challenges:

(1) Weak connections among stakeholders and weak supporting systems for startups.

(2) Low entrepreneurship and limited opportunities for immersion in a culture of entrepreneurship.
(3) Limitation on the capital size: the governments' budgets, the risk capital, and R&D expenditure by companies.

The policy recommendations for overcoming challenges and the key actions for universities to develop the ecosystem in Japan are summarized below:

(1) Forming a platform for stakeholders in the ecosystem.
(2) Increasing the opportunity for applying for pre-seed money.
(3) Eliciting entrepreneurship of researchers and faculties by changing the activity of the academia-industry collaboration office in universities.

In the actual implementation of the policies, the relationship with other policies cannot be ignored, as mentioned with regard to future work. Keeping and strengthening the competitiveness of academic research is essential for developing the startup ecosystem because academic research is the fundamental resource of the ecosystem - both knowledge and human resources. Thus, we also need to consider how we can keep the resource for the ecosystem in this competitive and globalized world, though the policy for fostering the strength of academic research requires long time perspective, its results are difficult to measure, and it does not directly affect the short-term economic strength.

11. Data Source

Without notion, all the data of each university is from its website.

Harvard University:	https://www.harvard.edu
Massachusetts Institute of Technology:	https://web.mit.edu
University of California, Berkeley:	https://www.berkeley.edu
Stanford University:	https://www.stanford.edu
The University of Tokyo:	https://www.u-tokyo.ac.jp/en/index.html
Keio University:	https://www.keio.ac.jp/en/
Kyoto University:	https://www.kyoto-u.ac.jp/en/
Osaka University:	https://www.osaka-u.ac.jp/en

Table 14 Location of Headquarters or Business Offices

Takeda:	https://www.takeda.com
Astellas:	https://www.astellas.com/en/
Daiichi-Sankyo:	https://www.daiichisankyo.com
Otsuka:	https://www.otsuka.co.jp/en/
Eisai:	https://www.eisai.com/index.html
Chugai Pharmaceutical:	https://www.chugai-pharm.co.jp/english/
Sumitomo Dainippon Pharma:	https://www.ds-pharma.com
Mitsubishi Tanabe Pharma:	https://www.mt-pharma.co.jp/e/
Ono Pharmaceutical:	https://www.ono.co.jp/eng/
Kyowa Hakko Kirin:	https://www.kyowa-kirin.com

Table 18 Area, GDP and population of each country and region

The U.S. data: the United States Census Bureau
https://www.census.gov/en.html

Japanese data: Statistics, Cabinet Office
https://www.esri.cao.go.jp/index-e.html

Table 19 Funding on R&D by federal/national government and local governments

The U.S. federal/state funding: Science and Engineering State Profiles, NSF
https://www.nsf.gov/statistics/states/

Japanese national funding: "Overview of the science and technology budget in FY2018 and the supplemental budget in FY2017", Cabinet Office[87]

Japanese local funding: "Survey on the budget for science and technology in prefectures", MEXT[88]

Table 20 Top 5 States awarded by NIH funding in FY2018

Awards and Funding: Research Portfolio Online Reporting, NIH https://report.nih.gov

Population: U.S. Census Bureau https://www.census.gov

Table 25 Location and the type of facilities in the clusters by top 20 companies

Pfizer:	https://www.pfizer.com
Novartis:	https://www.novartis.com
Roche:	https://www.roche.com
Merck & Co.:	https://www.merck.com
Johnson & Johnson:	https://www.jnj.com
Sanofi:	https://www.sanofi.com/en
GlaxoSmithKline:	https://www.gsk.com
AbbVie:	https://www.abbvie.com
Gilead Sciences:	https://www.gilead.com
Amgen:	https://www.amgen.com
AstraZeneca:	https://www.astrazeneca.com
Bristol-Myers Squibb:	https://www.bms.com
Eli Lilly:	https://www.lilly.com
Teva Pharmaceutical Industries:	https://www.tevapharm.com
Bayer:	https://www.bayer.com
Nov Nordisk:	https://www.novonordisk.com
Allergan:	https://www.allergan.com/home
Shire:	https://www.shire.com
Boehringer Ingelheim:	https://www.boehringer-ingelheim.com
Takeda:	https://www.takeda.com

Table 26 Location of Headquarters and R&D facilities of top 10 Japanese pharmaceutical companies

Same as Table 14.

Table 31 Number of universities, graduate students in S&E and doctorate recipients in S&E by clusters

Number of universities in US: http://www.univsearch.com/state.php

Number of graduate students, doctorate recipients in US: https://www.nsf.gov/statistics/states/

Asll the data in Japan is from School Basic Survey AY2018 (MEXT)

Table 32 Financial and administrative demographics of universities

All the data is from each university's website except ones shown below.

The number of Ph.D. recipients in the U.S.:

NSF Science & Engineering Doctorates Awards
https://www.nsf.gov/statistics/doctorates/

Table 33 Research funding by universities

Harvard, MIT, Stanford: Best college, "Highest Research and Development Funding" (data is in 2016) [91]

UC Berkeley: the university's website

Universities in Japan:

- Finance report in FY2017 of each university. The budget of R&D spending is calculated by summed up Kakenhi, the collaborative research, and the contract research.
- The amount of industry sponsored funding is from "Report on the academia-industry collaboration in universities" (2017) [74]

Table 34 Number of researchers and awards

Number of researchers:

MIT: the website of the university

Japanese universities:
"Report on the academia-industry collaboration in universities" (2017)[74]

Number of post-doctoral fellow, National Academy Membership:

"The Top American Research Universities, 2017 Annual Report"
The Center for Measuring University Performance [92]

Number of Nobel Laureate: Each university's website

Table 36 Number of patents and the total revenue from patents by universities

Universities in the U.S.:
Data in 2018 (UC Berkeley: 2017).
All are from each university's website.

Universities in Japan:
Most of the data is from each university's website, except Osaka University's patent application and the total revenue from patents of

all universities are from "Report on the academia-industry collaboration in universities" (2018)[72].

Table 38 Number of university-affiliated startups

(A) "Top Universities And Business Schools For Funded Founders," Crunchbase news, 2018.[89]
(B) "Survey on university spin-off startups and seeds for research 2017", METI[75]

Table 51 Number of researchers per industry-academia management officer by universities

Universities in the U.S.: each university's website

Universities in Japan:

Number of faculty: each university's website

Number of researchers: Institutional data from "Report on the academia-industry collaboration in universities", MEXT[72]

12. References

[1] OECD, "Main Science and Technology Indicators." [Online]. Available: https://stats.oecd.org/Index.aspx?DataSetCode=MSTI_PUB.

[2] WIPO, "WIPO IP Statistics Data Center." [Online]. Available: https://www3.wipo.int/ipstats/index.htm.

[3] MEXT, "Investment to universities and national research and development agency for promoting the research and dvelopment collaboration among academia and industries." 2013.

[4] Cornell University, INSEAD, and WIPO, "The Global Innovation Index 2018: Energizing the World with Innovation," *Ithaca, Fontainebleau, and Geneva.*, 2018.

[5] Clarivate Analytics, "Highly Cited Researchers 2018: Identifying top talent in the sciences and social sciences."

[6] Massachusetts Biotechnology Council, "2018 Industry Snapshot."

[7] "Top 10 U.S. Biopharma Clusters," *Genetic Engineering & Biotechnology News*, 2018. [Online]. Available: https://www.genengnews.com/a-lists/top-10-u-s-biopharma-clusters-6/.

[8] J. Owen-Smith and W. W. Powell, "Knowledge Networks as Channels and Conduits: The Effects of Spillovers in the Boston Biotechnology Community," *Organ. Sci.*, vol. 15, no. 1, pp. 5–21, 2004.

[9] P. Budden and F. Murray, "MIT ' s Stakeholder Framework for Building & Accelerating Innovation Ecosystems," 2019.

[10] P. Budden and F. Murray, "Kendall Square & MIT : the Innovation Ecosystems and the University," 2015.

[11] B. Aulet and F. Murray, "A Tale of Two Entrepreneurs: Understanding Differences in the Types of Entrepreneurship in the Economy," 2013.

[12] The World Bank, "Tech Startup Ecosystem in West Bank and Gaza - Findings and Recommendaitons," 2018.

[13] World Economic Forum, "The Global Competitiveness Report 2018," 2018.

[14] OECD, "OECD Science, Technology and Industry Outlook 2012," 2012.

[15] Center for Research and Development Strategy JST, "Supports for technology-based startup in the world," 2017.

[16] D. Farrell and T. Kalil, "Innovation Policy around the World: United States: A Strategy for Innovation | Issues in Science and Technology," *Issues Sci. Technol.*, vol. 26, no. 3, 2010.

[17] The White House, "Startup America," 2011. [Online]. Available: https://obamawhitehouse.archives.gov/economy/business/startup-america.

[Accessed: 31-Jan-2011].

[18] Cabinet Secretariat, "Growth Strategy 2018," 2018. .

[19] Cabinet Office, "Integrated Innovation Policy," 2018. [Online]. Available: https://www8.cao.go.jp/cstp/english/doc/integrated_main.pdf.

[20] Cabinet Secretariat, "Japan Revitalization Strategy -Japan is Back-," 2013. [Online]. Available: https://www.kantei.go.jp/jp/singi/keizaisaisei/pdf/en_saikou_jpn_hon.pdf.

[21] M. E. Porter, "Clusters and the New Economics of Competition," *Harv. Bus. Rev.*, no. November-December, 1998.

[22] M. E. Porter, "Location, Competition, and Economic Development: Local Clusters in a Global Economy," *Econ. Dev. Q.*, vol. 14, no. 1, pp. 15–34, Feb. 2000.

[23] "Top 10 Asia Biopharma Clusters," *Genetic Engineering & Biotechnology News*, 2018. .

[24] "Top 10 European Biopharma Clusters," *Genetic Engineering & Biotechnology News*, 2018. .

[25] L. G. Zucker, M. R. Darby, and M. B. Brewer, "Intellectual Human Capital and the birth of US . Biotechnology Enterprises," *Am. Econ. eview*, vol. 88, no. 1, pp. 290–306, 1998.

[26] W. W. Powell, K. W. Koput, J. I. Bowie, and L. Smith-Doerr, "The spatial clustering of science and capital: Accounting for biotech firm - Venture capital relationships," *Reg. Stud.*, vol. 36, no. 3, pp. 291–305, 2002.

[27] L. Leydesdorff and H. Etzkowitz, "Emergence of a Triple Helix of - Government Relations," vol. 23, pp. 279–286, 1996.

[28] P. Budden and F. Murray, "A systematic MIT approach for assessing 'innovation-driven entrepreneurship' in ecosystems (iEcosystems)," 2019.

[29] OECD, "University-Industry Collaboration: New Evidence and Policy Options," 2019.

[30] D. Schartinger and C. Rammer, "Knowledge interactions between universities and industry in Austria: sectoral patterns and determinants," *Res. Policy*, vol. 31, pp. 303–328, 2002.

[31] L. G. Zucker, M. R. Darby, and J. S. Armstrong, "Commercializing Knowledge: University Science, Knowledge Capture, and Firm Performance in Biotechnology," *Manage. Sci.*, vol. 48, no. 1, pp. 138–153, 2002.

[32] Murray, Fiona, "Innovation as co-evolution of scientific and technological networks: exploring tissue engineering," *Res. Policy*, vol. 31, no. 8, pp. 1389–1403, 2002.

[33] J. Owen-Smith and W. W. Powell, "Accounting for Emergence and Novelty in

Boston and Bay Area Biotechnology," in *Cluster Genesis: Technology-Based Industrial Development*, 2006, pp. 61–83.

[34] C. H. Wong, K. W. Siah, and A. W. Lo, "Estimation of clinical trial success rates and related parameters," *Biostatistics*, pp. 1–14, 2018.

[35] Biotechnoloby Innovation Organization, "The Biotechnology Ecosystem : By the Numbers," 2018.

[36] J. A. DiMasi, H. G. Grabowski, and R. W. Hansen, "Innovation in the pharmaceutical industry: New estimates of R&D costs," *J. Health Econ.*, vol. 47, pp. 20–33, 2016.

[37] A. Schuhmacher, O. Gassmann, and M. Hinder, "Changing R&D models in research-based pharmaceutical companies," *J. Transl. Med.*, vol. 14, p. 105, 2016.

[38] Pfizer, "Centers for Therapeutic Innovation." [Online]. Available: https://www.pfizer.com/science/collaboration/centers-therapeutic-innovation.

[39] Johnson&Johnson, "Johnson and Johnson Innovatoin." .

[40] Evaluate Pharma, "World Preview 2018 , Outlook to 2024," 2018.

[41] the International Telecommunication Union, *Accelerating digital transformation*. 2018.

[42] European Innovation Management Academy, "Effective Innovation Management Support," 2016.

[43] Scientific American, "The 2016 Scientific American Worldview," 2016. .

[44] B. Booth, "Why Biotech's Talent, Capital And Returns Are Consolidating Into Two Key Clusters," *Forbes*, 2017. [Online]. Available: https://www.forbes.com/sites/brucebooth/2017/03/21/inescapable-gravity-of-biotechs-key-clusters-the-great-consolidation-of-talent-capital-returns/#ca6220a52e92.

[45] The Times Higher Education, "THE World University Ranking 2019," 2019. [Online]. Available: https://www.timeshighereducation.com/world-university-rankings/2019/world-ranking#!/page/0/length/25/sort_by/rank/sort_order/asc/cols/stats.

[46] "Innovation Cities TM Index 2018: Top 100 Cities," *2thinknow Innovation Cities Program*, 2018. [Online]. Available: https://www.innovation-cities.com/worlds-top-100-cities-for-innovation-2018/13973/.

[47] The Times Higher Education, "THE Japanese University Rankings 2018," 2018. [Online]. Available: https://www.timeshighereducation.com/rankings/japan-university/2018#!/page/0/length/25/sort_by/rank/sort_order/asc/cols/stats.

[48] C. Pece, "State Government R&D Expenditures Increase 7% in FY 2017;

Health-Related R&D Up 13%," *Info Brief, Natl. Cent. Sci. Eng. Stat.*, vol. December, 2018.

[49] MEXT, "MEXT Science and Technology Directory 2018." [Online]. Available: http://www.mext.go.jp/b_menu/toukei/006/006b/1413901.htm.

[50] NIH, "About NIH." [Online]. Available: https://www.nih.gov/about-nih.

[51] National Center for Science and Engineering Statistics, "Survey of Federal Funds for Research and Development FY2017."

[52] Massachusetts the Executive Office for Administration and Finance, "FY2010 House 1 Budget Recommendation: Policy Brief." [Online]. Available: https://budget.digital.mass.gov/bb/h1/fy10h1/prnt10/exec10/pbudbrief23.htm.

[53] TEConomy Partners and Mass Economics, "Public-Private Partnerships in Action: The Statewide Impact of the Massachusetts Life Sciences Center on the Life Sciences Ecosystem," 2018.

[54] Withum, "Massachusetts Life Sciences Initiative Reauthorization," 2018. [Online]. Available: https://www.withum.com/resources/ma-life-sciences-initiative-reauthorization/.

[55] Cabinet Secretariat, "Healthcare Policy," 2014.

[56] AMED, "Cyclic Innovation for Clinical Empowerment (CiCLE)." [Online]. Available: https://www.amed.go.jp/en/program/list/07/01/001.html.

[57] METI, "Ito Review 2.0: Biomedical Edition," 2018.

[58] AMED, "Overview of Medical R&D supported by AMED FY2017," 2018.

[59] MEXT, "Allocation of Grants-in-Aid for Scientific Research in FY2017."

[60] Center for Innovation in Regulatory Science, "R&D Briefing 67," 2018.

[61] Statista, "Top 10 Pharmaceutical Companies in Sales." [Online]. Available: https://www.statista.com/statistics/273029/top-10-pharmaceutical-companies-sales-and-rundd-spending-in-2010/.

[62] Venture Enterprise Center, "VEC Year Book 2018," 2018.

[63] OECD, "Entrepreneurship at a Glance 2018 Highlights," 2018.

[64] TEConomy Partners and Biotechnoloby Innovation Organization, "Investment, Innovation and Job Creation in a Growing U.S. Bioscience Industry 2018," 2018.

[65] TEConomy Partners, "Strengthenig Biopharmaceutical Innovation: The Growing Role of Corporate Venture Capital," 2018.

[66] California Life Sciences Association, "California Life Sciences Industry Report 2018," 2018.

[67] California Life Sciences Association, "California Life Sciences Industry Report 2019," 2019.

[68] entrepedia, "Japan Startups Finance Report 2018," 2018.

[69] National Institute of of Sicence and Technology Policy, "Japanese Science and Technology Indicators 2018."

[70] Clarivate Analytics, "Ranking of Japanese research institutes by the analysis of high impact articles," *Clarivate Analytics Japan*, 2019. [Online]. Available: https://clarivate.jp/news-releases/2019/esi2019/.

[71] National Institute of of Sicence and Technology Policy, "Survey on Career Decision-Making of Japanese Master Course Students in Science and Engineering," no. RM165, 2009.

[72] MEXT, "Report on the academia-industry collaboration in universities."

[73] N. Bosma and D. Kelley, *Global Entrepreneurship Monitor 2018/2019 Global Report*. 2019.

[74] SME, "White Paper on Small and Medium Enterprises in Japan, 2017."

[75] METI, "Survey on university-spinoff startups and research seeds 2017," 2017.

[76] E. B. Roberts, F. Murray, and J. D. Kim, "Entrepreneurship and Innovation at MIT Continuing Global Growth and Impact," 2015.

[77] P. Miller and K. Bound, "The Startup Factories The rise of accelerator programmes to support new technology ventures," 2011.

[78] M. Tom, "One-third of U.S. startups that raised a Series A in 2015 went through an accelerator," *PitchBook*, 2016. [Online]. Available: https://pitchbook.com/news/articles/one-third-of-us-startups-that-raised-a-series-a-in-2015-went-through-an-accelerator.

[79] gust, "Global Accelerator Report 2016 by Gust," 2016. [Online]. Available: http://gust.com/accelerator_reports/2016/global/.

[80] A. Cremades, "10 Startup Accelerators Based On Successful Exits," *Forbes*, 2018. [Online]. Available: https://www.forbes.com/sites/alejandrocremades/2018/08/07/top-10-startup-accelerators-based-on-successful-exits/#16e2d7924b3b.

[81] S. Buhr, "SOSVentures Takes On Y Combinator With A Pure Biotech Accelerator," *Techcrunch*, 2014. [Online]. Available: https://techcrunch.com/2014/10/22/sosventures-takes-on-y-combinator-with-a-pure-biotech-accelerator/.

[82] M. Terry, "4 Big Pharma Biotech Accelerators: Investing in Innovation," *BioSpace*, 2018. [Online]. Available: https://www.biospace.com/article/4-big-pharma-biotech-accelerators-investing-in-innovation/.

[83] Boston Startups Guide, "Boston Startup Accelerators, Incubators, & Support Programs." [Online]. Available: https://bostonstartupsguide.com/guide/every-boston-startup-accelerator-

incubator/.

[84] Japan Open Innovation Council and NEDO, "White Paper on Open Innovation," 2018.

[85] LINK-J and Mitsui Realestate, "Establishment of LINK-J," 2016. [Online]. Available: https://www.mitsuifudosan.co.jp/corporate/news/2016/0603/.

[86] H. Murohashi, "The Network and Cluture of TNK, the University of Tokyo's student group for entreprneurship," *BUSINESS INSIDER JAPAN*, 2018. [Online]. Available: https://www.businessinsider.jp/post-164920.

[87] Cabinet Office, "Overview of the science and technology budget in FY2018 and the supplemental budget in FY2017," 2018.

[88] MEXT, "Survey on the budget for science and technology in prefectures," 2017.

[89] J. Glasner, "Top Universities And Business Schools For Funded Founders," *Crunchbase news*, 2018. [Online]. Available: https://news.crunchbase.com/news/top-universities-and-business-schools-for-funded-founders/.