EU-Japan Centre for Industrial Cooperation

# Opportunities for Cooperation between EU and Japan on Biotechnology in Healthcare: Japan Bioventures Landscape

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**Executive Summary**

Japan is one of the major countries that European biotech companies target in their expansion when it comes to internationalisation. This report intends to be a useful source of information for European SMEs and clusters considering potential cooperation with Japan.

In the healthcare sector, and more specifically in the therapeutics development field, partnerships between European and Japanese pharmaceutical companies well established in their respective local markets has typically involved License agreements on co-development and commercialisation rights. The Japanese inlicensor would typically get the rights on a product of European origin to pursue its clinical development in Japan, obtain the local regulatory approval, and commercialise it in the domestic Japanese market. The reverse situation was possible as well, when products developed in Japanese companies pipelines were licensed-out to European based companies.

In an era of open innovation, partnership models are evolving, and can go well beyond pharma licensing deals on co-development and product commercialisation rights. Moreover, European biotech SMEs often present alternatives to the traditional therapeutic product development, and business models are frequently based on discovery platforms and services to facilitate research and drug development.

This report is therefore focussing on public research institutions and academic bioventures in Japan, which may hold great potential for collaboration with European SMEs.

Biotechnology policies in Japan are presented in the first section of the report, exploring the Regulatory mechanisms for approval of regenerative medicines which Japan pioneered (sections 2&·3). A brief presentation of Japan science and technology indicators, and major cooperation programs in health with the European Union is given in sections 4&5. The chronology of the evaluation of Academia-Industry relations in Japan, leading to the current situation of academic bioventures is presented in sections 6 & 7.

Section 8 includes an overview of the Japanese biotech academic landscape. A comprehensive description of all the laboratories doing biotech research in Japan was beyond the scope of this report. Major universities and flagship research centres are presented, explaining how relations with industry are organised for each centre. **A selection of innovative academic bioventures** is provided, linked to the research laboratory which was at the origin of the technology offered by these companies.

The global health innovative technology fund is presented in section 9, as an interesting model of tripartite collaboration with Japan, potentially interesting to EU biotech companies.

Section 10 describes the most active Japanese clusters and innovation hubs with interest on international collaboration biotechnology and healthcare.

The report concludes with some practical recommendations for EU biotech companies considering entering the Japanese market.

**List of abbreviations**

| | |
|---|---|
| AMED | Agency for Medical Research and Development |
| ALS | Amyotrophic Lateral Sclerosis |
| CiRA | Center for induced pluripotent stem cell Research and Application |
| CDMO | Contract development and manufacturing organization |
| CRO | Contract Research Organization |
| EMA | European Medicines Agency |
| EU | European Union |
| ES | Embryonic stem cell |
| FDA | Food and Drug Administration (US) |
| GDP | Gross Domestic Product |
| GHIT | Global Health Innovative Technology Fund |
| GMP | Good manufacturing Practices |
| HFSP | Human Frontier Science Programme |
| HGF | Hepatocyte Growth Factor |
| iPSC | Induced Pluripotent Stem Cell |
| IFReC | The Immunology Frontier Research Center |
| IMSUT | Institute of Medical Science University of Tokyo |
| ICGC | International Cancer Genome Consortium |
| IHEC | International Human Epigenome Consortium |
| IHMC | International Human Microbiome Consortium |
| IMPC | International Mouse Phenotyping Consortium |
| IoT | Internet of Things |
| JABEX | Japan Association of Bioindustry Executives |
| JBA | Japan biotechnology Association |
| JPY | Japanese Yen |
| LiC | Lifescience Industry Center in Kanagawa |
| LINK-J | Life science Innovation Network Japan |
| MHLW | Ministry of Health Labour and Welfare |
| MAB | Monoclonal Antibody |
| METI | Ministry of Energy Trade and Industry |
| MEXT | Ministry of Education, Culture, Sports, Science and Technology |
| MOTHERS | Market of High Growth and Emerging Stocks (Tokyo Stock Exchange) |
| MoU | Memorandum of Understanding |

| | |
|---|---|
| M&A | Mergers and Acquisitions |
| NEDO | New Energy and Industrial Technology Development Organization |
| NGS | Next Generation Sequencing |
| NISTEP | National Institute of Science and Technology Policy |
| OECD | Organisation for Economic Co-operation and Development |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PMI | Preventive Medicine and Diagnosis Innovation Program |
| QbIC | Riken Quantitative Biology Center |
| RCAST | Research Center for Advanced Science and Technology |
| RMP | Regenerative Medicine Product |
| RPE | Retinal Pigment Epithelium |
| SMEs | Small and Medium Size Enterprises |

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**List of Bioventures/companies mentioned in the report:**

| Company name | Originating from University/ Institution | Cluster/ innovation hub/area |
|---|---|---|
| Ambicion | RIKEN | |
| AnGes | Osaka | |
| Brightpath Biotherapeutics Co Ltd | Kurume, Fukuoka | LiC & Fukuoka Bio incubation |
| Cellink | Kyoto | KU innovation hub, EU |
| Chiome bioscience | RIKEN | LiC Kanagawa |
| Chordia therapeutics | Kyoto | Shonan Park, Kanagawa |
| Chromocenter Inc. | Osaka | |
| Cyfuse biomedical KK | Kyushu | Tokyo U entrepreneurs plaza |
| DNAform | RIKEN | Venture plaza Yokohama |
| Edigene | Tokyo | Cambridge,MA, USA |
| Epigeneron Inc. | Osaka | |
| Epsilon Molecular Engineering | Saitama | Saitama |
| Funpep | Osaka | |
| GlyTech Inc. | Tokyo | |
| HanaVax Inc | Tokyo | Tokyo |
| Healios | RIKEN | |
| Human Metabolome Technologies | Keio | Tokyo, EU/US |
| iHeart Japan | Kyoto, CiRA | |
| Jisak bioengineerng | Tokyo | |
| JTEC corpo | Osaka | |
| K Pharma | | Shonan Park, Kanagawa |
| Kinopharm | Kyoto | Kyoto innovation hub |
| Kotai Biotechnologies Inc. | Osaka iFReC | |
| Kyoto drug discovery KDDD | Kyoto | |
| Matrixiome Inc. | Osaka iFREC | |
| Medinet | Tokyo IMSUT | Tokyo Yokohama Osaka |
| MegaKaryon Corporation | Kyoto, Tokyo | Kyoto |
| Metcela | Keio | LiC Kanagawa |
| Molcure | Tokyo | |
| Myoridge | Kyoto | KU pharma research institute |
| NB Health Laboratory Co. Ltd | Sapporo University | Hokkaido |

| | | |
|---|---|---|
| Noile Immune | Yamaguchi University | Shonan Park, Kanagawa |
| Nuprotein | Nagoya | Nagoya University Incubation |
| Organ technologies | RIKEN | |
| Peptidream | Tokyo RCAST | LiC Kawasaki |
| Peptistar | Tokyo RCAST | LiC Kawasaki |
| PharmaBio | Tokyo | Tokyo |
| RegCell | Kyoto, Osaka | |
| ReproCell | Kyoto iCeMS | LiC Kanagawa /EU/USA |
| Rhelixa | Tokyo RCAST | Tokyo |
| Rikenbio | RIKEN | |
| SCAD | Kyoto ICeMS | |
| SCI | Kyoto | |
| Scohia Pharma Inc. | Takeda | Shonan park Kanagawa |
| TagCyx biotechnologies | RIKEN | Tokyo Komaba open lab |
| Thyas | Kyoto | |
| Two cells | Hiroshima | Hiroshima |

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## 1. Introduction

This report intends to provide an overview of the current biotechnology landscape in Japan, focussing on key academic institutions and bioventure companies which are developing applications of biotechnology to healthcare.

The objective of the report is to be a useful source of information for European SMEs and Clusters, wishing to explore collaborative research and potential business opportunities in Japan. With this aim, a selection of academic institutions is presented, highlighting those centres with worldwide recognition for their research, broad support for internationalisation, and a track record of openness for Industry-Academia collaborations.

Research for the preparation of this report was undertaken during the last quarter of 2017 and first quarter of 2018. During that period, the monitoring of Japanese biotechnology specialised press, tradefairs, seminars, and related events, revealed the bioventures ecosystem as a very dynamic group of innovative companies in the Japanese biotech landscape today, increasingly attracting interest and support both from public and private sectors.

This report has focussed on Japanese bioventures, created to commercialise results of research and development from Japanese forefront academic research institutions. Information on governmental, university-related, and private initiatives supporting these bioventures is also presented, as it may be of interest to European biotechs wishing to interact with their Japanese counterparts.
For a European company considering business development in Japan, it may be relatively easy to access information on main players in the Japanese market, such as big pharmaceutical corporations. In contrast, information on emerging companies and start-ups in Japan is scarce, and less broadly available. Small biotech research firms correspond to a reservoir of industrial competitiveness, scientific and technologic innovation worldwide, and Japan is no exception to this.

European biotech start-ups interested in the Japanese market, dealing with advanced therapy medicinal products, often have questions concerning the **regenerative medicine regulatory provisions** that Japan has been promoting. A specific section of this report is devoted to these regulatory changes and mechanisms, providing detailed examples of products authorised for commercialisation in Japan under the revised legislation. The author hopes to have contributed to shed some clarity on this topic.

The terms **"venture"** and **"bioventure"** are frequently used in English language in Japan. They refer to biotech start-up companies, often based on technology developed at universities, and usually funded through venture capital and/or public sector funding.
The terms "biotechnology" and "biotech" are used interchangeably throughout the report, the latter often referring as well to companies operating in the field.

Biotechnology**,** as commonly understood in the public science & technology policy and in economic analysis, is defined as the application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services. For the identification of target academic research institutions and companies of interest in this report, the applications listed under "Human Health", and biotechnology list based statistic definitions[1] published by OECD in January 2018, have been considered.

Nanotechnology has not been specifically covered in this report. For an overview on the Japanese nanotechnology landscape, see the report[2] "Nanotech Cluster and Industry Landscape in Japan" by Andrej Zagar, published in 2014 by the EU-Japan Centre for Industrial Cooperation.

**Table 1.1: OECD Biotechnology list based statistic definitions**

- **DNA/RNA:** Genomics, pharmacogenomics, gene probes, genetic engineering, DNA/RNA sequencing/synthesis/amplification, gene expression profiling, and use of antisense technology, large-scale DNA synthesis, genome- and gene-editing, gene drive.
- **Proteins and other molecules:** Sequencing/synthesis/engineering of proteins and peptides (including large molecule hormones); improved delivery methods for large molecule drugs; proteomics, protein isolation and purification, signalling, identification of cell receptors.
- **Cell and tissue culture and engineering:** Cell/tissue culture, tissue engineering (including tissue scaffolds and biomedical engineering), cellular fusion, vaccine/immune stimulants, embryo manipulation, marker assisted breeding technologies, metabolic engineering.
- **Process biotechnology techniques:** Fermentation using bioreactors, biorefining, bioprocessing, bioleaching, biopulping, biobleaching, biodesulphurisation, bioremediation, biosensing, biofiltration and phytoremediation, molecular aquaculture.
- **Gene and RNA vectors:** Gene therapy, viral vectors.
- **Bioinformatics:** Construction of databases on genomes, protein sequences; modelling complex biological processes, including systems biology.
- **Nanobiotechnology:** Applies the tools and processes of nano/microfabrication to build devices for studying biosystems and applications in drug delivery, diagnostics, etc..

NOTE: 2016 additions to the statistical definition adopted in 2006 are highlighted in grey.

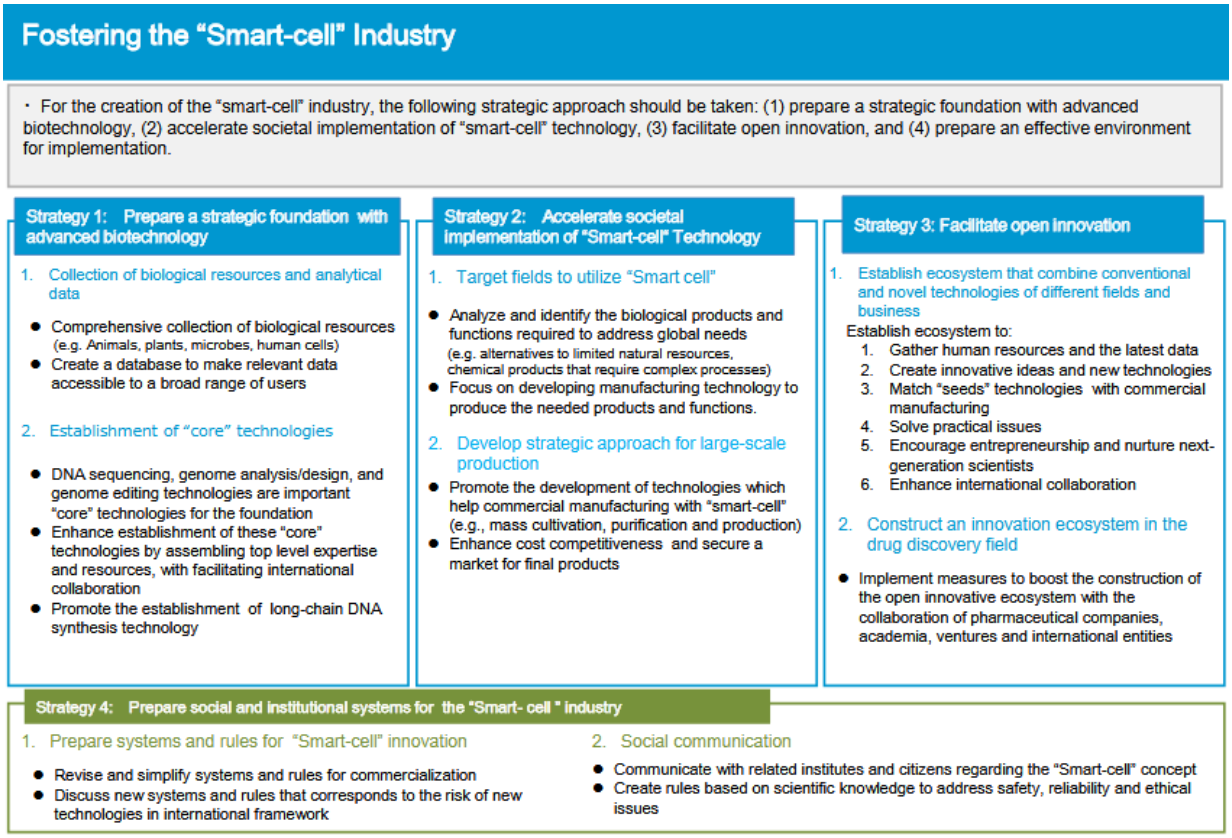
[1] Friedrichs, S. and B. van Beuzekom (2018), "Revised proposal for the revision of the statistical definitions of biotechnology and nanotechnology", OECD Science, Technology and Industry Working Papers, 2018/01, OECD
[2] Nanotech Cluster and Industry Landscape in Japan

## 2. Japan Biotechnology Policies

For the government of Japan, the biotech-based economy/industry is an integral part of Prime Minister Abe Administration growth strategy, as captured in the "Basic Policy on Economic and Fiscal Management and Reform 2015"[3]. The Ministry of Energy Trade and Industry (METI) aims to foster the biotech-based economy, projected to grow as large as six times by the year 2030, through the development and commercialization of the innovative technologies, products and services, notably including **regenerative medicine.**

In 2016, METI issued the document **"New trends in the field of biotechnology and its impact on society and economy: Creating Smart Cell Industry"**[4] where it was recognised that cell technology, with its innovative potential, will bring about transformative changes in industrial structure and operation of major industrial fields and provide the basis to address global challenges.

**Figure 2.1: Japan government strategies fostering the Smart-cell Industry**




**Source: METI**

[3]

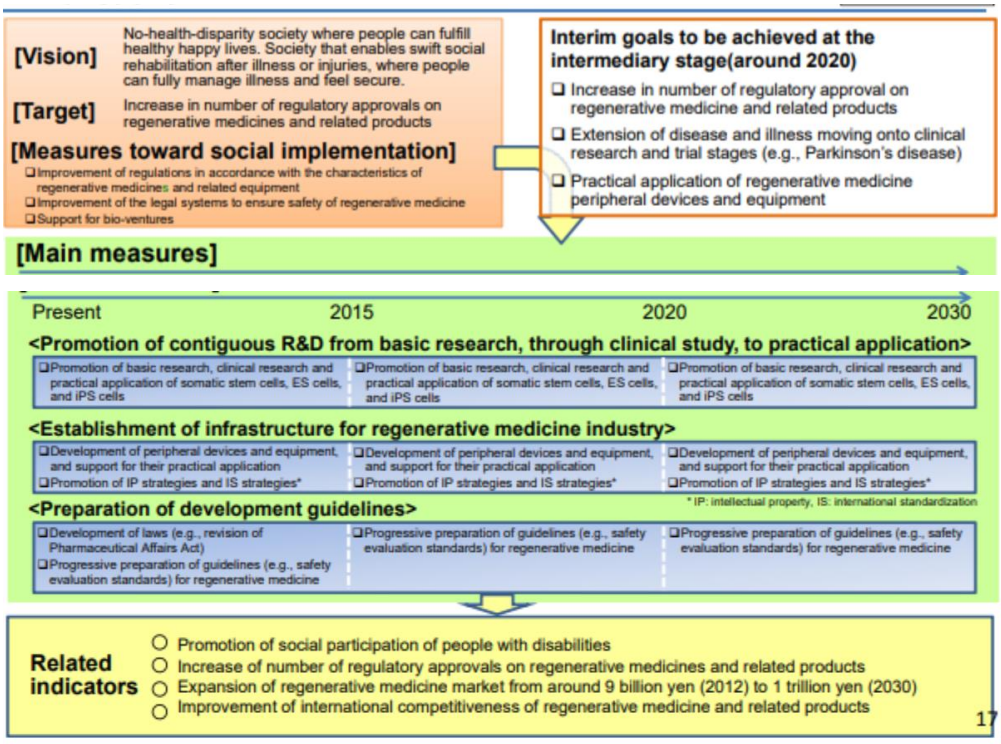
[4] New trends in the field of biotechnology and its impact on society and economy: Creating Smart Cell Industry http://www.meti.go.jp/english/press/2016/pdf/0714_01a.pdf

In Japan, the Science and Technology Policy is administered according to the directives and principles contained in the Science and Technology Basic Plan, which is approved every five years. Currently, the **5th Science and Technology Basic Plan**[5], endorsed in by Cabinet Decision in January 2016, is running for the period 2016-2021. The objective of the plan is to achieve a higher standard of science and technology, to contribute to the development of the economy and society of Japan.
It includes a series of measures **to promote translational R&D**, particularly in the field of regenerative medicine, where the market is expected to expand from 9 billion yen (€67.5 million) in 2012 to 1 trillion yen (€7.5 billion) in 2030.

Since 2014, the roadmaps of the comprehensive strategy on Science, Technology and Innovation, include promotion measures towards the social implementation of regenerative medicine:

- Promotion of contiguous basic research, clinical research and practical applications of somatic stem cells, embryonic stem cells (ES cells) and induced pluripotent stem cells (iPS cells)
- Establishment of infrastructure for regenerative medicine industry
- Preparation of development guidelines

**Figure 2.2: Image from the roadmap of the comprehensive strategy on STI**




SOURCE: GoJ

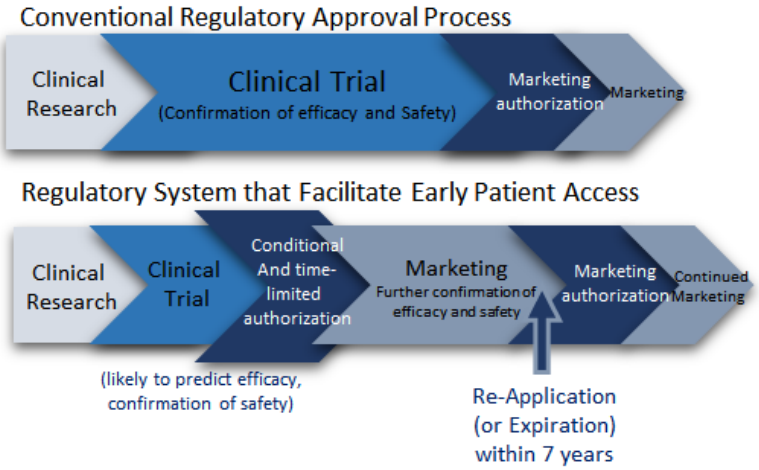
[5] http://www8.cao.go.jp/cstp/english/doc/chapter2_roadmap_provisional.pdf

## 3. Regulatory policies for the promotion of Regenerative Medicine

Several regulatory-led initiatives were designed in Japan to promote the research and development of regenerative medicine products[6]. In November 2013, two legislative acts were promulgated by the Japanese Diet (Parliament), and enacted in November 2014: The PMD Act and the Safety RM Act.

- **PMD. Act**: The Pharmaceutical Affairs Law was revised and renamed Pharmaceuticals, Medical Devices and Other Therapeutic Products (PMD Act)**,** to include a new independent classification for regenerative medical products (RMPs)**.** It established a **conditional approval** scheme for commercialization of RMPs based on confirmation of probable benefit and safety, whereby RMPs would receive a temporary approval, initially valid for up to 7 years.

**Figure 3.1: Timelines for conditional approval vs normal approval**




SOURCE: PMDA

- The Act on the **Safety of Regenerative Medicine (RM Act)** created a framework to provide regenerative therapies in early-stage, small scale clinical research, under physician discretion. These provisions are similar to the **"Hospital Exemptions"** existing in many EU member states. The act also enabled the **outsourcing of cell processing** to contract GMP compliant manufacturing organizations, holding a license as "Cell Processing Center".

RMPs were defined in legislation as processed human/animal cells that are intended to be used either

1) for the reconstruction, repair or formation of structures or functions of the human body; or for the treatment or prevention of human diseases.
2) for gene therapy.

[6] Azuma K., Yamanaka S. Recent policies that support clinical application of iPS cell based regenerative therapies. JSRM, 2016

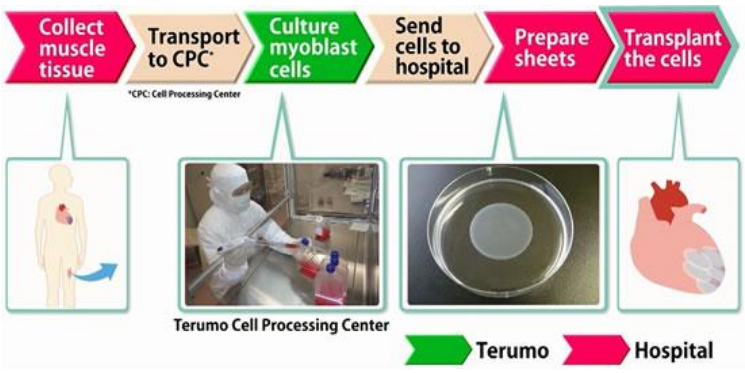
**Table 3.1: Regenerative medicines approved in Japan under the revised legislation**

**TEMCELL® HS Inj., by JCR Pharmaceuticals Co. Ltd.** are human allogeneic bone marrow derived mesenchymal stem cells (MSCs) for the treatment of acute graft versus host disease, arising from hematopoietic stem cell transplant.

It was approved under regular authorization in September 2015, and launched in February 2016. Temcell was developed in Japan with a license on the technology from Australian company Mesoblast Ltd., who had acquired the product (Prochymal) from Osiris Therapeutics Inc. (US). Prochymal was approved in Canada and New Zealand in 2013.

The clinical package submitted for its marketing authorization application in Japan, included around 40 Japanese patients treated with Temcell. Overseas experience with Prochymal, as supportive data, included 173 patients treated with the product. Data on all cases treated with the product must be collected as postmarketing surveillance.

**Heartsheet®, by Terumo Corporation.** The autologous skeletal myoblast sheets for severe heart failure due to ischemic heart disease, obtained a 5 year **conditional approval** in September 2015. It had demonstrated probable benefit in one multicenter, open-label, single-arm, feasibility study with 7 patients. The ongoing postmarketing study will include 60 patients in the product arm and 120 in the control arm. [7]




[7] Jokura et al. Comparison of the new Japanese legislation for expedited approval of regenerative medicine products with the existing systems in the USA and EuropeanUnion. J Tissue Eng Regen Med 2017.

In 2015, based on the Japan Revitalization Strategy and the Health and Medicine Strategy, the Ministry of Health Labor and Welfare (MHLW) launched a project to lead the world in the **practical application** of innovative products. The strategy included an **advanced review designation system named "Sakigake"** for pharmaceuticals, medical devices, and regenerative medical products targeting revolutionary therapeutic methods, and promising large improvements over existing therapies.

Sakigake designation is based on initial clinical trial data (phase I or early phase II trials). The designation **streamlines procedures for consultation and review:** It grants priority for clinical trial consultations, and the review time of the marketing application dossier is halved, with the aim of bringing the products into use as promptly as possible.

Other major regions, like US and Europe have also implemented specific schemes for regenerative medicine (ATMPs in Europe; RMAT in USA). Accelerated approval pathways and designations by their regulatory agencies ("Breakthrough therapy" at FDA; "PRIME, Priority medicine" at EMA), are on-par with Japanese Sakigake. All these mechanisms enable expedited access to the market under conditions of demonstrated **early clinical efficacy and safety.**

**Table3.2: Sakigake comparison with other regulatory designations for expedited approval**

| ***SAKIGAKE vs*** **Breakthrough therapy (US) vs PRIority MEdicines (EU)** | | | |
|---|---|---|---|
| | **SAKIGAKE** | **Breakthrough therapy** | **PRIority MEdicines (PRIME)** |
| Establishment | April 2015 (trial) | July 2012 | March 2016 |
| Designation Criteria | • New mode of action<br>• Life threatening or no radical treatment<br>• Prominent efficacy<br>• First NDA in the world | • Serious condition<br>• Substantial improvement on clinically significant endpoint(s) | • Unmet medical need<br>• Potential to address to unmet medical need |
| Project Manager | • Review partner (Concierge) | • Senior manager<br>• Cross-disciplinary project lead | • Dedicated contact point<br>• Appointment of rapporteur |
| Consultation | • Priority consultation | • Intensive guidance on an efficient drug development program | • kick-off meeting about the overall development plan and regulatory strategy<br>• Scientific advice at key development milestones |
| Rolling review | • Eligible (SAKIGAKE comprehensive assessment Consultation) | • Eligible | — |
| Priority review | • Review within 6 months (shorter than 9 months in ordinal priority review) | • Not automatically designated | • Eligible (Accelerated assessment) |
| Other | • Relation with drug pricing | | |

**Source: PMDA**

Table 3.2 below, shows the products that have received Sakigake designation by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) in the two rounds of assignment held so far (2016, 2017)

**Table 3.3: Sakigake designations for regenerative medicine products 2016-2017.**

| **1st round of Sakigake designations: Medical Devices & Regenerative Products, as of Feb. 2016** | | |
|---|---|---|
| **Product name** | **Proposed indication** | **Name of Applicant** |
| Titanium Bridge (Hinge type plate with Ti) | Adduction-type spasmodic dysphonia | Nobelpharma Co. Ltd. |
| Bioresorbable adhesion barrier (THN-01 trehalose solution) | Postoperative adhesion prevention | Otsuka Pharmaceutcal Factory, Inc. |
| STR01 autologous bone marrow derived mesenchymal stem cell | Nerve syndrome and dysfuction due to spinal chord injury | NIPRO Medical Co., Ltd. |
| G47 Growth controlled oncolytic herpes simplex virus type 1 | Malignant glioma | Daiichi Sankyo Co. Ltd<br>The University of Tokyo IMSUT |
| Autologous cardiac progenitor stem cells | Paediatric congenital heart disease (single ventricle) | Japan Regenerative Medicine Co. Ltd. |
| **2nd round of Sakigake designations: Medical Devices & Regenerative Products, as of Feb. 2017** | | |
| **Product name** | **Proposed indication** | **Name of Applicant** |
| Oral mucosa derived esophageal cell sheet | Re-epthelialisation after extensive endoscopic submucosa dissection in esophageal cancer | CellSeed<br>(Tokyo Women's Medical University Hospital) |
| Dopamine neural precursor cell derived from non-autologous iPS cell | Novel therapy inducing dopamine discharge to mitigate neural symptoms in Parkinson | Sumimoto Dainippon Pharma<br>(Kyoto University CiRA) |
| Pluripotent progenitor cell derived from human allogenic adult bone marrow. (stem cell suspension) | Novel therapy for improving functional impairment caused by acute brain infarction | Healios K.K. in Japan<br>Athersys Inc.(US company) |

It is noticeable that most products were originally "seeds" from Japanese Universities, and their development involves collaboration between academia and a private company. Sakigake regulatory designation program explicitly indicates that the product **should be of Japanese origin, or include Japan in the first countries where it is developed.**

Athersys, a US company, has set a precedent being the first overseas company to obtain a Sakigake designation for the regenerative medicine product that it co-develops with the Japanese bioventure Healios KK (see page 75). European SMEs pursuing an accelerated approval in Japan, may consider a partnership with a local Japanese bioventure to access Sakigake streamlined procedures with PMDA.

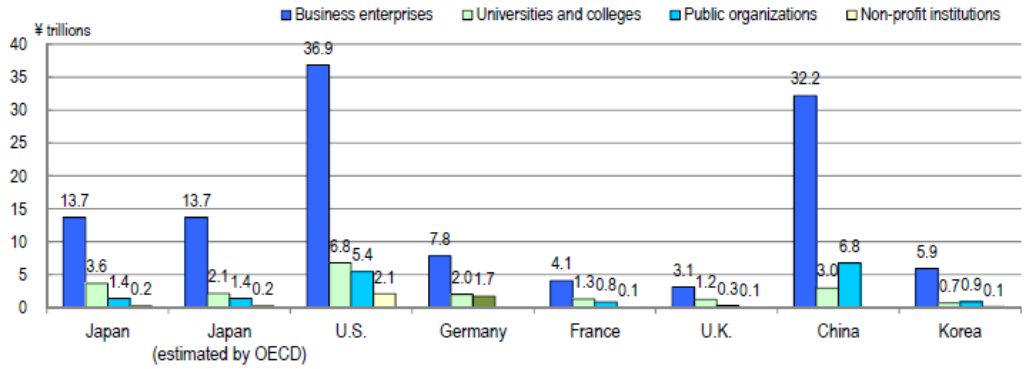
## 4. Japan Science and Technology Indicators

With 3.35% of the country gross domestic product (GDP) dedicated to R&D, Japan ranks among the world's most R&D-intensive countries[8].

Total R&D expenditure was 18.9 trillion yen (€14.5 Billion) in 2015. In 2017, Japan Science and Technology Indicators[9] show that the R&D expenditure and the number of researchers in Japan, is the 3rd largest in the world (after US and China).

However, public R&D expenditure is modest in Japan, especially in light of its high gross domestic expenditure on R&D dominated by private sector contribution, which has made the country a world technology leader.

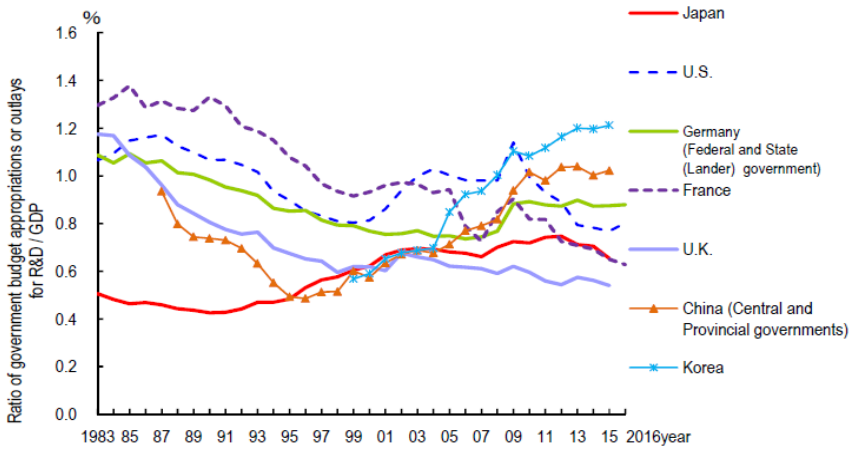
**Figure 4.1: R&D expenditure in selected countries.**




**Source: NISTEP**

In international comparison, Japan government budget for R&D (0.65% of GDP) ranks sixth, behind Korea (1.21%), China (1.02%), Germany (0.88%), US (0.80%) and France (0.63%).

**Figure 4.2: Changes in government budget for Science and Technology as percentage of GDP**




[8] OECD 2015

[9] Japanese Science and Technology Indicators 2017, August 2017, Research Unit for Science and Technology Indicators , National Institue of Science and Technology Policy (NISTEP), Ministry of Education, Culture, Sports, Science and Technology (MEXT)

After years of stagnant support for the sector, Japan will increase funding for science and technology in 2018[10]. The government's science advisory body announced in January 2018 a total investment in science and technology climbing to 3.84 trillion yen (28.8 billion euro), an increase by 7% compared with 2017. The government of Prime Minister Shinzo Abe aims to boost Japan's science and technology budget by 300 billion yen (€2.28 billion) per year, to meet a goal of 1% of the country's gross domestic product (GDP) by 2020, up from 0.65% in 2015.

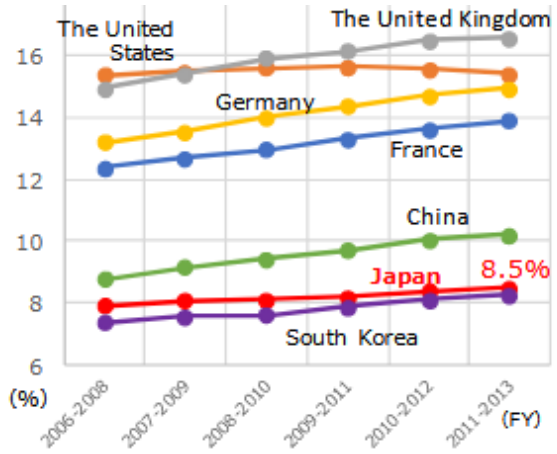
R&D funds from Japan government are dedicated to "Universities and Colleges" (41.9%) and "Other Public Organizations" (49.6%). The latter includes research institutions outside University, like RIKEN for example[11]. In 2018, operational funding for national universities remains at just over 1 trillion yen (€7.5 billion), the same as in 2017. Stagnant university funding follows substantial government cuts to their budgets: about 1% a year between 2004 and 2014.[7]

**R&D Output- Scientific publications**

In terms of **R&D output**, looking at the **number scientific research papers**, Japan ranks 4th in the world (after US, China and UK) and 9th on scientific publications with high citations (after US, China, UK, Germany, France, Italy, Canada and Australia).[7]

Looking at the last decade, the Japanese share of worldwide publications has dropped, unlike those of South Korea and China. Japan's **share of high-quality papers** has also declined. This is a concern recurrently voiced by Japanese research institutions leaders.

**Figure 4.3: Number of top 10% cited papers as a proportion of total papers by country.[11]**

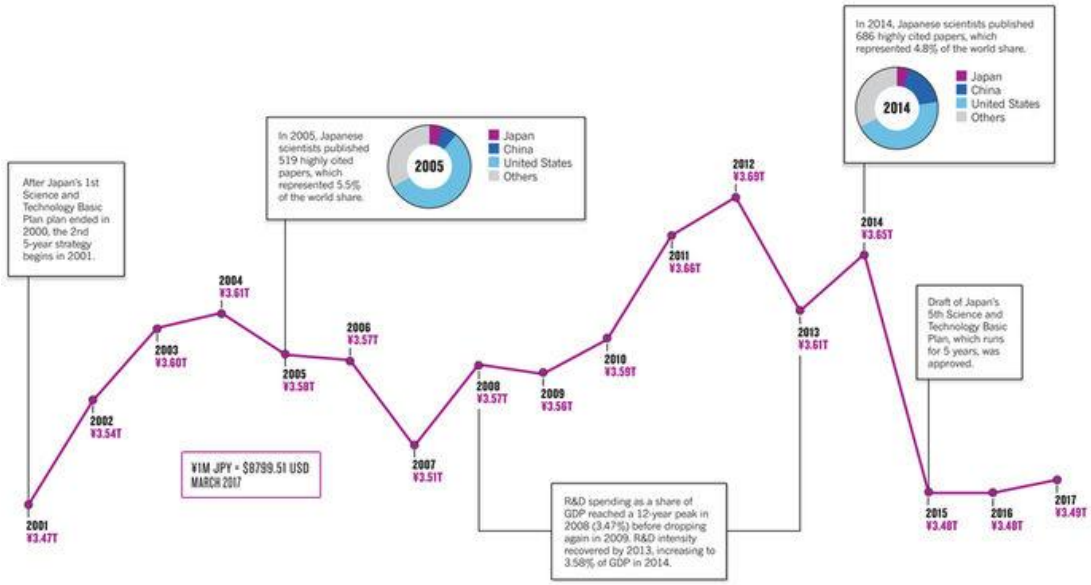



**Source: NISTEP**

[10] Nature article https://www.nature.com/articles/d41586-018-01599-w
[11] http://www.nistep.go.jp/wp/wp-content/uploads/NISTEP-RM261-Summary_E.pdf

To explain this loss of influence, some signal the abolishment of fundamental basic research at the core of big Japanese corporations. Others believe that it is the natural result of austerity in public science funding[12], and point to a structural problem in the budgetary system of public research: In order to access public funding, the majority of researchers are forced to join calls issued by the government with a pre-established subject of research. Such system precludes researchers to pursue investigations based on their own original center of interest[13]

**Figure4.4: Evolution in Japan R&D spending and share of highly cited papers[12]**




**Source: Nature**

NISTEP suggests that Japan's scientific knowledge is possibly not being sufficiently utilized by its own technologies, noting that while the number of papers in "clinical medicine" has been increasing, the share of “biotechnology/pharmaceuticals" in the number of patent families is low.

[12] nature https://www.nature.com/articles/543S10a

[13] personal communication, Prof. Matsumoto, RIKEN president conference at the EU-delegation, January 2018

Japan has the world's second most Nobel Prize laureates in **life sciences**, in the 21st century[14]

**Table 4.1: Japan Nobel Prize laureates in life sciences**

| | | | |
|---|---|---|---|
| 1981 | Kenichi FUKUI | Kyoto University | for their theories concerning the course of chemical reactions |
| 2001 | Ryoji NOYOR | Nagoya University | for their work on chirally catalysed hydrogenation reactions |
| 2002 | Koichi TANAKA | Shimazu corp. | for their development of soft desorption ionisation methods for mass spectrometric analyses of biological macromolecules |
| 2008 | Osamu SHIMOMURA | Boston University | for the discovery and development of the green fluorescent protein, GFP |
| 2010 | Akira SUZUKI<br>Ei-ichi NEGISHI | Hokkaido University | for palladium-catalyzed cross couplings in organic synthesis |
| 2012 | Shinya YAMANAKA | Kyoto University | for the discovery that mature cells can be reprogrammed to become pluripotent |
| 2015 | Satoshi OMURA | Kitasato University | for their discoveries concerning a novel therapy against infections caused by roundworm parasites |
| 2016 | Yoshinori OSUMI | Tokyo Institute of Technology | for his discoveries of mechanisms for autophagy |

## 5. European Union-Japan Cooperation on Health

The EU and Japan cooperate in multilateral initiatives[15] aimed at addressing global health challenges. These are in particular the International Human Epigenome Consortium[16] (IHEC), the Human Frontier Science Programme Organisation (HFSP)[17], the International Human Microbiome Consortium (IHMC)[18], the International Cancer Genome Consortium (ICGC)[19], and the International Mouse Phenotyping Consortium (IMPC)[20].

The Japan Agency for Medical Research and Development (AMED)[21], launched in 2015, represents an important interlocutor on health research cooperation with Europe. AMED has joined the International Rare Diseases Research Consortium (IRDiRC)[22] and the Global Research Collaboration for Infectious Diseases Preparedness (GloPID-R)[23], as well as the Global Alliance for

14 Source: The Japan Association of National Universities/ Nobel prize HP
15 Roadmap for EU-Japan ST cooperation- EC October 2017
16 http://ihec-epigenomes.org/
17 http://www.hfsp.org/
18 http://www.human-microbiome.org/
19 http://icgc.org/
20 http://www.mousephenotype.org/
21 https://www.amed.go.jp/en/index.html
22 http://www.irdirc.org/
23 https://www.glopid-r.org/

Chronic Diseases (GACD)[24]. These initiatives will constitute the frame to ensure cooperation between the EU and Japan in the future via regular meetings among members.

AMED has a permanent representation in the UK. On bilateral agreements, AMED signed a MoU with Spain in 2017, and in March 2018 the first Joint funding call was launched for collaborative research (Japan-Spain) in early stage nanomedicine projects[25].

There is further scope for cooperation through the European and Developing Countries Clinical Trials Partnership[26] (EDCTP). An area where cooperation might be strengthened is anti-microbial resistance, in the frame of the Joint Programming Initiative on Anti-Microbial Resistance which Japan joined in 2016.

Japanese researchers, universities, research organisations and enterprises can team up with European partners to participate in projects under **Horizon 2020.** As a high-tech country, well advanced in research and innovation, Japanese participants are, however, not automatically funded through Horizon 2020. Japanese participants have to determine themselves the sources of funding and find the resources for their part of the project. These may be own funds, as well as funds received from Japanese ministries, agencies, foundations and other organisations that fund research and innovation activities in Japan.
One way to implement the targeted opening of Horizon 2020 to third country participants is through "coordinated calls", which are organised jointly with funding organisations from third countries. This has worked well with Japan for nine calls during the period 2011-2017 in the fields of ICT and ICT robotics/health (with the Ministry of Internal Affairs and Communications - MIC - and the National Institute of Information and Communications Technology of Japan - NICT).

[24] https://www.gacd.org/
[25] http://www.idi.mineco.gob.es/stfls/MICINN/AEI/ficheros/Japan_Spain_Nanomedicine_Call.pdf
[26] http://www.edctp.org/

## 6. Industry- Academia Collaborations in Japan.

Industry-Academia collaboration has evolved in Japan in order to facilitate interactions between the two institutions. Until 1980, restrictive government regulations caused levels of collaboration to remain low. After the introduction of the 1995 Science & Technology Basic Law, and the Technology Licensing Organisation (TLO) Act, the level of interaction improved.

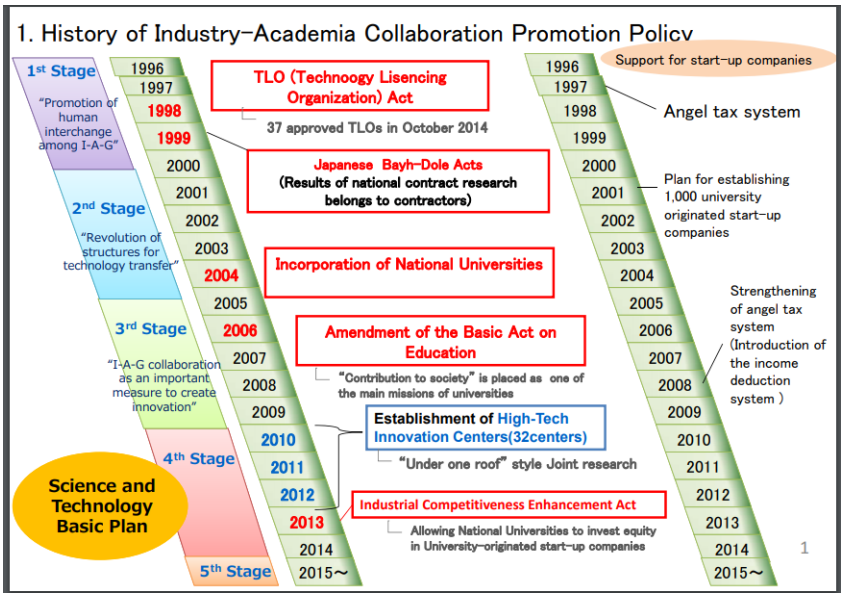
Japan National universities used to be government organizations until 2004, when they became independent agencies. With their incorporation, national universities increased their degree of freedom in activities such as investment on Technology Licensing Organizations (TLOs) and possession of patents. Universities can be officially the owner of the IP generated by its researchers, and TLO is the operating arm that performs technology transfer activities on behalf of or together with the University. For more information on the nature and characteristics of technology transfer system and TLOs in Japan, see the report by Luca Escoffier published in 2015 by the EU-Japan Centre for Industrial Cooperation.[27]

In 2006, the amendment of the Basic Act on Education meant that contribution to society, including university-industry collaboration, was placed as one of the principle missions of universities along with education and research.

From 2008 to 2013, METI supported establishment of facilities of potential strongholds, in major regions, where Industry-Academia-Government get together “under one roof” in order to bridge leading technologies in the region for practical development.

[27] Japan’s Technology Transfer System: Challenges and Opportunities for European SMEs

**Figure 6.1: Industry Academia Collaboration Promotion Policy in Japan**[28]




In 2013, based on the Industrial Competitiveness Enhancement Act[29], National Universities started to be allowed to invest equity in university- originated start-up companies.

In 2016, Japan Revitalization Strategy decided by the Cabinet, set the following governmental goal: "Tripling the investment value from companies to universities and national R&D institutes by 2025 to surpass the average investment level of other OECD member states".

In light of that goal, METI and MEXT recognize the importance of fortifying related systems in universities to deepen the industry-academia collaboration. To this end, the ministries jointly established the Council of Industry-Academia-Government dialogues for the promotion of innovation.

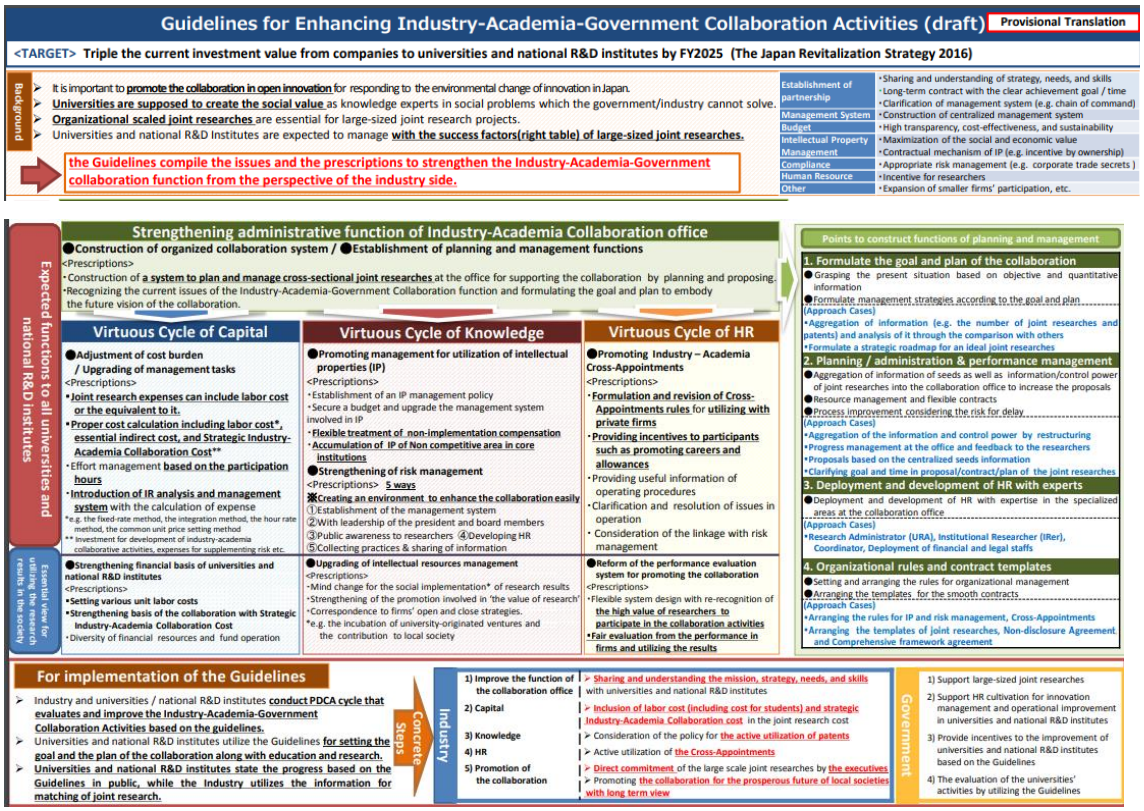
Guidelines were issued in November 2016, clarifying the prescriptions to strengthen the **Industry-Academia-Government** collaboration activities[30], from the perspective of Industry.

https://www.rieti.go.jp/en/events/bbl/16110101_watanabe.pdf https://www.rieti.go.jp/en/events/bbl/16110101.html

[29] http://www.meti.go.jp/english/press/2016/1130_001.html

[30] http://www.meti.go.jp/english/press/2016/pdf/1130_001a.pdf

**Figure 6.2: Guidelines for enhancing Academy-Industry-Government Collaboration activities**




## Collaborative Research

While license agreements on the use of university technologies are a common way of knowledge transfer between research institutions and companies, contractual research is also a major channel of university-industry collaboration in Japan[31]**.** Research results from such cooperation contracts are likely to be licensed smoothly because there is already an industrial partner, and industrial property rights are at the center of the contract negotiation process.

If a company, or any organization, wants to have a formal research collaboration agreement with a national university in Japan, then it has to enter into **either a joint research contract** or **commissioned research** with the university.

- Under **joint research,** the University receives funds and researchers **mainly from private firms** to conduct research on common projects. Researchers from private companies are allowed to work at the University premises.

[31] "Academic Patenting in Japan: Illustration from a Leading Japanese University" by Makiko Takahashi, René Carraz. http://www.beta-umr7522.fr/productions/publications/2009/2009-07.pdf

- **Commissioned research contracts** involve governmental agencies in 80% of the cases (rather than private firms), or private companies under a national project scheme.

In Japan the ratio of corporate research and development (R&D) investment in domestic universities is **less than 1% of the total corporate R&D budget**. For comparison, OECD data for 2013 report a 3.73% ratio in Germany, and 1.7% in the UK. The expense of each industry-academia collaboration remains small, less than $30,000, compared to some other countries (in the US it averages around 1 Million US$)[32].

Specific data on the **life sciences industry-academia** linkage in Japan, published in 2007 by Professor Kneller[33] from the University of Tokyo, show that **only 18% of life science inventions arise under joint research,** and of these, only one third involve large companies (the remaining arising from joint research with start-ups or other small companies). The situation in the Japanese life sciences sector is different from other fields, such as engineering, chemicals and IT software, where joint research with large Japanese companies, usually accounts for a much larger proportion of inventions.

32 https://www.rieti.go.jp/en/events/bbl/16110101_watanabe.pdf
33 Kneller, R. J Technol Transfer (2007) 32: 435. https://doi.org/10.1007/s10961-006-9024-9 The beginning of university entrepreneurship in Japan: TLOs and bioventures lead the way

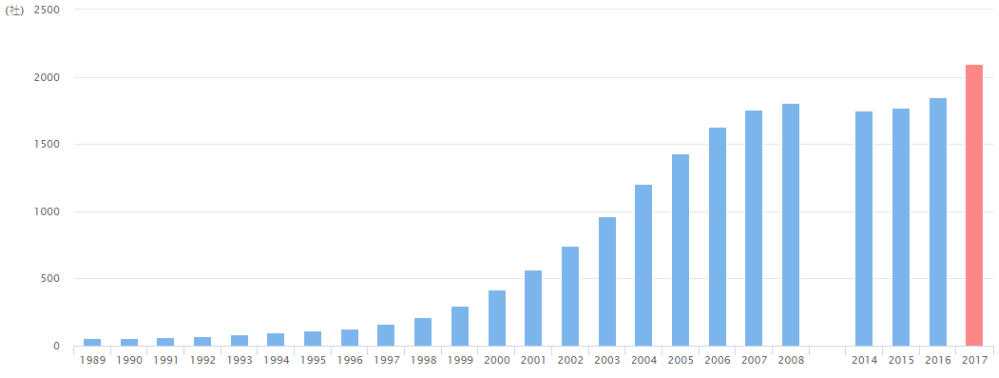
## 7. Entrepreneurship and policies supporting Bioventures in Japan

Business start-up rates for all fields are quite low in Japan (around 5% compared to 14 % and 12 % in UK and France respectively). The proportion of population with entrepreneurial motivation lags behind in Japan (around 23%) compared to USA (77%), Germany (69 %) or France (61%).[34].

On academic entrepreneurship, the year 2000 law to strengthen industrial technology is considered to have facilitated start-ups foundation, by enabling university researchers to consult openly for companies and to manage ventures. [35]

In fiscal year 2017, the number of start-ups created to commercialize results of R&D from Japanese Universities rose by 13% according to METI surveys[36], surpassing a total of two thousand companies for the first time, with 2093 university- based startups.

**Figure 7.1: Trend in the number of university based start-ups in Japan**



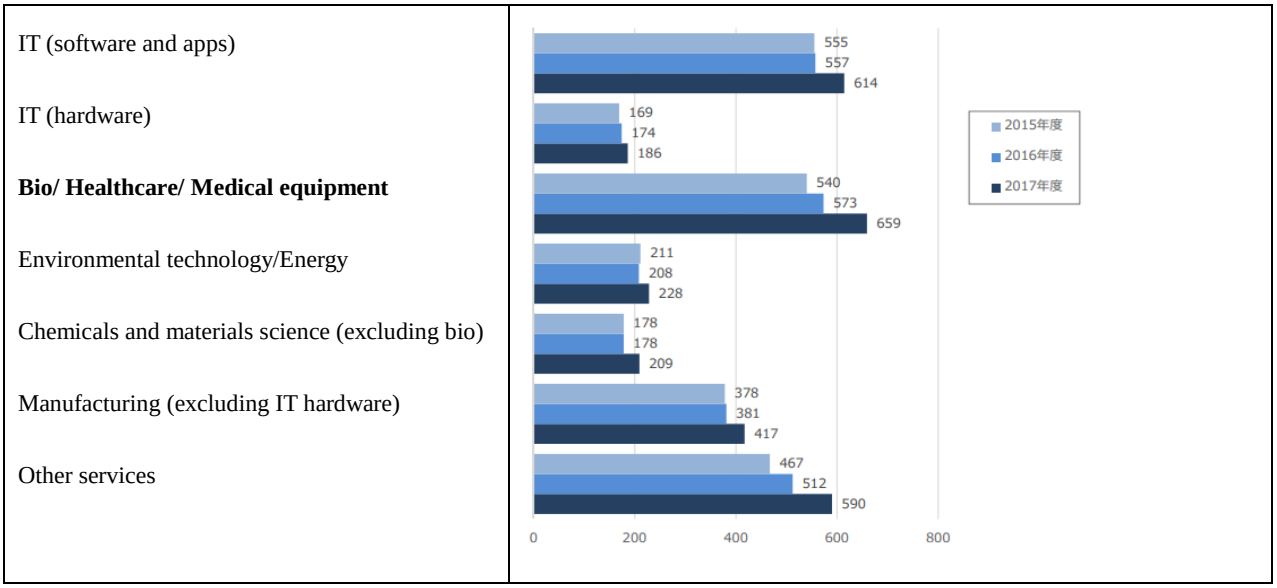

Source: METI

The biggest category of university ventures are **bio, healthcare and medical equipment start-ups (659),** followed by IT applications and software (614 start-ups)[37].

The number of biotech, healthcare and medical equipment start-ups has increased a 13%, in fiscal year 2017, with 86 new bioventure companies created. Survey data show that this category was also the one with highest growth.

[34] NISTEP
[35] Kneller http://www.kneller.tokyo/pdf/New_Japanese_technology_transfer_system_and_entrepreneurship.pdf
[36] http://www.meti.go.jp/press/2017/03/20180309007/20180309007.html; Full report (in JP) http://www.meti.go.jp/press/2017/03/20180309007/20180309007-1.pdf
[37] NIKKEI Asian Review, March 9, 2018.

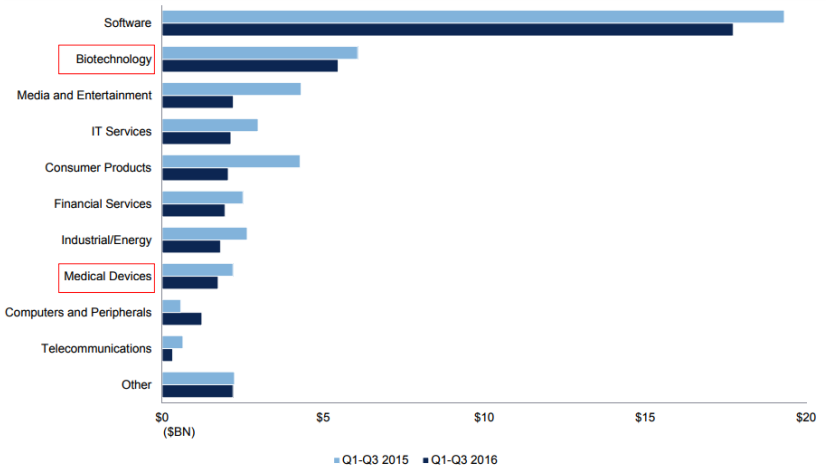
**Figure 7.2: Number of university based start-ups in Japan, per sector**




METI launched in March 2018, a new online university venture database, which at the time of finalizing this report was still under construction. The database was expected to include information on the ventures creation, company data on major investors and alliances, as well as company expectations for overseas expansion.[38]

In terms of venture capital investment worldwide, biotech is the second field receiving more funds

**Figure 7.3: Worldwide Venture Capital investment distribution by industrial sector**




**Source Thompson-Reuters**[39]

[38] http://www.meti.go.jp/policy/innovation_corp/univ_startups_db/
[39] PwC/NVCA MoneyTreeTM Report, Data: Thomson Reuters (from UTEC presentation Feb 2017)

In recent years, the government of Japan has acknowledged the importance of biotechnology innovations for economic growth, and the driving force role of healthcare ventures as a vehicle that will be key to the success or failure of innovation.

In 2016, the Ministry of Health Labour and Welfare (MHLW) sponsored a **"Roundtable on promotion of venture businesses responsible for medical innovation"**. It was realized that despite its high potential due to excellence in research and number of seeds, Japan medical venture development was lagging when compared to situation in western countries. Problems identified concerned three main areas:

- Human Resources: Scarcity of entrepreneurs and people with necessary skills. Low movement between academia-industry-government.
- Financial: Lack of financial support for venture businesses
- Weak connection with overseas, low visits inbound and outbound

**"Make Medical Ventures a Driving Force for Innovation!"**[40], was the title of the report thereafter issued by MHLW in July 2016 , prescribing promotion measures to be put in place to *"*incentivize medical venture blossom". The main actions cited in the report include the construction of a **"Venture Support System"** at MHLW as well as at the Pharmaceuticals and at the Medical Devices Agency (PMDA). **MHLW** responds to questions from ventures on R&D, regulatory aspects on conduct of research, and **overseas development**. **PMDA** is providing specific consultation procedures on R&D strategy, with a 90% fee discount for the venture biotech business and academia.

In October 2017, MHLW organized the first **Japan Healthcare Venture Summit**, taking place within BioJapan exhibition, one of the biggest biotechnology trade fairs in Japan (see page 90). Bioventures present at the Summit[41], around 60 companies, were start-ups arising from universities, or young ventures originating as spin-offs from pharmaceutical companies. The full list of companies exhibiting at the Summit is presented in Annex 1 to this report (see page 92).

In November 2017, the Bio-Industry Division, Commerce and Service Industry Policy Group, in charge of the relevant policies on Bioventures at METI, announced the establishment of a Study Group to discuss how **to enhance the competitiveness of the drug development industry by improving the environment in which bioventures are able to raise funds**[42].
According to METI, the comparison between number of shareholders of listed biotech venture businesses Japan and the United States shows that individual investors account for the majority of

[40] http://www.mhlw.go.jp/english/dl/20160729.pdf
[41] http://www.jhvs.jp/en/index.html
[42] http://www.meti.go.jp/english/press/2017/1113_003.html

these shareholders in Japan, while institutional investors account for the majority in the US. METI estimates the market value of Japan listed bio-venture businesses at approximately 1 trillion yen (€7.6 billion), which is lower than the figures not only from western countries, but also from other Asian countries.

Specifically, METI promotes the Study Group with the objective to:

- Encourage dialogues between **Japanese and Overseas investors** with domestic bioventures
- Streamline processes and minimize obstacles for bioventures listed on Tokyo Stock Exchange Markets (Mothers and JASDAQ) in Japan
- Discuss approaches to drafting and implementing necessary policy measures.

Support from the government of Japan for the development of bioventure ecosystem is a trend set to continue in 2018. In the budget for **MHLW for fiscal year** 2008 (April 2018-March 2019) 7.3 billion yen (€54 Million) are allocated to this end.

**In conclusion:**

Entrepreneurship has been positioned as crucial for innovation in Europe, and certainly the same is true for Japan and other Asian countries. More than ever before, programs to promote entrepreneurial ventures and startups are being implemented through industrial, academic and government collaboration in Japan.

Japanese bioventures are developing services, including support to drug developers, typically in screening, synthesis, non-clinical pharmacology, pharmacokinetics, and safety assessment. The externalization of these R&D activities provides more flexibility to pharmaceutical groups, and also a richer source of seeds.

The bioventures being created may contribute to the establishment of a new ecosystem in the Japanese pharmaceutical industry and biotech field. This transition towards a less integrated model of pharmaceutical companies in Japan **may open new possibilities for European SME companies providing technologies and services** to Japanese drug developers.

Potential partnerships between European biotech SMEs/ startup companies, and Japanese bioventures may be worth exploring, looking for synergies between technologies and potentially enabling an expansion of the client base for both sides. Partnering with a local Japanese bioventure may enable for example, a European start-up to approach MHLW or PMDA more easily for regulatory consultations and questions on product development requirements in Japan.

## 8. Japan Academic Landscape- An Overview

A comprehensive description of all the biotechnology research laboratories in Japan, which are engaged in basic science and applied research, was beyond the scope of this report. A selection of universities and research institutes is presented, based on criteria that a priori would favour their approachability by European SMEs and clusters: the support they receive for **internationalisation** projects, the support from the university in **creation of academic ventures**, or their track record of **collaborative research** with biotech companies and pharmaceutical industry.

Research for this report was performed in 4Q2017-1Q2018. News on collaborative research published during that period by Japanese specialised media, like "Nikkei Biotech online" and "Pharma Japan Web" will also have influenced the inclusion of certain institutions in the report.

To illustrate the potential of innovative technology applications developed in Japan, **examples of relevant bioventures,** originated based on research seeds by academia, are described at the end of each section, mapping the origin of bioventure companies. The examples include recently established academic ventures, as well as some commercial stage companies, which originated as bioventures, and today have marketed products or clinical stage projects. Some of the bioventures have become public companies, and are listed in Tokyo Stock Exchange Market, most often on the Mothers or the Jasdaq indexes.

Japan has **86 national universities** (annex with list). Each university is expected to conduct operations with independence, developing their own unique style of education and research.

**Internationalization of Japan Universities: Japan Top Global Universities Project**

To strengthen the international competitiveness and compatibility of Japan's institutions of higher education, the Japan Society for the Promotion of Science (JSPS) in coordination with MEXT, gives priority support[43] to 13 world class universities designated as "top type" that proactively carry out **collaborations with top-level institutions overseas** and engage in thorough reforms toward globalization of their institutions.

43 https://tgu.mext.go.jp/en/universities/index.html

**Table 8.1: List of Japan Top Global Universities (as of January 2018)**

| Top Global University | Internationalization initiative |
|---|---|
| Hokkaido University | Hokkaido Universal Campus Initiative. Collaborate with the World |
| Tohoku University | Tohoku University Global Initiative |
| University of Tsukuba | Transforming Higher Education for a Brighter Future through transborder University Initiatives |
| The University of Tokyo | Constructing a Global Campus Model at UTokyo |
| Tokyo Medical and Dental University | Health for All－ TMDU initiative in creating next generation professionals for global health promotion |
| Tokyo Institute of Technology | Enhancing Tokyo Tech Education and Research Quality through Administrative Reforms for Internationalization |
| Nagoya University | Asian Hub University contributing to a sustainable society in the 21st century |
| Kyoto University | Japan Gateway: Kyoto University Top Global Program |
| Osaka University | Global University "World Tekijuku" |
| Hiroshima University | Hiroshima University Global Campus Expansion and Innovation Initiative |
| Kyushu University | Strategic Hub Area for top-global Research and Education, Kyushu University |
| Keio University | Enhancing Sustainability of Global Society through Jitsugaku (Science) |
| Waseda University | Waseda Goes Global: A Plan to Build a Worldwide Academic Network that is Open, Dynamic and Diverse |

**World Premier International Research Center Initiative (WPI)**[44]

WPI was launched by the Ministry of Education, Culture, Sports, Science and Technology in 2007, based on the 3rd science and technology basic plan (issued by the Cabinet in 2006) with a mission to create **globally open and appealing centers of research that serve as pivotal hubs** for international researchers circulation.

The program has four basic objectives: advancing leading-edge research, establishing international research environments, reforming research organizations, and creating interdisciplinary domains. Under the Program's second phase, started in 2017, new centers are being launched

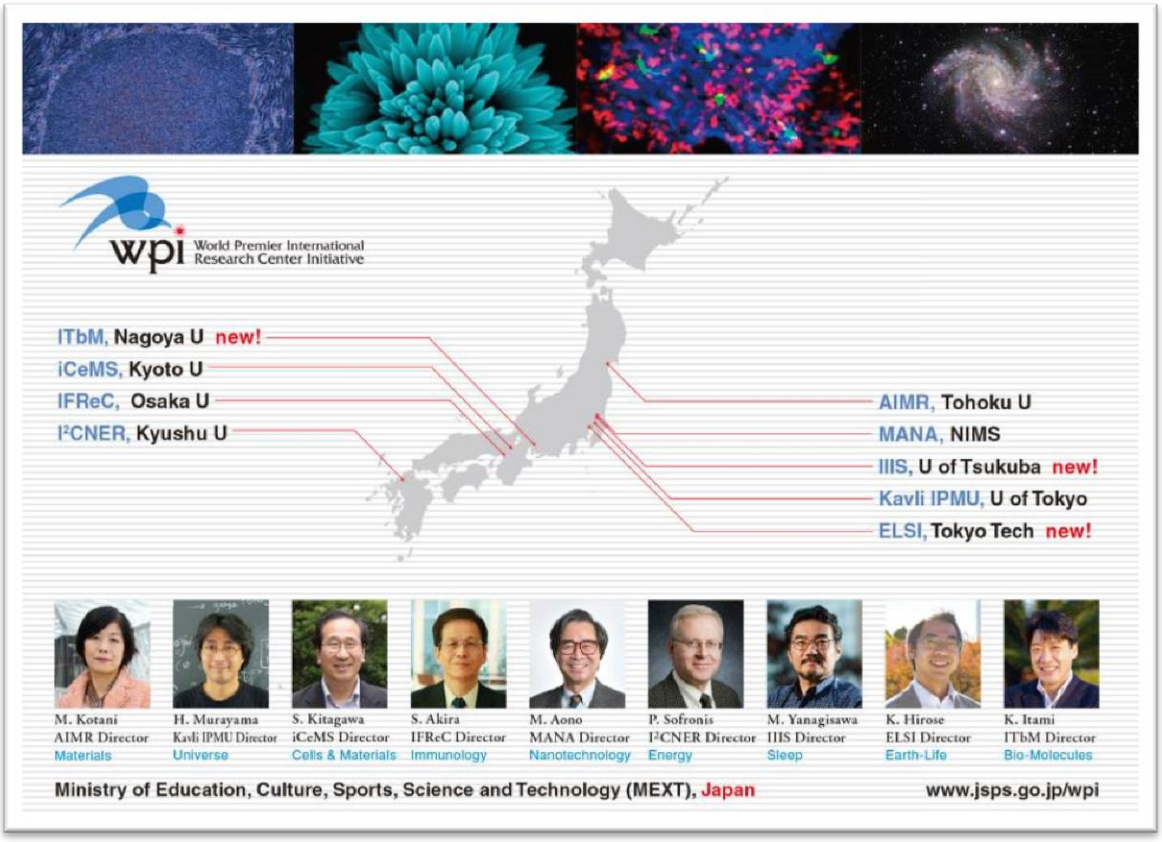
Within the **biotech life sciences area**, we can highlight the following centers which have been selected by the government to take part in the WPI initiative

[44] http://www.jsps.go.jp/english/e-toplevel/

**Table 8.2: WPI research centers related to healthcare biotechnology**

| | |
|---|---|
| Kyoto University | **Institute for Integrated Cell-Material Sciences (iCeMS)** (see page 50) |
| Osaka University | **Immunology Frontier Research Center (IFReC)** (see page 58 ) |
| Nagoya University | **Institute of Transformative Bio-Molecules (ITbM)**[45]<br>ITbM is world-leading molecular research institute for designing and synthesizing molecules directed towards the discovery, visualization, and manipulation of biological systems. ITbM will be **establishing a consortium in April 2018 to build a network between industries** in ITbM. |
| Kanazawa University | **Nano Life Science Institute (NanoLSI)** selected for WPI in 2017, aims for acquiring a fundamental understanding development, disease and aging through transdisciplinary research of Nanometrology, Biological, Medical, Pharmaceutical Science, Supramolecular Chemistry and Computational Science. |

**Figure 8.1: World Premier International Research Center Initiative**




[45] http://www.itbm.nagoya-u.ac.jp/en/news/2017/08/itbm-consortium.php

**Industry-Academia track record of collaborations**

The table below lists the Japanese universities with receiving higher income from collaborative research with Industry (in all fields confounded)

**Table 8.3: Ranking of universities receiving highest income from collaborations with Industry**

| Ranking 2014 | University Institute | Amount (in thousand JPY) | Amount (in Million €) | Ranking in 2013 |
|---|---|---|---|---|
| 1 | University of Tokyo | 4.840.830 | 36.45 | 2 |
| 2 | Kyoto University | 4.792.490 | 36.42 | 1 |
| 3 | Osaka University | 3.215.597 | 24.4 | 4 |
| 4 | Tohoku University | 2.743.606 | 20.84 | 3 |
| 5 | Kyushu University | 1.901.041 | 14.44 | 5 |
| 6 | Keio University | 1.585.213 | 12.04 | 6 |
| 7 | Nagoya University | 1.431.172 | 10.87 | 7 |
| 8 | Tokyo Institute of Technology | 1.409.436 | 10.71 | 8 |
| 9 | Hokkaido University | 994.079 | 7.55 | 10 |
| 10 | Waseda University | 592.542 | 4.5 | 11 |

**Source: Adapted from Kyoto University "Research Report of Industry Academia collaborations, 2014"**

**University start-up creation: Accumulated number of academic ventures**

The latest survey on university-originated ventures conducted by METI in Fiscal Year 2017 (published in March 2018)[46], ranks Japanese Universities based on the accumulated total of number of ventures originated per academic institution.

**Table 8.4 : Japanese universities by number of ventures (all fields confounded) in Fiscal year 2017. (METI)**

| | University | Accumulated # Ventures | | University | Accumulated # Ventures |
|---|---|---|---|---|---|
| **1** | University of Tokyo | 245 | **7** | Nagoya University | 69 |
| **2** | Kyoto University | 140 | **8** | Tohoku University | 56 |
| **3** | University of Tsukuba | 98 | **9** | Tokyo Institute of Technology | 53 |
| **4** | Osaka University | 93 | **10** | Digital Hollywood Unversity | 52 |
| **5** | Kyushu University | 81 | **11** | Keio University | 51 |
| **6** | Waseda University | 74 | **12** | Hokkaido University | 49 |

[46] http://www.meti.go.jp/press/2017/03/20180309007/20180309007-1.pdf

**The University of Tokyo**

The University of Tokyo has been ranked Japan's top research-intensive university in every edition of the Times Higher Education World University Rankings[47] since they began in 2004.

With regard to biotech applications in healthcare, we can highlight some initiatives and research institutes from the University of Tokyo, often involved in public-private collaborative research:

- The Institute of Medical Sciences (IMSUT);
- The Translational Research Initiative of the University of Tokyo;
- The Research Centre for Advanced Science and Technology (RCAST)

**The Institute of Medical Sciences of the University of Tokyo (IMSUT)**


With its own affiliated hospital, **IMSUT**[48] is one of the leading university-associated research institutes for medical and life science in Japan. Focusing on **infectious disease, cancer and immunological diseases**, IMSUT mission is to translate basic research findings directly to novel drug, vaccine and medical therapies in a "bed to bench and bench to bed" approach.

IMSUT is engaged in numerous collaborative research projects with industry and academia.

For example, since December 2017 is working on a joint project with Astellas Pharma,Chiba University and Asahi Kogiosha, developping a rice-based oral vaccine " MucoRice-CTB"[49]genetically engineered to express vaccine antigens.

IMSUT is working on applications to vaccines against cholera, enterotoxigenic E. coli and viral gastroenteritis diarrhea. This is a CiCLE project, supported by the Japan Agency for Medical Research and Development (AMED).

Another example of collaborative research with Industry, are the results published in March 2018, on the development of a prototype diagnostic kit for bladder and hepatic cancer with Abott Laboratories (US), based on an antibody specific to laminin γ2 monomer discovered at IMSUT Division of cancer cell research.[50]

[47] https://www.timeshighereducation.com/news/times-higher-education-japan-university-rankings-2017-results
[48] http://www.ims.u-tokyo.ac.jp/imsut/en/
[49] http://www.ims.u-tokyo.ac.jp/imsut/files/171206e.pdf
50 http://www.ims.u-tokyo.ac.jp/imsut/files/180213e.pdf

In 2018, calls for collaborative research[51] have been issued by IMSUT covering three main research areas:

- Development of Cutting Edge Medical Therapies
- Genome/Cancer/Disease Systems Biology
- Infectious Diseases and Immunology

IMSUT has international cooperation agreements with multiple countries, including in Europe the **Institut Pasteur (France).** In 2015 the University of Tokyo established a New York based office, and one year later, IMSUT co-organized the symposium "**Tokyo - New York Stem Cell Summit**" with the New York Stem Cell Foundation.

**The Translational Research Initiative by the University of Tokyo**

The University of Tokyo has set up an initiative to oversee translational research (TR)[52] activities, under sponsorship of MEXT initiative. In TR, fundamental science results are bridged to clinical applications.
In addition to **drug development**, the initiative includes also TR in **medical devices, regenerative medicine,** and research on **platform technologies** for medical applications

The TR initiative includes a dedicated **Translational Research Advancement Center (TRAC)** managing the assessment of seeds and industrial property (IP) rights, as well as the formation of networks both internally and with external organizations and companies. The initiative extends to departments and laboratories conducting TR-related research.

The center is **open for cooperation with the industry** and promotes developing solutions and services to match the needs of each organization so as to turn research into practical applications.
It supports the process leading to commencement of clinical trials, and then the clinical research center takes over.

A **Cell Processing Center CPC** established in 2007, is also part of the available infrastructure, as well as the Medical Science and Research Hospital.

[51] http://www.ims.u-tokyo.ac.jp/imsut/en/lab/organization/
[52] http://plaza.umin.ac.jp/tri-u-tokyo/en/index.html

The **CFTV** is a core facility for GMP preparation of **viral vectors for gene therapy.**
The department of cell processing and transfusion operates the clinical cellular engineering facility and manufactures cells necessary for regenerative treatments and cell therapy, as well as cells for research purposes.

Facilities can be used by researchers from outside the University of Tokyo, and the center is also o**pen to contracted research from Industrial partners.** The center can also offer support in:

- Investigational product manufacturing
- Consultations on Regulatory Affairs with PMDA, MHLW (on R&D strategy, IND application, pharmaceutical affairs…)
- Clinical protocols. Data center tasks, etc.

Examples of ongoing research are described in the website, including projects for which the University is currently **seeking for industrial partners**[53].

In January 2015, the **TR Initiative** and the **U.K. Medical Research Council** technology transfer division (MRCT) concluded a memorandum of understanding on joint research. Accordingly, antibody preparations and small molecule drug products from UTokyo were adopted as MRCT drug development projects.

The TR initiative is supported by a promotion fund from corporate sponsors which includes major pharmaceutical companies:

| | |
|---|---|
| Asahi Kasei Corp. | Novo Nordisk |
| Eisai Co., Ltd. | Sanofi K.K. |
| Mitsubishi Tanabe | Shionogi & Co. |
| MSD K.K. | Sumitomo Dainippon Pharma |
| Novartis Pharma | Takeda |

In February 2018, the TR initiative held a symposium on the **future new possibilities of innovation funding**. It included presentations of alternative models by:

- Italian Fondazione Telethon, as a granting agency for the development of orphan drugs.
- The GHIT fund (see section 9) on global health development and partnering models.
- Crowd funding clinical research via READYFOR Inc. platform
- UTEC venture capital operation fund by the University of Tokyo (see page 42)

[53] http://plaza.umin.ac.jp/tri-u-tokyo/en/about/index.html

**The Research Centre for Advanced Science and Technology (RCAST)**

Since its founding, The Research Centre for Advanced Science and Technology (RCAST)[54] has pursued interdisciplinary research activities in a wide range of areas based on four principles: an interdisciplinary approach, mobility, an international perspective, and openness. Details of its Industrial partnership coordination unit are available online[55].

As an example, in January 2018, RCAST announced a collaborative research agreement for developing a **personalized cancer vaccine**[56] with the Kanagawa Cancer Center in Yokohama and **BrightPath Biotherapeutics**[57], a clinical stage biopharmaceutical company based in Tokyo. The collaboration consists of genomic, proteomic and immunology research, promising to lead to the next phase of clinical studies for a fully personalized cancer vaccine.

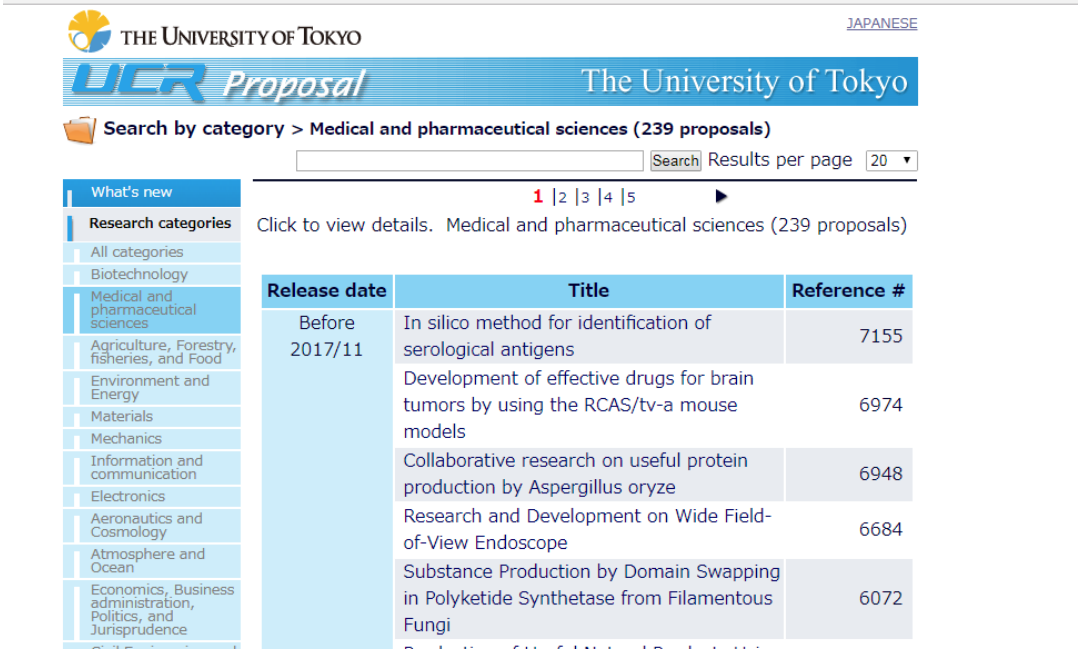
54 http://www.rcast.u-tokyo.ac.jp/index_en.html
55 //www.rcast.u-tokyo.ac.jp/IAG/index_en.html
56 http://pdf.irpocket.com/C4594/UV5D/wApI/wDyM.pdf
57 https://www.brightpathbio.com/english/

**The University of Tokyo- Organisation of the Collaborations with Industry**

The Division of University Corporate Relations (DUCR)[58] works to promote collaborations between Tokyo University researchers and society. Around 1600 public-private projects have already take place. DUCR also works on projects with overseas institutions and international organizations.

It is possible to search online the University Corporate Relations **(UCR) database**[59] which includes **proposals for collaborative research**. The database is searchable by key words and by categories (including Biotechnology and Medical and Pharmaceutical Sciences). Inquiries can directly be sent through an online form.

**Figure 8.2: University Corporate relations database of proposals- University of Tokyo**




**Support to venture companies at the University of Tokyo**

The University of Tokyo conducts venture support through cooperation with the University of Tokyo Edge Capital Co., Ltd. (UTEC), The University of Tokyo Cooperative Platform Development Co. Ltd (UTokyoIPC), and TODAI TLO, Ltd. an organization in charge of technology transfer activities.

The University of Tokyo has already created more than 250 university-related ventures, and their market capitalization exceeds 1 trillion yen (€7.6M).

[58] http://www.ducr.u-tokyo.ac.jp/
[59] http://proposal.ducr.u-tokyo.ac.jp/cgi-bin/ccr_usr/EN/srch_bunya.cgi?bunya=2

**The University of Tokyo Edge Capital Co., Ltd. (UTEC)**[60]

Founded in 2004, as a "technology transfer operator", this venture capital fund management operates through investment activities in venture companies utilizing technology and human resources of University of Tokyo and other research institutions.

By January 2018, UTEC had managed four funds totaling approximately JPY 45.6 billion (€350 million), and had invested in some 80 start-ups, 9 of which have gone public, and 10 have been acquired in M&A transactions.

UTEC plans to continue to support the creation and promotion of start-ups making of superior science and technology, collaborating with universities and research institutes **not only in Japan but also around the world.**

**The University of Tokyo Cooperative Platform Development Co., Ltd.**[61]

Founded in 2016, it was the second venture capital operating company owned by the University of Tokyo, to promote funding for investment in venture companies originating from Tokyo University.

**Table 8.5 : Examples of companies having originated as the University of Tokyo Bioventures**

| | |
|---|---|
| PeptiDream | **PeptiDream Inc**[62]**.** is one of the few Japanese biotech ventures that have grown into billion dollar companies. Its model of collaborative research and development, contributes solutions to facilitate drug discovery & testing. Core technology is based on the **peptide discovery platform system** (PDPS) developed by Prof. Suga at the **University of Tokyo Research Center for Advanced Science and Technology RCAST** (see page 41).<br><br>Set up in 2006 as an academic bioventure, the company went public in 2013.<br>The number of license agreements signed with pharmaceutical companies worldwide is a great example of Japan's scientific and technological capabilities.<br>Strategic alliances include major pharma companies from Japan and overseas. |

60 https://www.ut-ec.co.jp/
61 https://www.utokyo-ipc.co.jp/company/
62 Peptidream.com


In 2016, PeptiDream partnering strategy expanded to smaller companies and academia, e.g. with JCR on **brain penetrating drugs**, with Modulus on use of computational chemistry, with Heptares on GPCR targeting expertise and with kleo on **immunooncology**.

PeptiDream has labs at **LiC Kawasaki** (see page 80) and does joint research **in neurology with Kawasaki Medical School** on a novel treatment for Duchenne muscular dystrophy (DMD).

**A new spin-off (Peptistar) is expected to operate from 2019 as CMO.**

Prof. Suga received the Japan venture award by Prime Minister Abe, Innovators award in 2016, and the Japan Science Council chairman's award in 2011, for his promotion of Industry-Academia-Government collaboration.

**GlyTech Inc.**[63] is a pioneer in glycoscience/glycotechnology, having established the large-scale manufacturing process for highly purified and characterized human type N-glycans, as well as the chemical synthesis of glycopeptides and glycoproteins.

GlyTech expects to play a significant role in developing **innovative bio-betters** with high functionality. Its technologies can contribute to developing safer and lower-cost biopharmaceuticals.

**PharmaBio Corporation**[64], is Japan's first private sector contract development and manufacturing organization (CDMO) specialized in **cellular and tissue based** products. The company is **applying AI** to perform continuous tuning of the manufacturing process by feeding back analysis results of numerous combinations of regenerative medicine products manufacturing related

[63] http://www.glytech.jp/en/
[64] www.pharmabio.co.jp/en

| | |
|---|---|
| | parameters. Is included in the designated core project of the Tokyo Area zone in the National Strategic Special Zone. |
| TAGCyx Biotechnologies | **TagCyx biotechnologies**[65]<br>"Xenoligo™ system" is a technology for identification of novel nucleic acid based drugs. It enables screening of drug candidates from diverse oligonucleotide libraries containing the highly functional "fifth base", and stabilizing molecules using proprietary technology.<br>Founded in March 2007 as a spin out company of RIKEN, it is currently based at **Tokyo University, Komaba Open Laboratory.** In 2016, it raised 500 million Yen (€3.8M) financing by UTEC as a lead investor. In February 2017, TagCyx biotechnologies signed 2 year collaboration agreement with a European biopharma company (name not disclosed). |
| MOLCURE | **Molcure**[66]<br>High-functional antibody drug development platform based on next generation sequencing and bioinformatics. Funded by UTEC in 2014. |

Other bioventures originating from the University of Tokyo, are not part of UTEC portfolio. **Jiksak Bioengineering**, **EdiGene, HanaVax and Rhelixa** are interesting examples of emerging biotech companies, based on technology from Tokyo University; **Medinet** is now a well-established CMO in regenerative medicine, having started on technology from Tokyo University IMSUT.

| | |
|---|---|
| Jiksak bioengineering | **Jiksak Bioengineering Co., Ltd.,** launched in February 2017, offers a drug screening service with Nerve Organoids. The Nerve Organoid represents an in vivo-like nerve structure. Jiksak develops a unique screening technology specialized for neurodegenerative diseases (amyotrophic lateral sclerosis ALS, Parkinson's disease, etc). Jiksak's platform provides an efficient method to actively drive drug development and toxicity test.<br>Jiksak Bioengineering is actively seeking partners to **develop nervous-disease models with stem cells.**<br><br>In January 2018, CEO Dr Kawada received the Nakatsuji Award on practical application of results to industrialization and commercialization. Jiksak was selected to receive support by New Energy and Industrial Technology |

[65] tagcyx.com/en/
[66] http://molcure.com/

| | |
|---|---|
| | Development Organization (NEDO).<br>In February 2018, Jiksak. secured 170 Million JPY (€1.3M) from ANRI, OHARA Pharmaceutical Co.,Ltd, Essential Pharma Co., Ltd. and MediFuture Co., Ltd. |
| EDIGENE | **EdiGene corporation**[67] is a drug discovery start-up originated in 2015 from University of Tokyo, engaged in R&D on genome editing technology that has improved **CRISPR-Cas9**, and in constructing next-generation drug discovery systems.<br>EdiGene co- founder **Prof. Nureki, from Graduate School of Sciences, University of Tokyo**, won #2 position in Nature's 10 most popular CRISPR papers of 2017 with his paper "Real-space and real-time dynamics of CRISPR-Cas9 visualized by high-speed atomic force microscopy".<br>EdiGene is currently **headquartered in Tokyo and conducting R&D from Cambridge, MA, USA**.<br>In December 2017, **Fujifilm** signed an agreement for the investment of 470 million yen (€3.5 M) in EdiGene Corporation. In the joint research with EdiGene, Fujifilm aims to apply its liposomal formulation technologies to encapsulate ribonucleic acid (RNA) designed and developed by EdiGene. |
| Rhelixa<br>Decoding Life, Creating Future | **Rhelixa Inc**[68]**.** was founded in February 2015, based on technology from Tokyo University RCAST (see page 41). Rhelixa develops analysis of genome and epigenome information (data obtained via NGS techniques) in an integrated platform. Rhelixa's core competence lies in providing machine learning softwares and screening techniques for epigenetic analysis that best fits the clients' needs. |
| HanaVax | **HanaVax Inc**[69] is a start-up established in December 2016, developing vaccines administered by small sprays into the nose, based on novel delivery formulations from Tokyo and Kyoto Universities. Antigens are retained on respiratory mucosal surfaces to initiate antigen-specific immune responses via the mucosal immune system. A human pneumococcal nasal vaccine to prevent pneumonia, sepsis and otitis media is under development. |

[67] http://edi-gene.com/
[68] http://rhelixa.com
[69] http://www.hanavax.co.jp/en

| | |
|---|---|
| Emerging Bio-medical Technology MEDI NET | **Medinet Co. Ltd.**[70] originated in 1995 as a venture from IMSUT (see page 38) pioneering research in **cancer immunotherapy**. Today is a listed company on Tokyo stock exchange market. Contract cell development and manufacturing (CDMO) is its core business. It has cell processing facilities in Tokyo, Yokohama and Osaka. According to Medinet, the size of domestic immuno-cell therapy market is about JPY10.0B (€76M), and the company holds a 20%. Medinet in-licensed autologous chondrocyte cartilage implant **NeoCart** from US Histogenics Corporation in 2017, and is conducting clinical development in Japan targeting knee cartilage defects, estimating to market by 2021. The pipeline includes AGS-003 for the treatment of metastatic renal cell cancer a**nd UK-based TC BioPharm's** ImmuniCell®, in which MEDINET has invested. |

[70] https://www.medinet-inc.co.jp/english/

**Kyoto University**

Kyoto University was the second university to be established in Japan, after the University of Tokyo. It has 2700 faculty members, with two thirds dedicated to natural sciences, 18 graduate schools and 13 research institutes. Nine of the Nobel Prize laureates in natural sciences from Japan are associated with Kyoto University.
Kyoto Graduate School of Medicine has a strong tradition of supporting drug discovery efforts. As an example of Kyoto seeds, nivolumab(anti-PD-1 antibody) was originated from research by Kyoto University Prof. Tasuku Honjo and Prof. Nagahiro Minato.

In the biotech field, flagship research institutes from Kyoto University include **The Center for iPS Cell Research (CiRA)** and the **Institute for Integrated Cell Material Sciences (iCEMS)**.

**Center for iPS Cell Research and Application (CiRA)**

CiRA[71] was officially inaugurated in 2010 with the mission of using induced pluripotent stem (iPS) cells in new medical therapies. Directed by Dr Shinya Yamanaka, 2012 Nobel laureate for his work on iPS cells, the center is committed to research, production and shipment of high quality iPS cells for use in regenerative medicine.
Also involved in drug discovery, in 2017 CiRA identified a potential drug candidate for fibrodysplasia ossificants progressiva (FOP).

**Figure 8.3: Dr. Shinya Yamanaka at CiRA symposium for the general public on July in 2016.**

CiRA researchers at Prof. Yamashita laboratory have used iPS cells to find a type of progenitor cells that when transplanted into mice almost exclusively produced cardiomyocytes, giving these cells great promise for future heart cell therapies.

[71] http://www.cira.kyoto-u.ac.jp/e/

CiRA is also working on the development of cell replacement therapy using iPS cells for intractable neurological diseases, mainly Parkinson's disease. In January 2018, a case of fraud and fabricated data in a publication on Blood-Brain Barrier with Human iPSC -Derived Endothelial Cells had to be retracted by CiRA[72], and a number of measures to deter and detect research misconduct had to be reinforced.

Since 2015, CiRA has a large-scale collaborative research program (totaling 100 researchers) with Takeda (**T-CiRA )**[73] aimed at new drug development for a number of diseases. T-CiRA is based at Takeda Shonan Research Center, in Fujisawa, Kanagawa (see page 82). It receives a collaborative funding of 20 billion yen (€151 M) over a 10-year period.

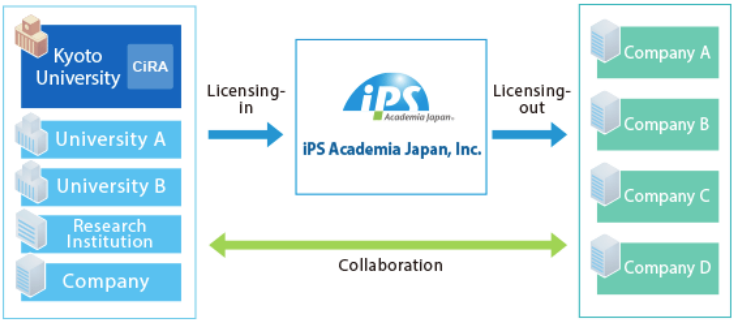
An increasing number of studies at CiRA are ongoing to bring iPS cells to clinical application.

As part of this effort, the **Facility for iPS Cell Therapy (FiT)** was founded within CiRA.

FiT is responsible for manufacturing clinical-grade iPS cells that will be distributed to institutes and organizations pursing regenerative medicine.

**iPS Academia Japan inc**[74] is acting as official iPS cell technology licensing organization (TLO) for CiRA (and other Universities in Kyoto and other regions).It is not involved in collaborative research agreements between the university and companies

**Figure 8.3: Collaborations from iPS Academia Japan Inc.**




As of September 2017, twenty-five entities from Europe had licensed from this TLO.[48] Some of these licensees are disclosed on iPS AJ website.

**Table 8.6: EU licensors of CiRA technology identified from iPS Academia Japan website**

| |
|---|
| Stemnovate , Elpis Biomed, Censo biotechnologies, Newcellsbiotech, Catapult (UK) |
| Myriamed , Repayron, Axiogenesis, Bayer, Merck (DE) |
| Univercell-biosolutions, Cellectis (FR); Pluriomics (NL) |

[72] http://www.cira.kyoto-u.ac.jp/e/pressrelease/news/150417-102717.html
[73] http://t-cira.takeda.com/t-cira/
[74] http://ips-cell.net/

## Institute for Integrated Cell Material Sciences (ICeMS)

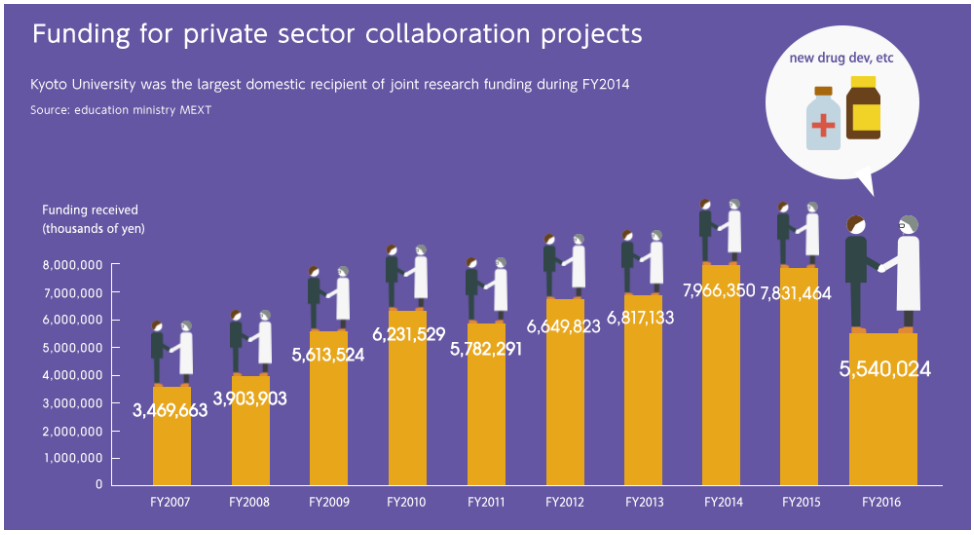
Founded in 2007, the Institute for Integrated Cell Material Science **iCeMS**[75] seeks to develop materials to comprehend cellular functions, produce materials to control processes in cells, and eventually to create functional materials inspired by cellular processes (cell-inspired materials). ICeMS is a WPI center (see page 35)

As an example of recent results (published in Nature Biomedical Engineering in March, 2018), the group of Koichi Hasegawa, has developed a novel culture solution for pluripotent stem cells such as ES cells and iPS cells, using three low molecular weight compounds that can be artificially synthesized without using growth factors. The material cost of the culture solution is said to be one fifth to one tenth that of the conventional one.

**Kyoto University: Industry-Academia Collaborations Organisation**

According to latest data by MEXT, in 2014 Kyoto University was Japan largest recipient of private sector research funds. Joint research funding from private sector totaled around €42 million in 2016.

**Figure 8.4: Kyoto University private sector collaborative projects**




Companies interested to collaborate with Kyoto University can liaise with **Society-Academia Collaboration for Innovation (SACI)**[76] which aims to promote effective networks with Universities, TLOs and private corporations, not only in Japan but also **globally.**

[75] iCeMS web
[76] http://www.saci.kyoto-u.ac.jp/wp-content/uploads/2017/03/society_academia_collaboration_method_pamphlet.pdf

SACI webpage[47] contains up-to-date information on technology developed by Kyoto University at various stages, i.e. patented results and also technology under research. SACI can coordinate and support such collaborations with the help of external organizations such as TLOs (Technology Licensing Organizations). SACI manages the "GAP Fund Program" and "Incubation Program" to support the commercialization of research results of Kyoto University.[77]

Other types of Industry-University linkage include Endowments and Endowed laboratories (donations), Commissioned Research, and Collaborative Research. Under **Collaborative research,** Kyoto University becomes an equal partner with companies in researching a particular topic by mutually providing researchers, research funds and facilities in order to produce optimal research results. Research can be conducted at university only or both at university and industrial partner site. Ownership of results, in terms of industrial property, is generally shared.

**Figure 8.5: Collaborative research schemes at Kyoto University**


There is no upper or lower limit as to how much collaborative research costs. Kyoto University indicates that 35% of projects cost between 1 and 3 million yen (7500 to 23000 euro).

More information on costs, direct and indirect expenses, and tax credit for collaborative projects is available on Kyoto University SACI website

In the medical science field, a specific organization at Kyoto University deals with relationships with Industry: **Kyoto University Medical science and Business Liaison Organisation (KUMBL)[78].**

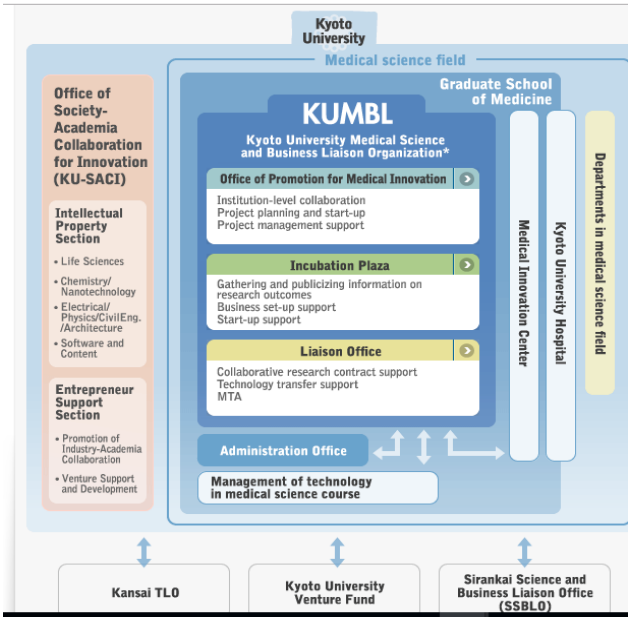
Successful collaborations initiated or supported by KUMBL include the 5 year institution level collaborative R&D agreements signed between the Graduate School of Medicine- Medical Innovation Center (MIC) and pharmaceutical companies Takeda, Dainippon Sumitomo Pharma Co.

[77] http://www.venture.saci.kyoto-u.ac.jp/
[78] http://www.kumbl.med.kyoto-u.ac.jp/e/index.html

Ltd. and Mitsubishi Tanabe Pharma Corporation**.** Research agreements have also been signed with Astellas and Canon on medical device development.[79]

KUMBL is also promoting the formation of ventures to exploit Kyoto university research results.
One of the programs supported by KUMBL to accelerate bioventures is **KYOTO-SPARK**, a training program for ventures in translational research. The SPARK network was originally developed at Stanford University (US), to showcase drug development programs that are ready for partnering or venture funding. SPARK has a global network, with representation of the program also taking place **in several European countries (Finland, France, Germany, Italy, Norway).**
SPARK biotech companies from Kyoto were presenting in Boston, US. in February 2018. Also in February 2018, the second KYOTO-SPARK Symposium "Value of Academic Translational Research" took place in Japan, with presentations by European start-ups like **Sartar therapeutics (FI).**

**Figure 8.6: KUMBL organization at Kyoto University**




**KyotoUniversity Innovation Capital Co. Ltd.**

京都大学イノベーションキャピタル株式会社
KYOTO-iCAP
KYOTO UNIVERSITY INNOVATION CAPITAL Co.,Ltd.

Kyoto University was the first to adopt the "support program for utilizing specified research results" approved by MEXT and METI based on the Industrial Competitiveness Enhancement Act, and participates in venture capital funds, through its own authorized Organisation

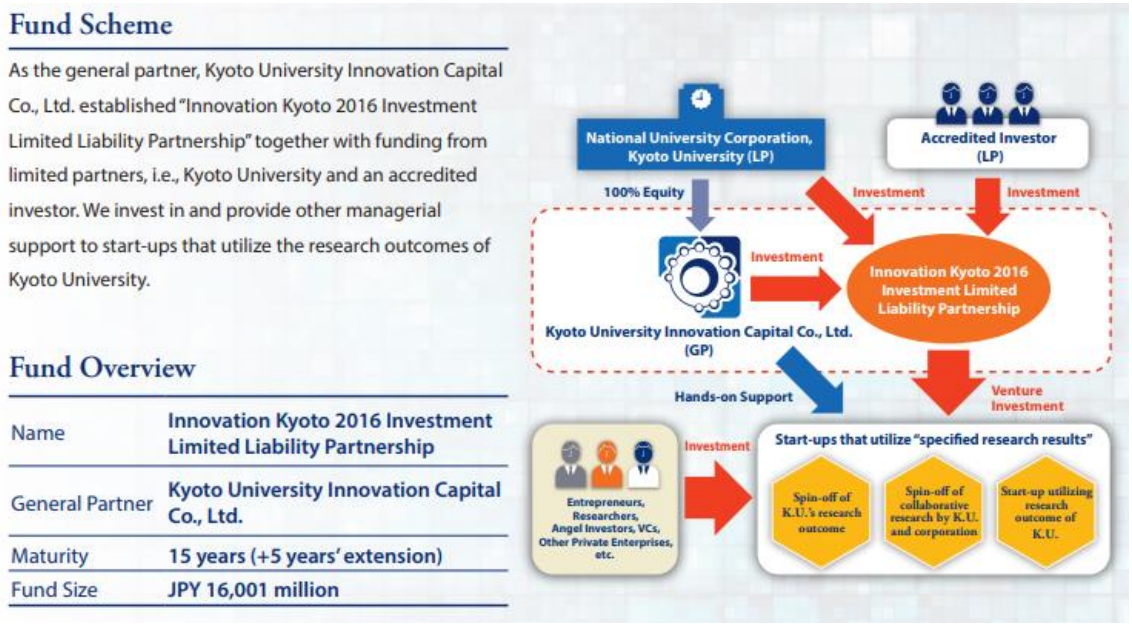
[79] http://www.kumbl.med.kyoto-u.ac.jp/e/innovation/results.html

**Kyoto University Innovation Capital Co. Ltd. (KU-iCap)[80].**

Founded in December 2014 as a wholly owned investment firm of Kyoto University, the venture fund mainly invests in start-ups and early-stage ventures, which endeavor to commercialize knowledge generated by the University's researchers.

In a "hands-on approach", it also provides assistance in designing a business and development plan, and a club for matching entrepreneurs and Kyoto University technology.

**Figure 8.7: Fund scheme by Kyoto University Innovation Capital Co. Ltd. (KU-iCap)**




Within Kyoto University, there is a venture incubation center[81] with office space. **Innovation Hub Kyoto[82] provides a wet lab for the life science field**. Outside the university, other facilities used by bioventures include: Creation Core Kyoto Takuma[83], Kyoto Research Park (KRP)[84], and Kyoto University Venture Plaza[85].

[80] http://www.kyoto-unicap.co.jp/unicap/wp-content/uploads/iCAP-PANF_en.pdf
[81] http://www.venture.saci.kyoto-u.ac.jp/?page_id=273
[82] http://www.ihk.med.kyoto-u.ac.jp/
[83] http://www.smrj.go.jp/incubation/cckm/
[84] http://www.krp.co.jp/
[85] http://www.smrj.go.jp/incubation / kkvp /

**Table 8.7: Examples of Bioventures supported by Kyoto University (KU-iCap)**

| | |
|---|---|
| SCAD Stem Cell & Device - Kyoto | **Stem Cell & Device Laboratory, Inc. (SCAD)**[86] was founded in May 2014, with the aim of commercializing stem cell and micro/nanotechnologies developed in the Kyoto University's Institute for Integrated Cell-Material Sciences **(iCeMS)**.<br>SCAD has developed proprietary human cell-based devices that serve the drug screening, safety and efficacy assay markets. SCAD-MT ™ cardiomyocyte is a quality-certified, ready-to-use nanofiber-based culturing device pre-plated with functional and stable human iPS cell-derived cardiac micro-tissues, characterized with 3D and highly oriented structures and **developed for drug discovery and development, and in vitro toxicology.** |
| SCi Kyoto Stem Cell Innovation | **Kyoto Stem Cell Innovation, Inc.**[87]**,** with CEO Professor Emeritus N. Nakatsuji, provides professional consultation services, through a global network of technical advisors, bridging academy and industry to support joint business development, advising and implementing the stem cell research outcomes.<br>Advisory services are offered to ventures and for investors interested in creating new stem cell technology. Fund research at universities and other institutions, including incubation and/or intermediary services for funding institutes |
| Chordia Therapeutics | **Chordia Therapeutics**[88]**,** founded in 2017, is dedicated to drug discovery in oncology areas of high unmet medical need, combining knowledge from Kyoto University with expertise in drug discovery. Its lead asset is a CDC-like kinase (CLK inhibitor) based on research by Professor S. Ogawa at Kyoto University on splicing abnormalities as causative events of cancer development. CLK is a kinase regulating RNA splicing.<br>Chordia receives support from Takeda, as other ventures based in the Shonan Park in Kanagawa (see page 84). By end of November 2017, the company had raised 1.2B Yen (€~9M) in Series A financing |

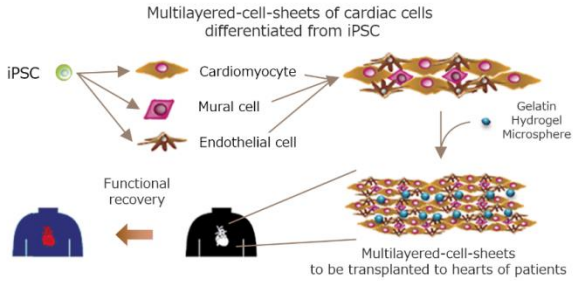
[86] Scad website
[87] http://kyoto-sci.com/biz-e.html
[88] http://www.chordiatherapeutics.com/eng/update/pdf/20171122_EN.pdf

| | |
|---|---|
| Kyoto Innovative for Neglected & Orphan diseases Pharma | **Kinopharma**[89] is a biopharmaceutical company, established in 2005 as drug discovery bioventure. Develops the clinical application of kinase inhibitors that founder Prof. Hagiwara discovered in his academic research. In July 2016 started an investigator initiated clinical trial with antiviral candidate compounds. In July 2017 opened drug discovery research centre at the innovation Hub of Kyoto University Pharmaceutical research building. |
| サイアス株式会社 | **Thyas Co. Ltd.**[90] was established in 2015, by CiRA and KYOTO-iCAP to focus on treating cancer and other chronic diseases with T-iPSC.<br>Thyas is developing autologous adaptive immunotherapy with iPS derived killer T cells for the treatment of cancers and chronic viral infections. |
| 京都創薬 Kyoto Drug Discovery & Development | **Kyoto Drug Discovery and Development Co., Ltd (KDDD)**[91]**,** founded in April 2015, is a spin-off company based on results of research by Kyoto University Department of Ophthalmology and Graduate School of Biostudies. It is working on protein modulators that would protect cells from degeneration and death. Neuroprotective effects on retinal nerve fibres and retina ganglion cells have been observed in animal models. By 2016, the company had raised 430Myen (€3.2M) |

**Table 8.8: Other bioventures companies based on technology originating from Kyoto University** (not necessarily supported by above mentioned VC)

| | |
|---|---|
| iHeart | **i-Heart Japan**[92] was founded in 2013 as spin-off from **CiRA**. In 2014 acquired license on iPS technology, based on research by Prof. Yamashita, and entered into alliance with Takara bio.<br>Boehringer Ingelheim signed a collaborative research agreement with iHeart on development of a cardiotoxicity test for new drug development.<br>In June 2016, Takara Bio Inc. started commercializing iHeart iPS cell derived cardiomyocytes **"iPSC-CM" for laboratory use**. Prepared from iPS cells artificially introduced with a drug resistance gene expressed only in cardiomyocytes, the purity of cardiomyocytes is increased by a method of killing |

[89] http://www.kinopharma.com
[90] http://thyas.co.jp/en/
[91] http://www.kyoto-drug.com
[92] http://www.iheartjapan.jp/

| | |
|---|---|
| | cells other than cardiomyocytes with a drug. **"iPSC-CM"**can be used for cardiotoxicity evaluation of drug candidate substances.<br>**iHeart** is also working on iPS technology based products for heart transplantation.<br>  <br><br>In 2016 **i-Heart Japan** was commissioned by NEDO with a project on functional development of 3D body tissue manufacturing.<br>In 2017, results of research collaboration with CiRA, supported by AMED, were published prof. Yamashita *et al.* in *Nature Communications*, showing success in **modeling torsade de pointes (TdP) arrhythmias** in in-vitro 3D human iPS cell engineered tissue. These results are expected to be applied in cardiotoxicity testing in the development of new drugs, and to better elucidate TdP mechanisms. |
| | **MegaKaryon corporation**[93] was founded in 2011 to commercialize the research results of laboratories by Prof. Nakauchi (University of Tokyo) and Prof. Eto (Kyoto University) on proliferating megakaryocytes from iPS cells, opening the way to **mass production of platelets.**<br>It has signed a collaborative research with Boston Children Hospital (US).<br>Initially an A-STEP project supported by a program of Japan Science and Technology Agency, by 2018 the company had raised 6240 million Yen (€47 M) of private funds. In 2017 it presented at the US-Japan innovation awards, at Stanford University. |
| | **ReproCELL**[94] was founded in 2003 based on stem cell technologies pioneered at the Institute for Integrated Cell-Material Sciences **(iCeMS)** Kyoto University, (see page 50) and The Institute of Medical Sciences (University of Tokyo) (see page 38). It offers human iPS cell derived products: cardiomyocites, neurons, |

[93] http://www.megakaryon.com/en/
[94] https://www.reprocell.com/

| | |
|---|---|
| | hepatocytes, cells for diabetes research, etc.<br>Reprocell is working with Tokyo Institute of Technology in the production of **pancreatic progenitor cells and beta cells from iPS cells**. It also has a joint R&D agreement with Tokyo Women's Medical University on "Development of **mass manufacturing system** of **Human iPS cell-derived cardiomyocyte**"<br><br>In April 2011, the company established facilities in USA. **ReproCELL Europe** was later established by acquiring around 2014 two **university** spin-offs from the UK: **Biopta**, providing human tissues to predict drug activity before clinical trials, and **Reinnervate** with expertise in 3D cell culture.<br>ReproCELL was listed on the Osaka Securities Exchange JASDAQ Growth Market in 2013. |
| RegCell | **RegCell**[95] was founded in January 2016 within the venture incubation activities implemented by **iPS Portal Inc**[96] (see page 48) based on technology by internationally-renowned immunology researchers Prof. Sakaguchi and Prof. Kawamoto from Kyoto and Osaka University.<br>Aiming to use regulatory T cells for handling immune rejection against organ transplantation and regenerative medicine, targeting autoimmune diseases and cancer, RegCell works on technology for multiplying and producing high-quality T cells. The company is also developing culture methods for practical application of such immune cells and aim for clinical application in a few years.<br><br>Reprocell received NEDO support in 2017, to create a new treatment for suppressing inflammatory reactions associated with **autoimmune diseases and allergies.**<br>In April 2017 Fujifilm signed a business partnership agreement with RegCell on development support of regenerative medicine products. |
| Myoridge | **Myoridge**[97] founded in August 2016, it is based in Kyoto University (KU) Pharmaceutical Research Institute. Applying technology licensed from KU on protein free myocardial differentiation, Myoridge produces cardiomyocite sheets from human and monkey iPS cells. |

From the point of view of a **European biotech Start-up considering deployment to the Japanese market**, the case study below makes an interesting example of an entry through the establishment of

95 http://regcell.jp/
96 http://ipsportal.com/en/about/#s05c
97 http://myoridge.co.jp/eng

an office at a Japanese University:

Cellink[98] is a Sweden based biotech company, commercializing bioinks for 3D bioprinting of human organs and tissue.
Due to the high demand of technology and its rapid partnership growth within Asia, in February 2018 the company decided to further establish themselves in the Asian market by opening office at Kyoto University Innovation Hub[99]
Kyoto office will serve as a base for research, as well as facilitating relationships with collaborators in Asia.

**Osaka University**

Osaka University comprises 17 Graduate schools, 6 Research Institutes and 2 University Hospitals amongst other facilities. In the biotech area we can highlight the **Institute for Protein Research**, the **Research Institute for Microbial Diseases**, and the **Inmunology Frontier Research Centre**[100].

A compilation of outstanding research projects conducted by Osaka University on life science and medicine is published annually (in English). It also describes international research projects, which for Europe includes collaborative projects with Germany and Ireland.[101]

**The Immunology Frontier Research Center (IFReC)**

Osaka University Immunology Frontier Research Center **(IFReC)**[102] was established in October 2007 with leading immunology researcher Shizuo Akira at its head. The institute conducts research integrating Immunology, Imaging and Bioinformatics to understand the immune system including spatiotemporal information by developing technologies to visualize and analyse the dynamics, activation state, and interaction of immune cells in vivo.

Such efforts are expected to lead to the establishment of new immunotherapies such as development of vaccines for infectious diseases based on control of immune dynamism and control of immune reaction against cancer cell. IFReC a WPI centre has innovative approaches through the interdisciplinary collaboration and participation of world-top **immunology and imaging** researchers.

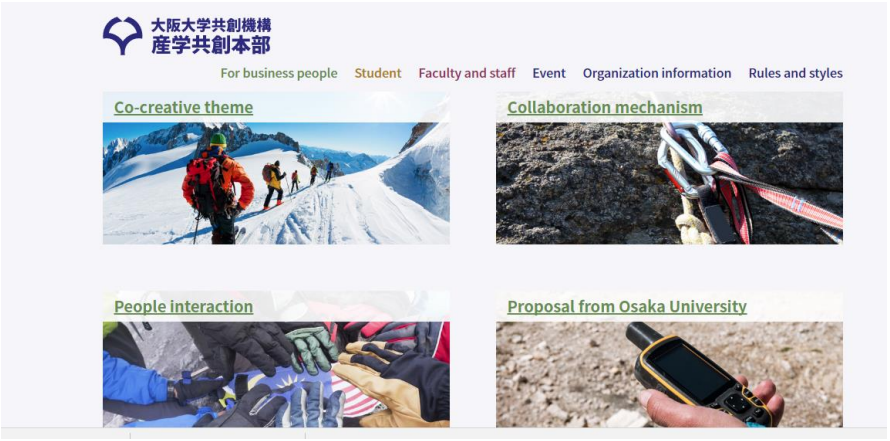
[98] https://cellink.com/
[99] https://cellink.com/cellink-opens-office-kyoto-university-japan/
[100] http://www.jsps.go.jp/english/e-toplevel/data/wpi.pdf
[101] file:///E:/_Users/EU-Guest/Downloads/researchprofile2017_s.pdf
[102] http://www.ifrec.osaka-u.ac.jp/en/

IFReC is open to collaborations with Industry. Osaka University established through IFReC a comprehensive collaboration agreement on cutting-edge immunological research activities with Chugai Pharmaceutical Co., Ltd. in 2016[103] and Otsuka Pharmaceutical Co. Ltd. in 2017. The agreement with Chugai will provide Osaka University with 1 billion yen annually (€7.5M) for a total of 10 billion yen (€75M) over 10 years.

**Osaka University: Industry-Academia Collaborations Organisation**

Osaka University has the **Office for Industry-University Co-Creation**, to enhance an environment for creating innovation so that it can serve as **a hub** for network-type industry-university projects[104].

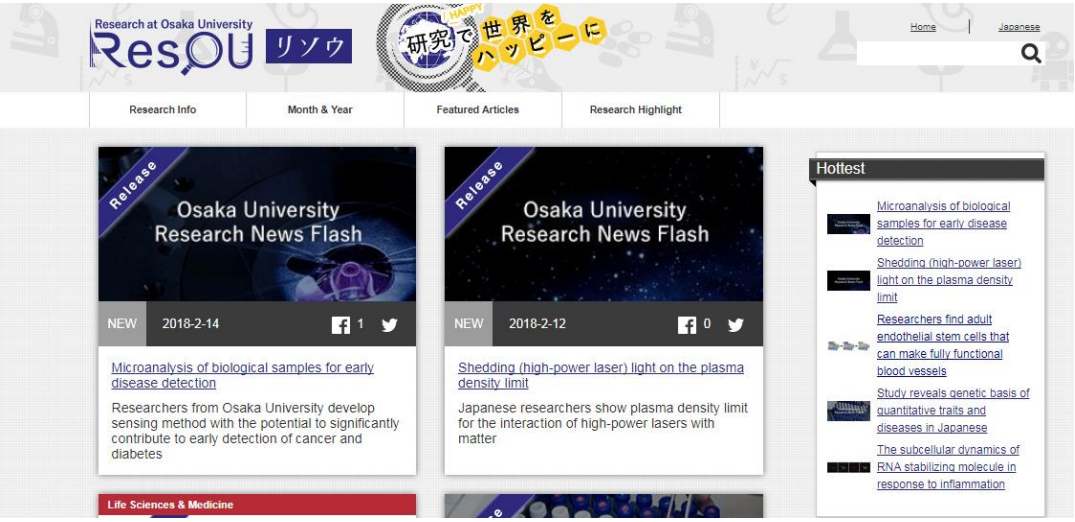
**Figure 8.8: Osaka University Office for Industry-University Co-Creation website**




The website can be consulted in English, and describes the different forms of collaborative mechanisms such as Joint Research, Commissioned Research, Collaborative Laboratories, Scholarship donations etc. Osaka University publishes information on research seeds on a database called **" ResOU "**[105] . The university welcomes inquiries on cooperation and collaboration toward commercialization of posted seeds.

103 http://www.osaka-u.ac.jp/ja/news/storyz/special_issue/research_topics_nl76/201706_special_issue01
104 **http://www.uic.osaka-u.ac.jp/target/company/co-creation/**
105 http://resou.osaka-u.ac.jp/en.

**Figure 8.9: Osaka University research seeds website**




As previously seen in this report with the Universities of Tokyo and Kyoto, Osaka University owns a venture capital organisation, to support creation and development of university originated ventures: OSAKA University Venture Capital Co., Ltd. (OUVC)[106].

## OSAKA University Venture Capital Co. , Ltd.

大阪大学ベンチャーキャピタル株式会社
OUVC Osaka University Venture Capital

Osaka University Venture Capital (OUVC) works closely with Osaka University Industry Co-creative Headquarters (founded in 2018) , not only to commercialize the research results of Osaka University, but also cultivating innovation human resources and entrepreneur support.

The table below lists some companies in the biotech space, which have been supported by OUVC (including JTEC, a company gone public).

**Table 8.9: Examples of Bioventures originated at Osaka University**

| | |
|---|---|
| JTEC CORPORATION | **JTEC Corporation[107]**<br>Established since 1993, in partnership with Osaka Computer Industries, it received investment from **Osaka University OUVC from 2015.**<br>Developed many joint research programs with Yokohama City univ., AIST and Osaka university.<br>Its innovative human elastic cartilage device creation using the three-dimensional cell culture system aiming at a clinical study was selected for |

106 http://www.uic.osaka-u.ac.jp/kyoso/
107

| | |
|---|---|
| | ACT-M program from AMED, and conducted joint research with Yokohama City University and Kanagawa Children's Medical Center.<br>In January 2018 it was listed on the Market of High Growth and Emerging Stocks (Mothers) of the Tokyo stock Exchange. |
| | **MATRIXOME, Inc.**[108] established in December 2015, with headquarters at Institute for Protein Research (iFREC, see page 58), Osaka University.<br>It contributes to the discovery and development of regenerative medicine by providing Laminin-E8 fragment products.<br>“Matrixome” is a term proposed by Professor K. Sekiguchi, from Osaka University, describing a subset of the proteome to define whole collections of extracellular matrix molecules that constitute the customized microenvironments of individual cell types.<br>The venture develops and commercializes various equipment coated with laminin derivative for use in cell culture technology. |
| | **FunPep**[109] was established in October 2013, based on technology for design, discovery and optimization of functional peptides from Osaka University Graduate school of medicine.<br>FunPep aims to commercialize "antibacterial peptides" and "antibody-derived peptides" which are research results on functional peptides.<br>Targeting intractable peptic ulcer disease, as well as highly marketable antibody-inducing peptides. |
| | **Chromocenter Inc.**[110] was created in 2016 based on research results of Professor T. Ohimasa of the Graduate School of Engineering, Osaka University, on artificial chromosome vector as fundamental technology.<br>Construction of stable gene expressing cell lines, such as construction of a transgenic animal prepared and protein high producing cells are expected to be used in a variety of applications. |

108 http://www.matrixome.co.jp/en/company
109 http://funpep.co.jp
110 http://chromocenter.com/eng/?m=201707

| | |
|---|---|
| | **KOTAI Biotechnologies, Inc.** [111] was founded in 2016 based on High-throughput structural modeling and analysis for immune cell sequences. Applications in biomarkers and drug discovery.<br>Osaka University Immunology Frontier Research Center (IFReC) Professor Daron M. Standley commercialized research results on "Structure modeling of immune repertoire"<br>By February 2018 it had received 147 M Yen (€1.1 M) investment from OUVC. |
| | **Epigeneron, Inc.**[112] founded in April 2015, is based on results from Osaka University Fujii Lab[113], on epigenetics regulation and transcription, by using locus-specific chromatin immunoprecipitation methods (ChIP) and engineered DNA-binding molecule mediated (enChIP) technologies.<br>Epigeneron develops new drugs and offers services for development of epigenetic drugs in cancer, CNS, anti-microbial drugs… |

A complete list of ventures in Osaka region can be consulted on the KANSAI bioventure website view http://www.kinkibio.com/venture/bios/index/lang:eng

An example of commercial stage biotech company, aiming to become a global **leader in gene medicine,** which also originated as bioventure based on technology from Osaka University is **AnGes Inc**[114]**.**

| | |
|---|---|
| | AnGes was one of the first two publicly traded venture firms in Japan to have been launched by university researchers. Founded in December 1999 under the name MedGene, its R&D focused on genetic and nucleotide based drugs. By 2002, under the new name name **AnGes Inc**[99]**,** it already had facilities in USA and Europe (UK).<br>In January 2018, AnGes submitted a marketing application to PMDA for its lead product: **HGF plasmid (gene therapy) for the treatment of critical limb ischemia**. It has an alliance with Mitsubishi Tanabe for this product.<br>AnGes has another genetic medicine in clinical development, an **NFκB decoy oligonucleotide,** a specific inhibitor for NF-κB that acts as a switch to a gene cluster involved in the immune inflammatory response, being developed in atopic dermatitis and disc degeneration. |

111 https://www.kotai-bio.com/
112 http://epigeneron.com/
113 http://www.biken.osaka-u.ac.jp/lab/microimm/fujii/top/index_e.html
114 https://www.anges.co.jp/en/

**Examples of Academic bioventures from other Universities (Hiroshima, Nagoya, Hokkaido, Kyushu, Kurume, Keio, Saitama)**

A selection of interesting bioventure examples originated from other universities in Japan, are presented in table below.

**Table 8.10: Examples of Bioventures spawning from other Japanese Universities**

| | |
|---|---|
| **Hiroshima University** | |
|  | **Two cells company Ltd[115].** winner **Japan venture awards 2018[116];**<br>Bioventure established in 2003, out of Hiroshima University. It works on regenerative medicine using Mesenchymal stem cells (MSC), which can be isolated from adult human or animal tissues such as bone marrow, adipose tissue, umbilical cord, and synovium.<br><br>From 2008, two cells has agreements with DS Pharma Biomedical Co., Ltd to develop and commercialize **STK® 2 (Serum-free culture medium)**.<br>In 2014 opened a **gMSC center (Cell Processing Center)**.<br>It has under clinical development:<br>- a **gastric cancer** regenerative cell therapy "gMSC® 1" which is a three-dimensional artificial tissue of MSC in Phase III (concluded a domestic license agreement with Chugai)<br>- "GMSC ® 2" **for cerebral infarction** cell therapy (has an option contract with Otsuka)<br>- R & D on early treatment "gMSC® 3" and **anti-renal failure drug** "gMSC® 4" |
| **Hokkaido University** | |
| NB HEALTH LABORATORY | **NB Health Laboratory Co. Ltd[117]**. was established in 2006 in Sapporo. NBHL has expertise in the generation of functional antibodies targeting G protein-coupled receptors (GPCRs) for the treatment of cancer, infectious diseases, metabolic diseases, pain and inflammation. It can also provide functional mAbs targeting GPCRs for use as a research tool to accelerate your GPCR-targeted drug discovery on a fee basis. |

[115] http://www.twocells.com/
[116] http://j-venture.smrj.go.jp/index.html
[117] http://www.nbhl.co.jp/

| | |
|---|---|
| **Keio University**<br>http://www.iab.keio.ac.jp/en/partnership/index.html<br>http://www.iab.keio.ac.jp/en/about/venture.html | |
| METCELA | **Metcela, Inc**[118]**.** is a regenerative medicine startup founded in March 2016, developing new treatments for heart failure based on cellular therapies from fibroblasts. In September 2017, announced in vivo non-clinical results in rodents. With headquarters at LiC Kanagawa, it has raised JPY150M (€1.3M) from VC and JPY 140 million(from NEDO). In April 2017 began collaborative research with the University of Tsukuba |
| HMT | **Human Metabolome Technologies**[119] **is a** venture that develops the metabolomics business with two core businesses of contract analysis / biomarker discovery by simultaneous multiple metabolite analysis by CE - MS technology developed at Keio University, by Prof. Soga.<br>World-leading metabolome analysis technology and metabolite library, in collaboration with Keio University Advanced Life Science Institute and Agilent Technologies.<br>Biomarkers research in collaboration with diagnostic drug manufacturers and others. HMT has a **European subsidiary in Leiden (NL)** and a US subsidiary in Boston, US. |
| **Kurume University** | |
| BrightPath Biotherapeutics | **BrightPath Biotherapeutics**[120] **Co. Ltd.** (former Green Peptide Co. Ltd) was originated in 2003 at Kurume University, with the mission of developing cancer peptide vaccines, as drug discovery bioventure. Listed in Tokyo Mothers Stock Exchange market since October 2015. Its consolidated subsidiary Advanced Immunotherapy Co. is conducting joint research with **Juntendo University** on the clinical application of iPS cell-derived rejuvenated cytotoxic T Lymphocytes. |
| **Kyushu University**<br>http://camiku.kyushu-u.ac.jp/lab/collaboration | |
| CYFUSE | **Cyfuse Biomedical KK**[121]**.** Established in August 2010, was selected for NEDO project together with Kyushu University, researching on osteochondral |

[118] www.metcela.com
[119] https://humanmetabolome.com/ir
[120] https://www.brightpathbio.com/english/company/index.html
[121] https://www.cyfusebio.com/en

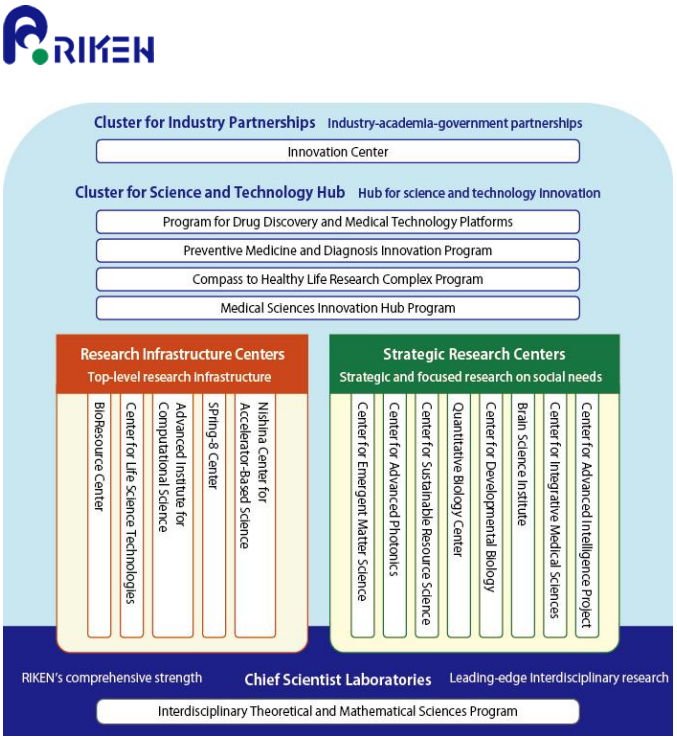
| | |
|---|---|
| | regeneration. Focused on 3D bio printing human tissue, e.g. human liver tissue useful for drug discovery.<br>In 2011 signed a licensing agreement with Kyushu university on Bio 3D printing, and started selling a 3D printer system (Regenova®)one year later.<br>In 2013 relocated the HQ to University of Tokyo entrepreneurs Plaza (page 42) |
| **Nagoya University**<br>**http://www.aip.nagoya-u.ac.jp/en/industry/support/index.html** | |
| NUProtein | **NUProtein**[122] is a bioventure from Nagoya University, founded in the summer of 2016, originating from a training program on venture development, was initially subsidized by NEDO, and later funded by venture capital.<br>Commercializes a cell-free protein synthesis kit, which can synthesize membrane proteins, transcription factors, kinase enzymes, etc. without cloning.<br>The protein synthesis technology from NUProtein is based on the protein synthesis function of wheat germ and adding DNA to it, skipping the cloning process that is required when using E. coli, reducing the total protein synthesis process to about one day.<br>It is currently based at Nagoya university incubation facilities.<br>In 2017 received a company award from Rohto Pharmaceutical Co., Ltd. and the EY Entrepreneur of the year award. |
| **Okinawa Institute of Science and Technology Graduate University (OIST)** | |
| | **Okinawa Protein Tomography**[123] is the first bioventure from OIST, established in June 2014. Provides contracted research services worldwide: macromolecular imaging service including proteins in various states at the single molecule-level by combining Cryo Electron Microscopy and a specifically designed 3D reconstruction software. Analysis of proteins and/or complexes in biological samples. |
| **Saitama University** | |
| EME | **Epsilon Molecular Engineering**[124] was established in August 2016 as a bioventure from Saitama University, designing next-generation antibody molecules, peptide aptamers against drug discovery target (in joint research, alliance or contract business). Also sell a cDNA display screening starter kit.<br>Drug discovery using next-generation antibodies and aptamers against GPCR. |

[122] http://nuprotein.jp/en/
[123] www.okinawa-pt.com
[124] http://www.epsilon-mol.co.jp/#aboutus

**RIKEN Research Institutes**

RIKEN is a top-class research hub at the heart of scientific research in Japan, its largest comprehensive research institution and a world leader in a diverse array of scientific disciplines, with strong focus on life sciences. Central to RIKEN's success is the collaboration and support between its many centers, distributed within Japan and abroad, laboratories, and state-of-the-art research facilities. The institution celebrated its century of existence in 2017.

Detailed information and contacts for each laboratory is available on RIKEN webpage, which can be seamlessly navigated in English. The selected institutes below will give an overview of potentially interesting collaborative research in biotechnology, and illustrate some of the venture companies recently created as spin-offs with technologies from RIKEN.




RIKEN activities can be divided into four main categories: Research Infrastructure, Strategic Research Centers, Chief Scientist Laboratories, and a Cluster for Industry Partnerships (CIP).

Flagship research centers in life sciences and biotechnology include **Bioressource Centre (BRC)** in Tsukuba, the **Center for Developmental Biology (CDB)** in Kobe, the **Quantitative Biology Center** (**QBic)** in Osaka , and the **Center for Integrative Medical Sciences.**

**RIKEN BioResource Center (BRC),** established in Tsukuba in 2001, is one of the world's most important repositories and distribution centers of biological resources. It handles a wide range of experimental animals, plants, cell lines, genetic materials, microbes, and associated bioinformatics to contribute to the international scientific community. It is particularly notable for providing human induced pluripotent stem cells (iPSC).

**Figure 8.10: Illustration on different bioressources provided by the BRC Divisions**


The bank has a wide range of **disease-specific iPS cells** that have been generated from patients with various disease backgrounds.

Further to an agreement signed in January 2018, iPSC from the bank are provided to academic and industrial clients through **ReproCELL** as preferred supplier for cell differentiation into functional cells such as neurons, cardiomyocytes, hepatocytes and others, specific to the client's request (see page 48).

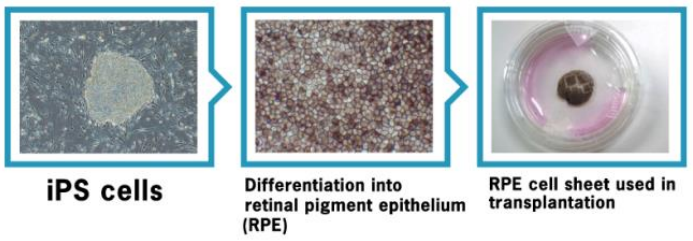
**The RIKEN Center for Developmental Biology CDB**[125] in Kobe is focused on Life Cycle Biology and Regenerative Medicine. Core programs include organogenesis, cellular environment and response, mathematical developmental biology, and regenerative medicine.
Moving forward, CDB plans to concentrate the research activity into three themes: Embryogenesis/Organogenesis, Regenerative Biology and Homeostasis & Aging

**Figure 8.11: Left exterior of RIKEN CDB. Right, photography of Kobe**


[125] http://www.cdb.riken.jp/en/

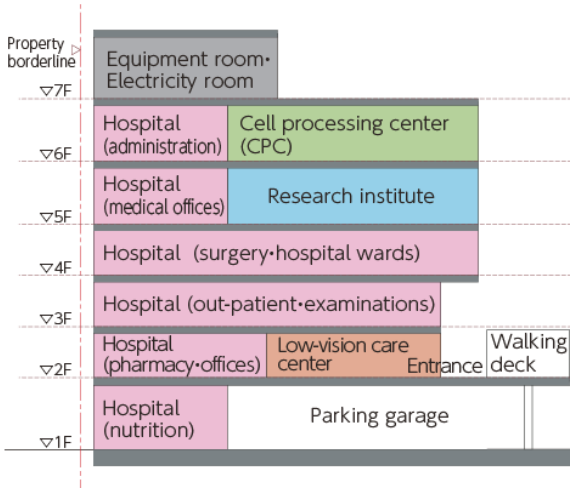
The research team headed by Professor Masayo Takahashi engages in basic science to translational research on cell-based therapy for blinding eye diseases. In 2014, the **clinical study in patients with age-related macular degeneration (AMD)** using iPS cell- derived retinal epithelium sheets was the world- first trial to use iPS cells in humans[126] .

**Figure 8.12: Left: iPS cells and RPE cell sheets; Right Prof. Masayo Takahashi**




From 2017 a new clinical study conducted in Kobe and Osaka hospitals uses **allogeneic iPS cells** (unlike the autologous iPSCs transplanted in the previous clinical study in 2014). Allogenic cells are prepared in suspension. 5 patients have received them during the clinical trial in 2017.

The CDB is an active participant in the Kobe Innovation Cluster (see page 85)




In December 2017, the **Kobe Eye Center** [127] (developed under National Strategy Special zone) started operations as a place to practice vision care in a continuum from basic research, applied research, clinical research, treatment, low vision care, and employment support. RIKEN will also conduct research activities within Kobe Eye center.

The CDB is engaged in **programs of cooperation** with a number of universities in Japan and around the world. This activity is based primarily on cooperation between individual researchers.

[126] http://www.cdb.riken.jp/en/research/laboratory/takahashi.html
[127] /www.kobeeyecenter.jp/english/#greeting

European institutions with RIKEN CDB agreement**s** may be a good bridging contact point for Europeans willing to initiate industry-academia research collaborations with CDB

| |
|---|
| Center for Genomic Regulation; Institute for Research in Biomedicine; Universitat Pompeu Fabra (Barcelona, ES) |
| Max Planck Institute of Molecular Cell Biology and Genetics (Dresden, DE) |
| German Research Center for Environmental Health (Neuherberg, DE) |
| Freie Universitat (Berlin, DE) |
| VU University (Amsterdam, NL) |

In September 2016, **RIKEN CDB–Otsuka Pharmaceutical Collaboration Center (COCC)**[128] was launched to pursue projects in **regenerative approaches related to neurodegenerative and kidney diseases.** The COCC is located inside the CDB in Kobe, and headed by Hiroshi Hamada, director of the RIKEN CDB. The collaboration is initially launched for 5 years.

**RIKEN CDB** has active **partnerships with multiple biotech and pharma companies**, yet according to its 2016 Advisory Council report[129] "*clearly this could be raised to a higher level through more outreach to companies to visit CDB and learn about the research there".*
**Opportunities for collaborative research with Industry** mentioned in the Advisory Council report include increasing **translational research** by finding appropriate clinical partners to explore:

- Kidney organoids in Nephrology,
- Oocyte chromosome anomalies in Reproductive Medicine
- Stem cells applications in Neurology, Dermatology and Respiratory Medicine

[128] https://www.otsuka.co.jp/en/company/global-topics/2016/20160906_vol95.html
[129] http://www.cdb.riken.jp/en/about/publicinformation/report/ac16.html

**RIKEN Quantitative Biology Center (QBiC),** in Osaka, aims to achieve "whole cell modeling". By combining techniques that can measure molecular dynamics, modeling cellular environments, and simulating molecular and genetic networks, scientists aim to predict and control the behavior of the cell. Collaborations are handled via RIKEN Business development Office[130]


**Computational Biology Research Core**

Computational Molecular Design
Biomolecular Function Simulation
Biochemical Simulation
Multiscale Biosystem Dynamics
Drug Discovery Molecular Simulation Platform
Developmental Morphogeometry

**Cell Design Research Core**

Laboratory for Synthetic Biology
Laboratory for Cell-Free Protein Synthesis
Laboratory for Integrated Biodevice
Laboratory for Mouse Genetic Engineering

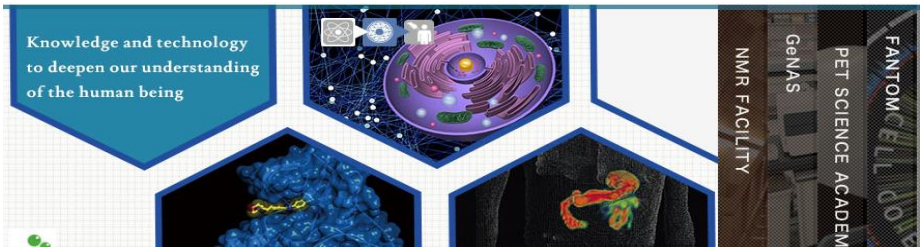
**Cell Dynamics Research Core**

Cell Dynamics Observation
Cell Signaling Dynamics
Comprehensive Bioimaging
Nano-Bio Probes
Single Cell Mass Spectrometry
Developmental Dynamics
Polarity Regulation
Biomolecular Structure and Dynamics
Single Cell Gene Dynamics
Cell Field Structure
Reconstitutive Developmental Biology
Integrative Omics

The **RIKEN Center for Life Science Technologies (CLST)** [131]aims to promote research on biomolecules and into life science technologies. Its focus is on 3 areas: Designing molecular structures at the atomic level, manipulating molecular function at the cellular level and tracing molecular dynamics at the whole-body level.

A Division of **Structural and Synthetic Biology**, a Division of **Genomic Technologies**, and the Division of **Bio-function Dynamics Imaging**, work together. R&D programs are carried out in collaboration with companies, universities, and international consortia.

130 http://www.riken.jp/bdo/index.html
131 http://www.clst.riken.jp/en/




Facilities of the center include the largest collection of NMR devices in the world, based in Yokohama campus; GeNAS is a technical service which aims to disseminate the genome-wide analysis technologies developed by CLST. In Europe, CLST has close ties with the Swedish **Karolinska Institutet.**

**RIKEN PMI**

The **Preventive Medicine and Diagnosis Innovation Program** from RIKEN (PMI)[132] is an initiative which may also be interesting to European companies wishing to develop in Japan medicinal products and devices for disease detection. Research groups taking part in the program are working on the discovery of **new biomarkers, the development of detection technology for clinical practice, and the development of diagnosis kits**.

The program promotes collaborations within RIKEN and with universities, research institutes and hospitals both inside and outside Japan.


Key areas:

- Large-scale gene analysis
- Gene expression analysis
- The development of nucleic acid measuring methods
- Medical applications
- Transcriptional regulation networks

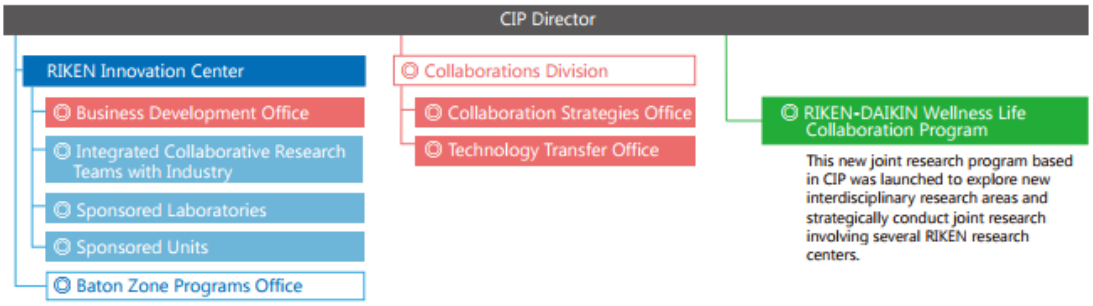
In October 2016, the report from RIKEN cluster for industry partnership advisory council recommended increasing its support and use of PMI, in the framework of promoting internationalization. .

[132] http://www.pmi.riken.jp/en

**RIKEN- Collaborations with Industry Organisation**

RIKEN collaborates with industry in many different ways and is open to inquiries about potential collaborations. Joint and sponsored laboratories, commissioned research, internships…

The Cluster for Industry Partnerships (CIP) promotes RIKEN's joint research with industrial partners by securing and managing intellectual property, handling administrative procedures for various contracts, assisting venture businesses, and conducting outreach activities.




Within the Cluster, The RIKEN Innovation Center (RInC) is the office managing the **Baton Zone program** for the transfer of RIKEN's scientific achievements into commercial products through partnerships with private companies. Under the Baton Zone program, named after the track-and-field relay, **researchers from RIKEN and private companies** work together on research projects tackling specific technological challenges, proposed by private companies. Some collaboration examples are given in figure below.

**Figure 8.13: RIKEN Baton Zone program**


| Teams | Partner Corporations |
|---|---|
| Cloud-Based Eye Disease Diagnosis Joint Research Team | Topcon Corporation |
| Transporter-Based Prediction of Drug Toxicity Lab | GenoMembrane Co., Ltd. |
| Vaccine Innovation Lab | Animal Allergy Clinical Laboratories Inc. |
| Bovine Leukemia Virus Vaccine Lab | Kyoto Biken Laboratories Inc. |
| Four-Dimensional Multicellular Dynamics Lab | Carl Zeiss Microscopy Co.,Ltd. & Andor Technology Ltd. |
| Hydrogen Filter Research Lab | ATSUMITEC CO.,LTD. |
| Plant Breeding Innovation Lab | Japan Tobacco Inc. |
| 3D Gel Dosimeter Research Lab | Nissan Chemical Industries, Ltd. |
| Organ Preservation and Resuscitation Lab | SCREEN Holdings Co., Ltd. |
| Glass Molding and Optics Simulation Lab | Integration Technology Co.,Ltd. |
| GlycoTargeting Research Lab | Gly Tech, Inc. |
| Voxel Engineering Lab | UEL Corporation |

Another channel for interactions of companies with RIKEN is joint research with "**Independent Chief Scientist Laboratories",** which held by outstanding researchers, carry out special research with corporate funding.

One of these independent laboratories, which are noteworthy for the high number of collaborations with industrial medicine developers, is Professor **Yuichi Sugiyama** lab, working on "Improving the success rate for drug discovery based on the quantitative prediction of pharmacokinetics".[133]
**Sugiyama laboratory** started in April 2012, with funds from 26 companies including Taisho Pharmaceutical, Mitsubishi Tanabe Pharma, Kyorin Pharmaceutical, Shimadzu Corporation, etc.
It aims to establish **Virtual clinical trials**, an integrated support system for drug discovery and improve the success rate significantly in drug discovery. In 2017 Dr. Sugiyama appeared in the Clarivate list of Highly Cited Researchers[134.]

The **Program for Drug Discovery and Medical Technology Platforms (DMP)** is another another platform leveraging RIKEN research centers and open for joint research with Industry.
Established in 2010, it is headed by Dr Tashio GOTO. Its business development office deals with Industry requests.

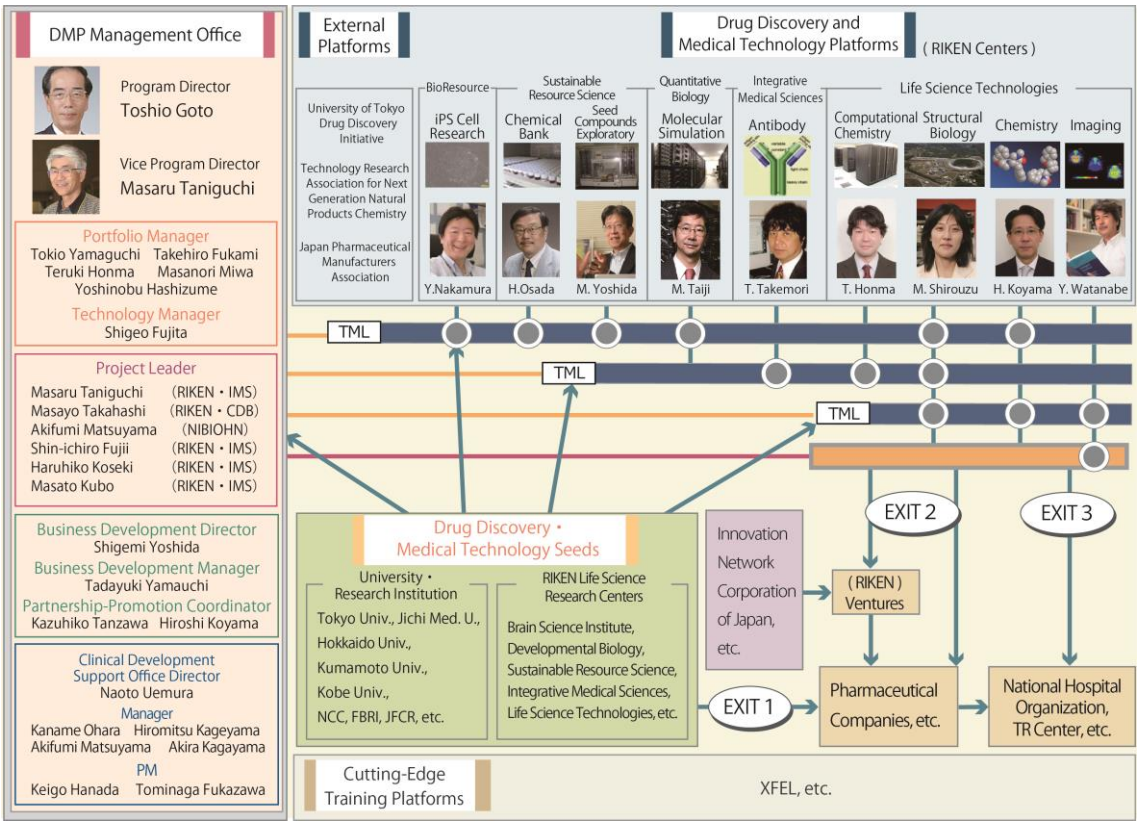
| | |
|---|---|
| Fields of focus:<br>1.Small molecule drugs<br>2.Monoclonal antibody drugs and vaccines<br>3.Cell-based drugs and regenerative medicine<br>4.R&D for the construction of drug discovery and medical technology platforms | RIKEN Industry Cooperation Headquarters<br>Drug Discovery and Medical Technology Foundation Program<br>Address: 1-7-22 Suehirocho Tsurumi-ku, Yokohama-shi, Kanagawa<br>Tel: 045-503-9153<br>**pharma-support @ riken.jp** |

As an example, in March 2018, **BrightPath Biotherapeutics, Co., Ltd**. (a clinical stage biopharmaceutical company) announced a collaborative research agreement with RIKEN regarding a natural killer T (NKT) pursued by the RIKEN Center for Integrative Medical Sciences, that aims at technology development and clinical application of this novel allogeneic cancer immunotherapy using NKT cells redifferentiated from induced pluripotent stem (iPS) cells ("iPS-NKT cell therapy").This is a RIKEN-led project, on the Program for Drug Discovery and Medical Technology Platforms. An investigator-initiated clinical trial targeting head and neck cancers is to start within fiscal year 2019.

[133] https://www.sugiyamalab-en.com/
[134] http://www.riken.jp/outreach/applied/people/

RIKEN DMP is developing comprehensive technological platforms such as the Drug Discovery Computational Chemistry Platform and the Biochemical and Cell-based Drug Discovery screening platform.

**Figure 8.14: Program for Drug Discovery and Medical Technology Platforms DMP**




## RIKEN Support to Venture Companies

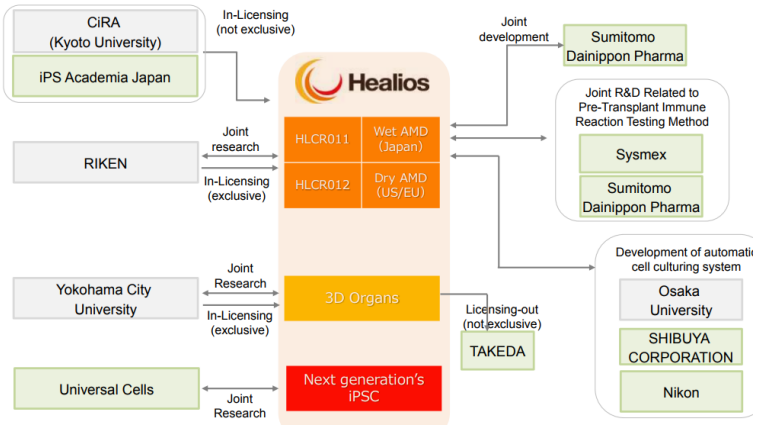
**RIKEN Venture system** enables researchers to put their own scientific achievements to commercial use and disseminate the fruits of research at RIKEN as quickly as possible. The venture support system by RIKEN had 20 companies certified as of November 2017, operating in diverse fields.

A company certified as RIKEN venture gets preferential treatment in licensing patent rights, use of space, research equipment, and permission to engage in research as staff of RIKEN etc.

A legislation modification (expected to be approved by mid 2018), will grant RIKEN centers the same rights that Japanese Universities currently enjoy regarding investments in stock acquisition rights and venture funding. This change is expected to incentivize venture formation and support from RIKEN.

In the biotechnology field, some successful examples of companies that originated as RIKEN ventures include the regenerative medicine companies **Healios, Organ Technologies Inc.;** companies based on genetic technology **DNAFORM,** and antibody generation platforms (**Chiome Bioscience**).

**Table: RIKEN Bioventures**

| | |
|---|---|
| Healios | **Healios corporation**[135] originated as RIKEN venture in 2011. It was listed in the Mothers Tokyo Stock Exchange market in 2015. It develops treatments based on **iPSC derived technology.**<br>In 2013 in-licensed technology from CiRA (Kyoto University) and signed a joint development agreement with Sumitomo Dainippon Pharma.<br>Healios does joint research with Yokohama City University on a platform technology to **induce organ bud growth** (induce multiple types of tissue to form physiologically functional tissue with vasculature and other cellular interconnections) in fields other than ophthalmology.<br><br>In February 2017, Healios received a **Sakigake designation** (see page 17) for regenerative medicine products from PMDA, which should accelerate the approval for its therapy for improving functional impairment caused by **acute brain infarction based on pluripotent progenitor cell derived from human (allogeneic) adult bone marrow**.(partnering with Athersys US)<br>In March 2017 Helios formed a business alliance with Nikon on contract manufacturing of cells / cell quality evaluation with image analysis etc.<br>  |

[135] https://www.healios.co.jp/en/

| | |
|---|---|
| | **Organ Technologies Inc**[136]**.** works on innovation based on **3D organ regeneration** technology. The company is developing iPS technology applications: Lacrimal glands and salivary glands (project with AMED); Artificial skin mimicking human skin structure for medical & cosmetic research; Hair follicle regeneration.<br><br>In December 2017 Organ Technologies formed a consortium based in open innovation model with 18 companies (Kyocera, Yahoo, NEC, Mitsui, Aderans, Shimadzu…). The objective of collaborative research being to develop and analyze health indicators and disease markers from composition of hair, aiming to establish hair analysis as a new noninvasive healthcare diagnostic system. |
| | **Chiome Bioscience**[137] was a certified RIKEN venture in 2005. In 2011 it was listed in on the Mothers Tokyo Stock Exchange market.<br>Their **drug discovery platform technology ADLib® system** (Autonomously Diversifying Library system) was originally developed through collaboration with Genetic Dynamics Research Unit at RIKEN, and Saitama SME development. With Tokyo headquarters, Chiome has R&D labs at LiC in Kawasaki (see page 82).<br>Chiome performs joint research or contract service producing antibodies for new clients (pharma) or for diagnostic and research purposes at academia or institutes on fee-for-service scheme.<br>**ADLib® is a monoclonal antibody generating system** providing a diverse array of complete antibodies in vitro, without using immunization.<br>ADLib® axCELL is a proprietary technology that Chiome Bioscience successfully developed to obtain antigens from cells for use in the ADLib® system.<br>Chiome has signed contracts with Chugai and Mitsubishi Tanabe.<br>In 2017 executed a license agreement with **ADC Therapeutics (Switzerland)** to develop, manufacture, and commercialize LIV-1205, as Antibody Drug Conjugate (ADC) for cancer treatment. LIV-1205 is a humanized monoclonal antibody targeting cell surface antigen "DLK-1 (Delta-like 1 homolog)" of liver cancer and other solid cancers.<br>**ProBioGen AG (Germany)** is Chiome's partner for the Master cell banking and GMP manufacturing. |

[136] http://www.organ-technol.co.jp/aboutus/

[137] http://www.chiome.co.jp/english/

| | |
|---|---|
| | It also signed a joint research contract in 2017 with **Trans CHromosomics Inc**[138]. (a venture on chromosome engineering technology developed by **Tottori University**), fostering drug discovery research on their fully human antibody producing mice/rat complementary to Chiome's existing antibody discovery toolbox. |
| | **DNAFORM Inc**[139]**,** certified as RIKEN venture in 1998, is a provider of comprehensive gene expression analysis technology and development & sale of genetic testing reagents.<br><br>In December 2016, DNAFORM signed a collaborative agreement with Russian company Eidos-medicine to develop a portable system to diagnose infections.<br><br>The company is based in Yokohama |
| RIKEN BIO Co. Ltd | **RIKEN BIO Co Ltd** was certified in September 2014 as RIKEN venture, working on pre-symptomatic diagnosis and prophylactic treatment of Alzheimers disease. With offices at RIKEN Brain Science Institute in Saitama, the venture generated a knock in mouse model that start accumulating Aβ at 6 months and show memory impairment at 18 months |
| AMBICION Co., Ltd. | **AMBICION Co Ltd.**[140], established in October 2015, although not a Riken venture, is included here because its technology originated from collaborative agreements with RIKEN, on the development of cell-processing products using a novel natural killer T cells (NKT) ligand (RK), and carrying out non-clinical and clinical studies.<br><br>in April 2016 RIKEN and AMBICION jointly applied for a patent covering efficient NKT cell activation. Ambicion is working on clinical programs with NKT cell-cancer targeted immunotherapies, within translational research strategic programs from AMED and Keio University. |

The Full list of RIKEN venture companies can be consulted online[141]

[138] http://trans-chromo.wixsite.com/transchromosomics/r-d
[139] https://www.dnaform.jp/en/about/
[140] http://www.ambicion.co.jp/en/technology/data.html
[141] ww.riken.jp/en/outreach/ventures/

## 9. Global Health R&D fund (GHIT): An alternative public-private partnership model

The Global Health R&D fund GHIT[142] facilitates international product development partnerships between Japanese and non-Japanese entities. The fund was initially launched in April 2013 between three key partners: **Japan government**, a group of leading **Japanese pharmaceutical companies**, and the Bill & Melinda Gates Foundation. To date, GHIT has invested a total of US 115M in 68 global partnerships. For the next 5 years, US$200M are committed to the fund replenishment.

GHIT focus is development of drugs, tests and vaccines for malaria, tuberculosis, HIV and neglected tropical diseases (NTDs). In an "open innovation" model of R&D, product development partnerships (PDPs) are created to facilitate international cooperation. The Japanese counterparts are Universities/ Public Research Centers or private companies.
While the fund does not seek financial returns, decisions are data-driven and outcome-oriented. Investments seek effective development of novel health technologies with the potential to save millions of lives and drastically improve health and economic outcomes.

Some of the partnerships **involve SMEs from outside Japan**. For example, VLP Therapeutics, an American start up, is contributing novel virus-like particle technology to a Dengue vaccine project, where Japanese partners are the National Institute of Infectious Diseases (NIID) and Institute of Tropical Medicine at Nagasaki University (ITM Nagasaki University).

Participation in a cooperative project funded by GHIT could be of high interest to **European SMEs,** particularly for those biotech startups developing test devices or ancillary drug development products and services. In addition to making an impact in Global Health R&D, European SMEs participation in this type of funded partnership would be a way to start collaborations with Japanese Academia and Japanese Industry and, potentially opening channels to further collaborations in other projects.

GHIT Fund

Global Health Innovative Technology Fund

[142] www.ghitfund.org

## 10. Industrial Clusters and Innovation Hubs

In 2001 Japan adopted the "Industrial Cluster Plan" to strengthen the capabilities of regional areas in developing new technologies and products. Grounded in the experience from other countries, industrial clusters were defined primarily for Biotechnology, IT, environment and manufacturing, with the goal of strengthening national industry.[143].

The biotechnology regional SMEs and start-up companies utilizing innovative research results or "seeds" obtained at local universities and research institutes would form clusters creating new business, strengthening the existing ones, and thereby fostering the evolution of a concentration of industries in a wide area around a focal core of highly competitive industries. This strategy was deployed in three phases[144]:

- A first term (2001-2005) where the national government had a central role in launching projects;
- a second term (2006-2010) considered a development phase;
- and a third term (2011-2020) were clusters should achieve financial independence and autonomous growth.

Japan External Trade Organisation (JETRO) has developed a mapping tool[145] that provides information about regional specialised industrial clusters, including a map on Life Sciences.

In 2013 the EU-Japan Centre for Industrial Cooperation conducted a survey on Japanese clusters and published a report based on the replies collected from forty five Japanese entities. This information was further updated in 2016[146], through web based screening and analysis of the international relations of the clusters. Twenty eight Japanese clusters were identified in the fields of *pharmaceuticals, biotechnology, healthcare, medical and welfare*.

For their potential interest to European SMEs engaged in **biotechnology healthcare applications**, this report has selected **some key Clusters and Innovation networks** of Japan currently promoting their activities and/or international collaborations, regardless of the public/private nature of their funders and sponsors.

[143] JETRO Oct 2007 publication on Biotechnology
[144] METI http://www.meti.go.jp/english/policy/sme_chiiki/industrial_cluster_en.html
[145] https://www.jetro.go.jp/en/invest/region/icinfo/
[146] https://www.eubusinessinjapan.eu/library/publication/report-cluster-mapping-in-japan-2016

**Table 10.1:Presented Industrial Clusters and Innovation Hubs**

| Area | Organisation name | Agreements signed with Europe |
|---|---|---|
| **Tokyo** | Life Science Innovation Network Japan **(LINK-J)** | Eurobiomed (FR)<br>One Nucleus (UK) |
| **Kanagawa** | Lifescience Innovation Centre **(LiC),** Kawasaki | Cell Therapy Catapult (UK), Oulu (Finland)<br>CVT Valorisation (FR)<br>Scottish Development Intl. (UK) |
| | Shonan Innovation Park (Takeda) | |
| **Osaka** | Osaka Bio | bioXclusters plus（bioPmed / Bioindustry Park（Italy）、Biocat（Spain）、BioM（Germany）、Lyonbiopole（France ）<br>Flanders Bio (BE), |
| **Kobe** | Kobe Biomedical Innovation Cluster **(KBIC)**<br>Procluster Kobe | Flanders Bio (BE),<br>Medicon Valley Alliance (DK, SE) |

**Life Science Innovation Network Japan (LINK-J) TOKYO**

The **Life Science Innovation Network of Japan (LINK-J)**[147], based in Tokyo, is a platform aiming for **open innovation** in the whole life science field, from medicine to science including engineering or new technologies, such as ICT or artificial intelligence. LINK-J promotes interdisciplinary human and technological exchange through industry-government-academia cooperation, and support to the creation of new industries.

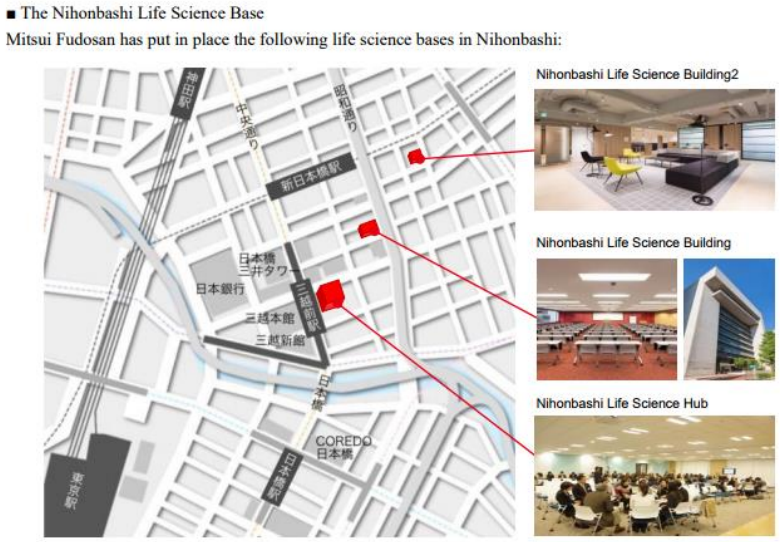
Operating since June 2016, LINK-J is a general incorporated association established by Mitsui Fudosan (a leading company in the Japanese real estate industry, active in venture business) and volunteers from life sciences academic circles. It counts over 180 members.

Prof. H. Okano, Keio University School of Medicine Dean, is the Chairman of the board. Management advisory committee is integrated by experts from industry and academia.

Based in the Nihonbashi area of Tokyo, where a number of pharmaceutical companies like Takeda, Astellas, Otsuka and many others have headquarters, the Nihonbashi Life Science Building is one of the three facilities made available to LINK-J (with two other smaller buildings in close proximity).

[147] **www.link-j.org/en**

**Figure 10.1: LINK-J Tokyo situation map**



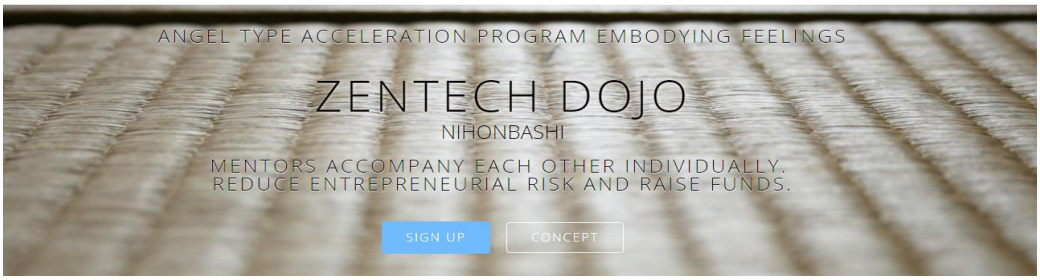

Facilities include conference rooms hosting most LINK-J events. At the time of this research, it is one of the venues most frequently used for presentations by Japanese ventures, as well as European companies in missions to Japan.

**Table 10.2: Multiple Japanese life science organisations have an office at LINK-J premises.**

| | |
|---|---|
| Japan Pharmaceutical Manufacturers Association | National University Corporation, |
| Japanese Society for Regenerative Medicine (JSRM) | Osaka University |
| FIRM (Forum for innovative regenerative medicine) | Kyoto University |
| Japanese Organisation for Medical Device Development | The University of Tokyo |
| Medical-Industry Cooperation Innovation Centre | Tohoku University |
| Japan CRO Association | Kyushu University |
| the Centre for Studies on Ageing Societies | Fukushima Translational Research |
| Clinical Research Education Centre Tohoku University Hospital (CRIETO | The University of California, San Diego (US) |

Shared office space with open desks is available, often rented by **would-be venture companies** or companies immediately after founding, promoting a concentration of smaller venture companies.
A start up acceleration program **"Zentech dojo"**, managed by INDEED Japan[148], provides educational programs and mentoring support. Link-J hosts partnering events and venture pitch meetings to procure funds from angel investors and venture capitalists.

[148] http://www.indee-jp.com/zentech/more-info.html




**International Cooperation**

LINK-J has demonstrated its interest in expanding partnerships in Japan and overseas.

MOUs on business collaboration were first signed with the University of California, San Diego (UCSD) and BIOCOM (US) in May 2016.

On the European side, LINK-J has signed MOUs with two organisations: **Eurobiomed** (FR) in June 2017and **One Nucleus** (UK) in December 2017. Start- up companies' presentations visits from Japanese companies to Europe, and networking events have since been co-organised by these organisations with Link-J.

**Life Innovation Centre (LiC) in Kawasaki, Kanagawa Prefecture**

**LiC Kanagawa**[149] is a private-public joint project, located in the city of Kawasaki (Kanagawa prefecture), very close to Tokyo Haneda airport. It was launched in 2016, as a hub to promote the i**ndustrialization of regenerative medicine**. Working closely with national government, it benefits from *National Strategic Special Zone* and *International Strategic Zone* policies.

LiC Kanagawa has an open lab[150], cell production manufacturing facilities, and office space available. As of October 2017, tenants at LiC Kanagawa (27 companies) included among others:

**Cellular Dynamics International** (acquired by Fujifilm, producing cardiomyocites from iPS)

**BrightPath biotherapeutics** (R&D on cancer immunotherapy, cancer vaccines in clinical trials)

**Takara bio** (CDMO and gene therapy development. Acquired Cellectis Sweden in 2014 )[151]

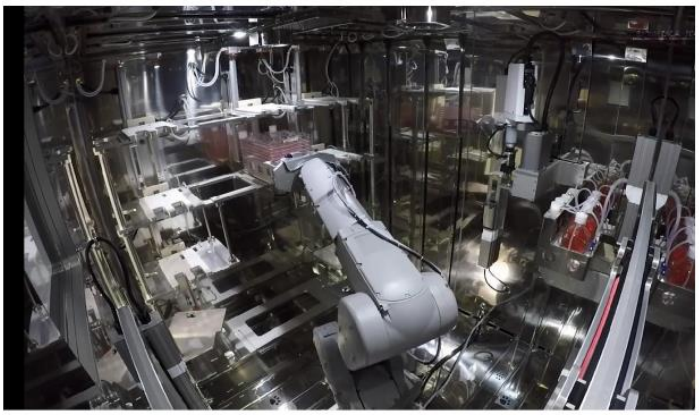
**Cyberdyne Inc**.[152] (projects combining cellular therapies and robot exoskeletons. Initially a startup from Tsukuba University)

**PeptiDream Inc** (see page 42)

[149] http://www.pref.kanagawa.jp/mlt/f531223/p1002234.html
[150] http://www.lic-openlab.com/
[151] http://www.takara-bio.com/release/?p=352
[152] www.cyberdyne.jp

**Tella pharma Inc**[153]. Opened a manufacturing facility at LiC in March 2017, with extensive use of robots automation and IoT, manufacturing investigation product for their clinical trials with dendritic cell vaccines.

**Figure 10.2: Tella pharma Inc manufacturing facility at LiC**



**source: Tella website**

Companies at LiC, have established **the Regenerative medicine & Cell therapy Industrialization Network of Kanagawa (RINK)**[154] to build a value chain for cellular processing, cultivation, evaluation, storage and transport processes. RINK organizes seminars, events, networking and information sharing between members, project planning and business matching support.
Within LiC, the **"Kanagawa Clinical Research Strategy Research Center**[155]" provides support on **clinical research** of regenerative medicine products and innovative medicines. It has an access to the Tohoku Medical Megabank organization, containing a large amount of genome cohort data.

LiC has signed MoUs with **several European organizations** such as Cell Therapy Catapult- UK, Oulu-Finland and CVT Valorisation France. Scottish Development International has an office at LiC.

A recent example of **overseas company partnering with a Japanese LiC counterpart** is **Agilis Biotherapeutics, a US biotech** company developing gene therapies which created a joint venture with the Gene Therapy Research Institution (GTRI), a Japanese bioventure founded in 2014 based on research by Prof. Muramatsu from Jichi Medical University, on adeno associated virus vector mediated (AAV) gene therapy. In February 2017 the joint venture **Agilis GTRI Japan**[156] R&D, developing AAV vectors for gene therapies targeting the CNS, was established at LiC Kanagawa. The company made use of METI subsidies to attract companies to Kanagawa prefecture, and was

[153] https://www.tella.jp/en/
[154] http://rinkrink.jp/en/about/
[155] http://en.kccr.co.jp/
[156] http://www.agilisbio.com/

supported by JETRO (see more details on this business case on Jetro website[157])

**European companies** considering the possibility to establish a manufacturing or R&D base in Japan should explore the advantages offered by **International Strategic Zones** like LiC Kanagawa.
An example is **TC BioPharm Ltd., company from Scotland (UK),** developing cancer immunotherapies. In February 2018[158] it established its first overseas office in Japan at LiC Kanagawa, to continue expansion of its Asian operations. The company worked with Scottish Development International to find a suitable location in Japan. Last year the firm announced an $8million equity funding round, including its first significant investment from the major Japanese pharmaceutical company NIPRO Corporation (Osaka).

**The Shonan Health Innovation Park, Kanagawa**

The **Shonan Health Innovation Park**[159] in Fujisawa, Kanagawa, was initiated by the Japanese pharmaceutical company **Takeda** in 2016. The park, envisioned as an open innovation project, is targeted to become *"*Japan's first innovative ecosystem led by pharmaceutical companies bringing together key players involved in health innovation from industry, government, and academia", according to Takeda speakers.


**Source: Takeda website**

A catalyst for public-private partnership, inviting human resources and investment from all over the world, Takeda is seeking for diversified investors for new projects starting in the park.

It offers access to research equipment and workspaces. Immediate research access without initial investment.

Over 50 R&D partnerships have been formed in two years, with future aspirations voiced as reaching a scale of thousands of researchers and stakeholders in the Innovation Park.

[157] https://www.jetro.go.jp/en/invest/success_stories/agilis.html
[158] https://www.insider.co.uk/news/tc-biopharm-launches-new-office-12023842
[159] https://www.shonan-health-innovation-park.com/en

**T-CiRA**, a research unit founded in collaboration with Kyoto University's Center for iPS Cell Research and Application (CiRA), is a prime example.(see page 48)

New venture companies are joining the park, for example **K Pharma**[160] (a bioventure spinning out from Keio University doing drug discovery with iPS cells) and **Noile-Immune Biotech**[161] (exclusive licensee of the platform technology for next generation CAR-T cell therapy developed by Yamaguchi University).

Other companies in the Shonan Park are developing drugs from Takeda's divested pipeline: **SCOHIA PHARMA Inc**.[162] with clinical stage programs in diabetes, and diabetic nephropathy hypertension; **Chordia therapeutics**[163] developing new therapeutic agents for cancer treatment (see page 54) and **FIMECS, Inc**[164]. established in January 2018 to develop protein degradation therapeutics for cancer and other difficult to treat diseases.

**MIT Startup Exchange Showcase Japan**[165] was held at the Shonan Health Innovation Park in October 2017.

**Kobe Foundation for Biomedical Research and Innovation**

At the Foundation for Biomedical Research and Innovation (BRI)[166], **Pro-Cluster Kobe**[167] is the organisation supporting companies from the **Kobe biomedical research cluster (KBIC)**[168]**,** and fostering collaborations with foreign life science clusters.

International agreements have been signed with the **German cluster Life Science Nord** (from the Northern German States of Hamburg and Schleswig-Holstein); with the Belgian **Flanders Bio** and **Medicon Valley Alliance (**from **Denmark** & **Sweden)**. Agreements with China Medical City (CMC) in Thaizou (China), are also in place.

KBIC, one of the largest biomedical clusters in Japan, celebrated its 20th anniversary in 2018.

It includes research institutes (RIKEN Centre for Developmental Biology (CDB) (see page 66), Translational Research Informatics Centre (TRI), Advanced Institute for Computational Sciences

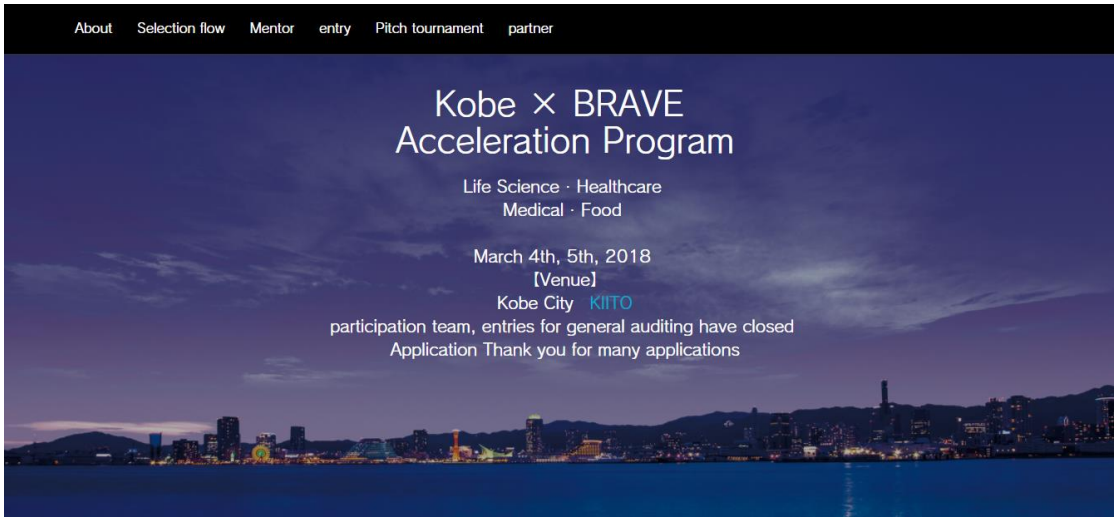
160 http://kpharma.co.jp/information/
161 https://www.noile-immune.com/english/
162 https://www.scohia.com/eng/
163 http://www.chordiatherapeutics.com/eng/update/pdf/20171122_EN.pdf
164 http://www.fimecs.com/eng
165 https://ilp.mit.edu/conference.jsp?confid=180&tabname=overview
166 http://www.ibri-kobe.org/
167 http://www.ibri-kobe.org/english/cluster/
168 http://www.kobe-lsc.jp/en/

(AICS) K Computer...), highly specialized hospitals, and multiple medical companies and groups, related to a variety of themes including treatment, diagnosis, prevention, caregiving, welfare, etc., in pharmaceuticals, medical equipment, regenerative medicine, and other fields.

On regenerative medical research, contract manufacturing and a cell processing centre are also available at the Foundation for Biomedical Research and Innovation. (IBRI laboratory)[169], which is open to collaborative research with enterprises and universities. Examples of regenerative research projects include: Repair of cornea with autologous mucosal sheet, treatment of unhealed fractures with mobilised CD34+cells, or Regeneration of tympanum membrane by bFGF/ sponge.

Acceleration programs such as **Kobe x BRAVE** for entrepreneurs[170] in life science/health/medical device take place at KBIC, under sponsorship from NEDO, Kobe city, Pharmaceutical/Medical device companies (Bayer, Merck, BMS, Ikeda Scientific Co. Ltd…) and Venture Capital Funds (Beyond Next Ventures).

**Figure 10.3: Kobe BRAVE Program**




[169] https://www.fbri-kobe.org/kbic/
[170] https://kobexbrave.tech

**Osaka Bio**

Osaka Bio Headquarters[171], is an initiative for increasing Osaka and Kansai region international competitiveness in the life science field, promoting activities at large-scale overseas trade fairs working on creating a foundation for international exchange programs with overseas life science clusters. It support the overseas business exchanges between the companies based in Osaka and Kansai. Universities and research institutions are concentrated mainly in the northern part of Osaka, and many pharmaceutical companies have their headquarters in that area. Major Institutions include:

- **The Saito life Science Park**[172], established in 2004 as a major base for R&D, including incubation facilities. Very active in organising seminars dealing with various themes related to the field of life science, offering an opportunity for information gathering, networking and exchange.
- The **Northen Osaka** Health and Biomedical innovation town (KENTO), a cluster around the National Cerebral and Cardiovascular Centre.
- The National Institutes of Biomedical Innovation Health and Nutrition **(NIBIOHN)**
- Universities and Research institutes previously mentioned in this report, such as Osaka Universities, the Immunology Frontier Research Center (IFReC) (see page 58), and RIKEN Quantitative Biology Center (QBiC) (see page 70).

Osaka has stablished numerous MoU with European organisations and life science clusters: bioXclusters plus（bioPmed / Bioindustry Park（Italy）、Biocat（Spain）、BioM（Germany）、Lyonbiopole（France) and FlandersBio.

## 11. Academic Societies and Associations

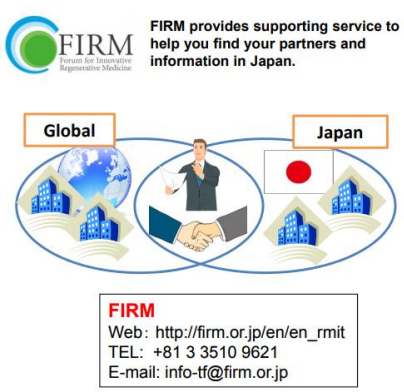
**Japan Bioindustry Association (JBA)[173]**

JBA in cooperation with organizations supporting venture companies of each region in Japan. maintains an **online directory of Japan bioventure companies**[174].
By broadly disseminating this information, JBA aims to promote the creation of business alliance opportunities in Japan and abroad, and contribute to their activity.

[171] https://osaka-bio.jp
[172]https://osaka-bio.jp/support/seminar/
[173] https://www.jba.or.jp/en/about/
[174] https://area34.smp.ne.jp/area/table/5697/FDN_H3/M?S=lbsfn2mbnak

In March 2018, the bioventures directory included 114 companies: 60 hits corresponding to companies performing *"pharmaceutical/drug discovery"* and 53 hits for the activities *"Drug discovery support/Contract service"*

**The Forum for Innovative Regenerative Medicine (FIRM)**




FIRM, the trade association in Japan regenerative medicine field, was established in 2011, and today has more than 230 member entities.

Since 2014, FIRM provides assistance to overseas companies, in cooperation with the Japan External Trade Organisation (JETRO), providing information relating to RMPs and introducing member companies that would make appropriate partners. RMIT is a task force within FIRM, working as contact on questions about industrialization of regenerative medicine.
The booklet edited by FIRM, and online listing[175] of member companies are very useful to get an idea of Japanese RM companies and activities at a glance.
FIRM signed MoU with Catapult, UK in 2017.

FIRM organizes **"crossroads meetings"** to facilitate networking to those seeking partners and licensees in Japan. Several companies from Europe have attended these meetings in 2017

**The Japanese Society for Regenerative Medicine JSRM**

Established in 2001, JSRM[176] is the largest society for regenerative medicine in the world, with approx. 6000 members involved in research in basic medicine/dentistry, clinical medicine, tissue engineering, cell biology, as well as bioethics, regulatory science, law and medical economics.
After 2016, JSRM acquired funds from the Agency for Medical Research and Development (AMED), and has been supporting clinical research, development of human resources, and coordination between academia and industry. One of its latest projects is the **National Regenerative Medicine Database (NRMD), an important contribution to the field of acquisition of real world evidence from all cases of regenerative medicine and cell therapies.**

In February 2018, JSRM signed a MoU with Catapult (UK).

[175] https://firm.or.jp/en/introduce
[176] www.jsrm.jp

JSRM coorganises the TERMIS World congress (Tissue Engineering and Regenerative Medicine International Society) congress which is held every three years, and brings together researchers, scientists, clinicians, and students from academia and industry to discuss critical developments. The 5th TERMIS world congress will take place in September 2018, in Kyoto.


**Japan Society of Gene and Cell Therapy**

Established in 1995 , the Japanese Society of Gene and Cell therapy[177] JSGT coorganises symposia[178] with The Institute of Medical Science, The University of Tokyo (IMSUT) (see pg 38)

**Table 11.1: Other Japanese Academic Societies of interest to biotech companies in Europe**

| | |
|---|---|
| Japanese Society for Bacteriology | http://jsbac.org/ |
| Japanese Society for Chemical Biology | http://www.jscb.jp/index_e.html |
| Japanese Society of Epigenetics | http://square.umin.ac.jp/jse2017/ |
| Japanese Society for Immunology | http://www.jsi-men-eki.org/english/ |
| The Biophysical Society of Japan | http://www.biophys.jp/index-e.html |
| The Japanese Society for Bioinformatics | https://www.jsbi.org/en/ |
| Protein Science Society of Japan | http://www.pssj.jp/en/ |
| Japan Human Proteome Organisation | https://www.jhupo.org/english/ |
| Japan Society for Cell Biology | http://www.jscb.gr.jp/en/ |
| The Japan Society of Human Genetics | http://jshg.jp/e/ |
| The Japanese Society for Genome Editing | http://jsgedit.jp/en |
| The RNA Society of Japan | https://www.rnaj.org/en/ |
| The Molecular Biology Society of Japan | http://www.mbsj.jp/en/index.html |

[177] http://www.jsgt.jp/
[178] http://www.jsgt.jp/ANNOUNCE/5cgct_program.pdf

## 12. Tradefairs and Organisations

The most common way of meeting new potential partners in Japan is via networking in tradefairs, congresses and conferences.

**BioJapan**[179]**,** the main exhibitions taking place in Japan on the life science biotech sector, is a partnering event, gathering over 1500 participants from 35 countries, including more than 800 exhibitors. With a very large representation of Japanese companies participating to the event, it is a very effective event to meet potential partners. **Next edition is scheduled to take place 10-12 October 2018, in Yokohama.**

**Cluster support Missions on Biotechnogies in Japan**[180] are organised by the EU-Japan Centre for Industrial Cooperation. The mission is a three day event structured in two parts:

- participation to a B2B matching event coorganised by European Enterprise Network (EEN) and the Senri Life science Foundation of the Osaka prefectural government
- participation to BioJapan, with possibility to display company information and hold meetings at the exhibition booth, with support from professional interpretation services

**The EU-Japan Centre for Industrial Cooperation**[181] is a unique joint venture between the European Commission and the Japanese government. It aims to promote all forms of industrial, trade and investment cooperation between EU and Japanese companies, to improve their competitiveness by facilitating exchanges of experience and know- how. The Centre is based in Tokyo with a branch office in Brussels.

## 13. Recommendations and Conclusion

European biotech companies with a successful entry on the Japanese market, frequently report that establishing an agreements with a Japanese counterpart can be a lengthy process. It may require longer timelines and more formal communication than in other regions of the world, leading to particularly solid and fruitful partnerships.

International tradefairs and scientific congresses are an excellent environment for EU SMEs to initiate discussions with potential Japanese partners. Participation to several editions of BioJapan, or

[179] https://www.ics-expo.jp/biojapan/en/
[180] https://www.eu-japan.eu/events/biotech-cluster-sme-mission
[181] https://www.eu-japan.eu/

persistently meeting both at Biojapan and then again at BioEurope, are strategies mentioned by some SMEs as key to the establishment of agreements.

EU SMEs can obtain very useful support from organisations like the bioclusters, local national and regional chambers of commerce in Japan, and the EU-Japan Centre for Industrial Cooperation.

Matching partnership events, offered by several of the organisations mentioned in this report, such as LINK-J, Japanese regional clusters like Osaka Bio, or the regenerative medicine FIRM events, are particularly tailored to benefit EU SMEs networking needs.

The possibility of working with a local intermediary, Japanese agency or broker company is also something to be considered.

The acquisitions of EU biotech companies by Japanese pharma, such as the take over of Belgian/Spanish TiGenix by Takeda in 2018, or the acquisition of Danish CMC Biologics by Asahi Kasei are examples showing that Japanese companies are more than ready to absorbe emerging technologies from Europe.

While major pharma groups make obvious targets, when it comes to finding partners in Japan, joining forces with small local players could also be a valuable strategy.
The establishment of **cooperation between European SMEs and Japanese bioventures** may be a way to overcome some of the obstacles that young biotech companies are facing for growth in both territories:

- Japanese bioventures tend to be oriented towards their domestic market. Focusing on forming alliances in Japan, they may be ignoring overseas opportunities which could also be very profitable to them. Language barriers are often an additional difficulty in their dealing with overseas companies.
- European SMEs usually lack the specific knowledge of local academic and industrial landscape in Japan, which could potentially enlarge their base of Japanese partners/clients.
- It can be very difficult for EU SMEs to offer the level of service required by Japanese clients without at a local contact.

In this context, European SMEs considering internationalization in the Japanese market, may find useful to explore alternative partnership and collaboration schemes with young Japanese bioventure companies, such as those presented in this report, which could potentially enable them to complete the services offered in both territories.

**European biotech SMEs** considering the possibility to establish a manufacturing, or an R&D base in Japan should explore the advantages offered by **International Strategic Zones** (like LiC Kanagawa, or Kyoto, for example), and JETRO can provide valuable support on the identification of applicable incentive measures to foreign investment.

## Annexes

### Annex 1: Japanese bioventures exhibiting at Japan Healthcare Venture Summit 2017

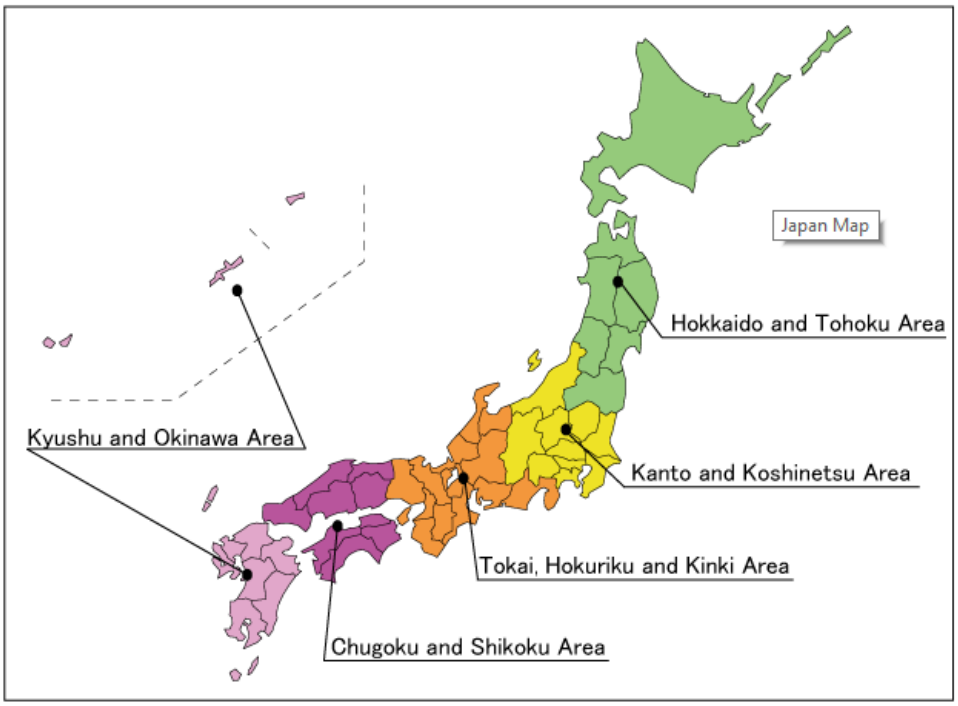
| | |
|---|---|
| **DD** | Drug and Drug Discovery |
| **DS** | Drug discovery Support, Research equipment/Contract services |
| **RM** | Regenerative medicine products |
| **VC** | Venture Capital Fund |

| | | |
|---|---|---|
| AMBICION Co., Ltd. | RM | |
| Amelieff Co., Ltd. | DS | |
| Axcelead Drug Discovery Partners, Inc. | DS | |
| Beyond Next Ventures, Inc. | VC | |
| Biomimetics Sympathies, Inc. | DS | |
| BioSeren Tach, Inc. | DD | |
| Brightpath Biotherapeutics Co. Ltd. | DD | RM |
| BTB Japan, Inc. | DS | |
| CellFiber Co. Ltd. | DS | |
| CHIOME Bioscience, Inc. | DD | DS |
| Epsilon Molecular Engineering, Inc. | DD | DS |
| Epigeneron LLC | DS | |
| GeneCare Research Institute Co. Ltd | DD | |
| Ginreilab Inc. | DS | |
| GORYO chemical Inc. | DD | |
| Hamamatsu University School of Medicine | DD | DS |
| Himuka AM Pharm. Corp. | DS | |
| Institute of Microbial Chemistry | DS | |
| Kyoto prefectural University of Medicine/ Minimum Lab | DS | RM |
| MC Data Inc. | DS | |

| | | |
|---|---|---|
| MEDINET Co. Ltd | DS | VC |
| MedVenture Partners, Inc. | VC | |
| MeSCue-Janusys Inc. | RM | |
| MIRTeL Co., Ltd. | DS | |
| Momotaro-Gene Inc. | DD | |
| NanoCarrier Co., Ltd. | DD | |
| NANOSION Co., Ltd. | DD | |
| Nobelpharma Co. Ltd | DD | |
| Noile-Immune Biotech, Inc. | DD | RM |
| Novumcella Inc. | RM | |
| Osaka City University | DS | |
| Osaka University Venture Capital (OUVC) | VC | |
| PrevenTec Inc. | DS | |
| ReqMed Company, Ltd. | DS | |
| Rhelixa Inc. | DD | |
| Saitama University | DS | |
| SEEDSUPPLY, Inc. | DS | |
| SENTAN Pharma Inc. | DD | |
| Shinjuku healthcare incubation park (SHIP) | DS | |
| Shonan Health Innovation Park | DS | |
| Sumitomo Dainippon Pharma PRISM partnerships | DD | |
| TAGCyx Biotechnologies, Inc. | DD | |
| Taiho Pharmaceutical Co., Ltd. / Taiho Ventures, LLC | DD | VC |
| TFK Co. Ltd. | DD | |
| The University of Tokyo Edge Capital (UTEC) | VC | |
| TWO CELLS Company, Ltd. | RM | |
| Unlog K.K. | DS | |

Medical Devices excluded from original list

## Annex 2 List of National Universities[182]




| | |
|---|---|
| Hokkaido and Tohoku 14 | Hokkaido University<br>Hokkaido University of Education<br>Muroran Institute of Technology<br>Otaru University of Commerce<br>Obihiro University of Agriculture and Veterinary Medicine<br>Asahikawa Medical University<br>Kitami Institute of Technology<br>Hirosaki University<br>Iwate University<br>Tohoku University<br>Miyagi University of Education<br>Akita University<br>Yamagata University<br>Fukushima University |
| Kanto and Kohinetsu 26 | Ibaraki University<br>University of Tsukuba |

[182] http://www.mext.go.jp/en/about/relatedsites/title01/detail01/sdetail01/1375122.htm

| | |
|---|---|
| | Tsukuba University of Technology<br>Utsunomiya University<br>Gunma University<br>Saitama University<br>Chiba University<br>The University of Tokyo<br>Tokyo Medical and Dental University<br>Tokyo University of Foreign Studies<br>Tokyo Gakugei University<br>Tokyo University of Agriculture and Technology<br>Tokyo University of the Arts<br>Tokyo Institute of Technology<br>Tokyo University of Marine Science and Technology<br>Ochanomizu University<br>The University of Electro-Communications<br>Hitotsubashi University<br>Yokohama National University<br>National Graduate Institute for Policy Studies<br>The Graduate University for Advanced Studies<br>Niigata University<br>Nagaoka University of Technology<br>Joetsu University of Education<br>University of Yamanashi<br>Shinshu University |
| Tokai, Hokuriku and Kinki Area 25 | University of Toyama<br>Kanazawa University<br>University of Fukui<br>Gifu University<br>Shizuoka University<br>Hamamatsu University School of Medicine<br>Nagoya University<br>Aichi University of Education<br>Nagoya Institute of Technology<br>Toyohashi University of Technology<br>Mie University<br>Shiga University |

| | |
|---|---|
| | Shiga University of Medical Science<br>Kyoto University<br>Kyoto University of Education<br>Kyoto Institute of Technology<br>Osaka University<br>Osaka Kyoiku University<br>Hyogo University of Teacher Education<br>Kobe University<br>Nara University of Education<br>Nara Women's University<br>Wakayama University<br>Japan Advanced Institute of Science and Technology<br>Nara Institute of Science and Technology |
| Chugoku and Shikoku 10 | Tottori University<br>Shimane University<br>Okayama University<br>Hiroshima University<br>Yamaguchi University<br>Tokushima University<br>Naruto University of Education<br>Kagawa University<br>Ehime University<br>Kochi University |
| Kyushu and Okinawa 11 | Kyushu University<br>Kyushu Institute of Technology<br>Saga University<br>Nagasaki University<br>Kumamoto University<br>Oita University<br>University of Teacher Education Fukuoka<br>University of Miyazaki<br>Kagoshima University<br>University of the Ryukyus |