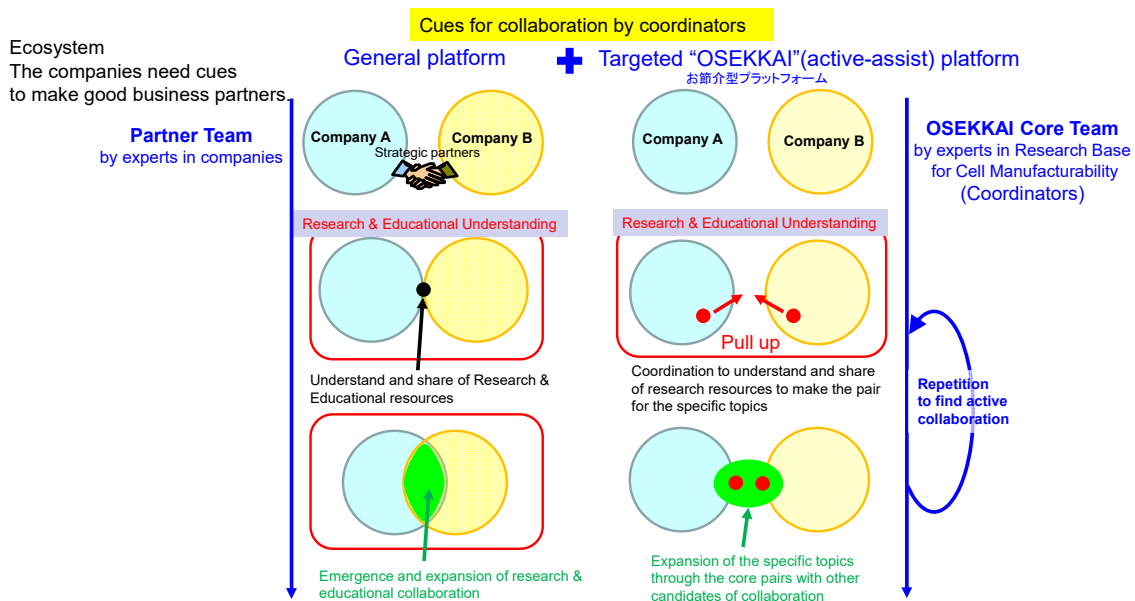


Research Base for Cell Manufacturability

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As novel medical technologies, such as regenerative medicine, are developed and industrialized, the nature of medical-engineering collaboration at universities is changing dramatically due to the **diversification of stakeholders**, including industry (private companies), government (national and local governments), schools (educational and research institutions), and the private sector (local residents and NPOs). In particular, in the field of cell manufacturing, where "**nurturing cells**" is the core technology, academic progress is still immature, and it is necessary to proceed simultaneously with academic construction and social implementation, making it essential to make **sophisticated formation of bases with good taste through a connecting mechanism between people, information, technology, and fields**. In order to from the consortium, we are aware that we cannot do it alone, and we feel that it is important to create an environment in which we can make platform with ‘**good-natured meddling** (active assistance)’ (**good ‘OSEKKAI’**). Therefore, we would like to ask the question, "What is good OSEKKAI?" We would like to clarify the direction of development (roadmap) for new **technology-driven industrial fields**, build unique concepts and technologies, and conduct rapid activities for implementation by forming an ecosystem that enables education, research, industrialization through cooperation among industry, government, academia, and the private sector.



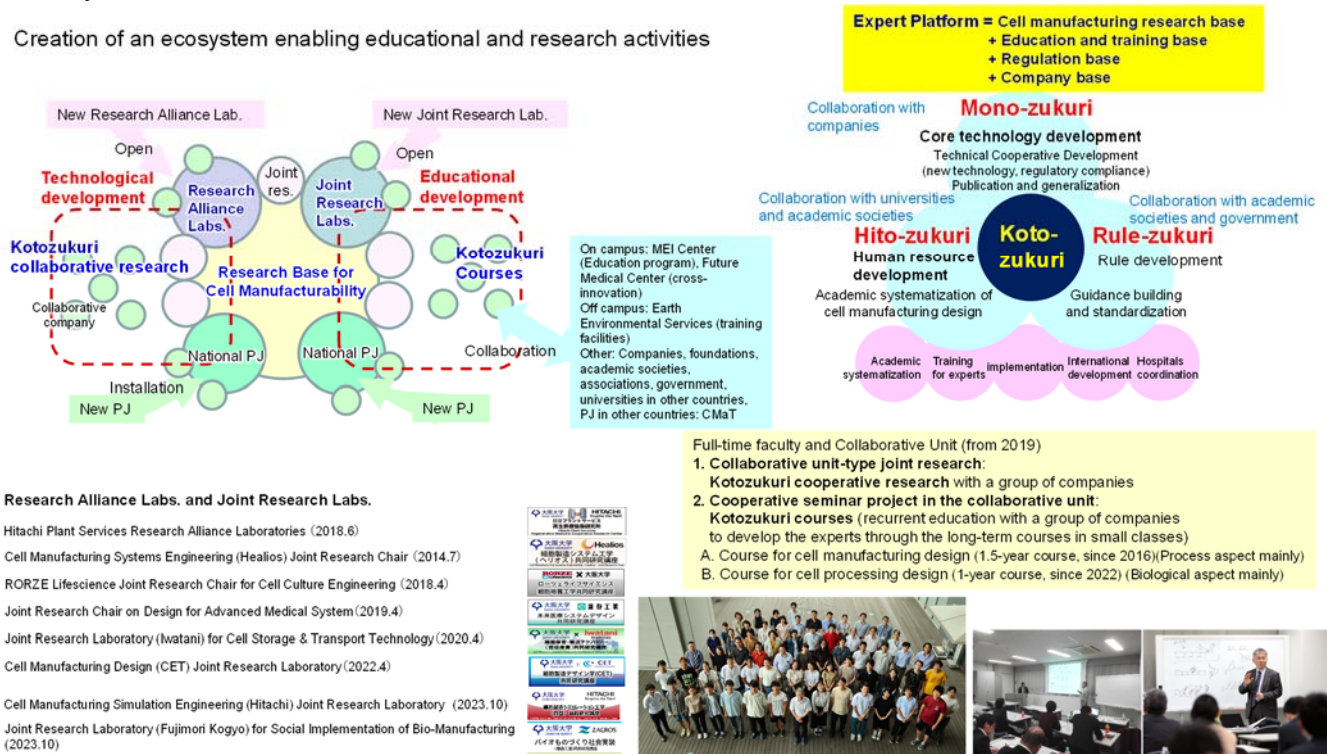
The ‘Research Base for Cell Manufacturability’, which started its activities in 2016 as a collaborative fusion research organization of the Graduate School of Engineering, was adopted as Innovation Base in Center of Excellence in Advanced Research Division of Techno Arena in 2021 and is now in full-scale activities.

There is no academic systematization in the field of cell manufacturing for regenerative therapy, and academic systematization and industrialization are proceeding simultaneously. Therefore, the education is indispensable by academia, industry and government. Thus, the Research Base for Cell Manufacturability is considered to contribute to cell manufacturing for regenerative medicine as the first novel field across companies (a place for professionals, a place for technological development, and a place for social implementation) through the establishment of Research Alliance Labs. and Joint Research Labs., and expansion of joint research (investment in industry-academia collaboration).

We have proposed a newly academic concept of ‘**cell manufacturability**’ as the cornerstone of our

studies to conduct research activities. Cell manufacturability refers to “capability of cell manufacturing through the process by bridging between biological and process aspects”. And its design ‘**Design for cell manufacturability**’ is defined to be ‘manufacturing design of cell-based products in such a way that they are easy to manufacture through **simple, safe and efficient (cost-saving) process with stable product quality and secure to customer** by considering transportation and preparation outside factory’.

Creation of an ecosystem enabling educational and research activities



We also recognize the importance of ‘make an epoch (**Koto-Zukuri**)’, which consists of ‘development of manufacturing technology (**Mono-Zukuri**)’, ‘development of regulation (**Rule-Zukuri**)’ and ‘development of human resources (**Hito-Zukuri**)’. Here, the ‘**stability**’ can be achieved by human and technology and the ‘**security**’ can be achieved under regulations. We have been striving to form a group of brains (think tank) for social implementation with progressing new technologies based on the concept of cell manufacturability, establishing guidelines and instructions for domestic regulations and international standardization in collaboration with industry and government, as well as providing recurrent education for company members and students.

Thus, the Research Base for Cell Manufacturability aims to form ‘**Core Japan**’, a new core ecosystem in Japan with good OSEKKAI, by forming a group of brainpowers, systematizing the cell manufacturability and Koto-Zukuri with Mono-Zukuri, Rule-Zukuri and Hito-Zukuri. In addition, Core Japan will be expanded internationally to be ‘**Global Japan**’, aiming to achieve the following goals together with our friends.

(1) Human resource development (Hito-Zukuri)

In novel technological and industrial fields that require the concept of cell manufacturability, companies that promote industrialization activities will gather at Osaka University to act as a group of brainpowers to conduct good ‘OSEKKAI’ for innovation and education (academic understanding, development research methods, regulations) that contributes to social implementation and produce human resources to the novel industrial field.

(2) Development of manufacturing technology (Mono-Zukuri)

In addition to the exploratory research, methodological research, and other new seeds research that have been conducted at the university, we will steadily and aggressively acquire basic data with low-

key efforts that is essential in the new technology industrial field. Through these activities, we will promote the construction of fundamental technologies and enable their implementation.

(3) Development of regulation (Rule-Zukuri)

Utilizing the human resources (human resource development) and fundamental technologies (manufacturing) developed above, we will promote social implementation by standardization and rulemaking based on empirical data.

(4) Making an epoch (Koto-Zukuri)

These activities described above will bring together many companies to form a stronger group of brains, and a virtuous cycle of 'Koto' (new field) consisting of Hito-Zukuri (human resource development), Mono-Zukuri (technological development), and Rule-Zukuri (rulemaking). We would like to prove that this Koto-Zukuri is the key to Core Japan by enriching the brain group and creating new seeds.

(5) Practice of Core Japan (good 'OSEKKAI' platform)

We will strive to create a good 'OSEKKAI' platform of practice in new technology industries that require the concept of cell manufacturability, so that the customers who benefit from the concept will be continuously happy. In particular, we would like to enhance Core Japan by pushing forward social implementation in the medical and private sectors in addition to industry, government, and academia through collaboration with hospital centers (ex. **International Center for Future Medical Care** in Osaka), which are places of practice for medical technologies such as regenerative medicine and cell therapy. Furthermore, we would like to extend our ideas and methods to other novel fields such as Food Technology fields based on cultured meat technology.

(6) Expansion to be Global Japan (global 'OSEKKAI' platform)

In addition, we will promote Koto-Zukuri, including international students and businesspeople from overseas, to lead a society that enhances the Japan Brand overseas. Through these overseas development activities, Global Japan, we would like to promote innovation by making it a place to practice Koto-Zukuri that contributes to the new technology-driven industrial fields.

We are considering the following good "OSEKKAI" for the implementation with the activities of this research base. We are not sure if we will be able to accomplish them, but we would appreciate the cooperation, participation, and teaching of those who are interested.

Action Plan

1. Establishment of expert platform

A platform consisting of research center for cell manufacturing, an education and training center, and a corporate center will be formed for new technology-driven industrial fields that require the concept of cell manufacturability, and good OSEKKAI will be carried out to build Core Japan. In doing so, we would like to establish a stream with forming a core group of brainpowers, accomplishing Koto-Zukuri, and communicating to the next generation in view of the significance and history of the core formation. These activities will generate next innovation.

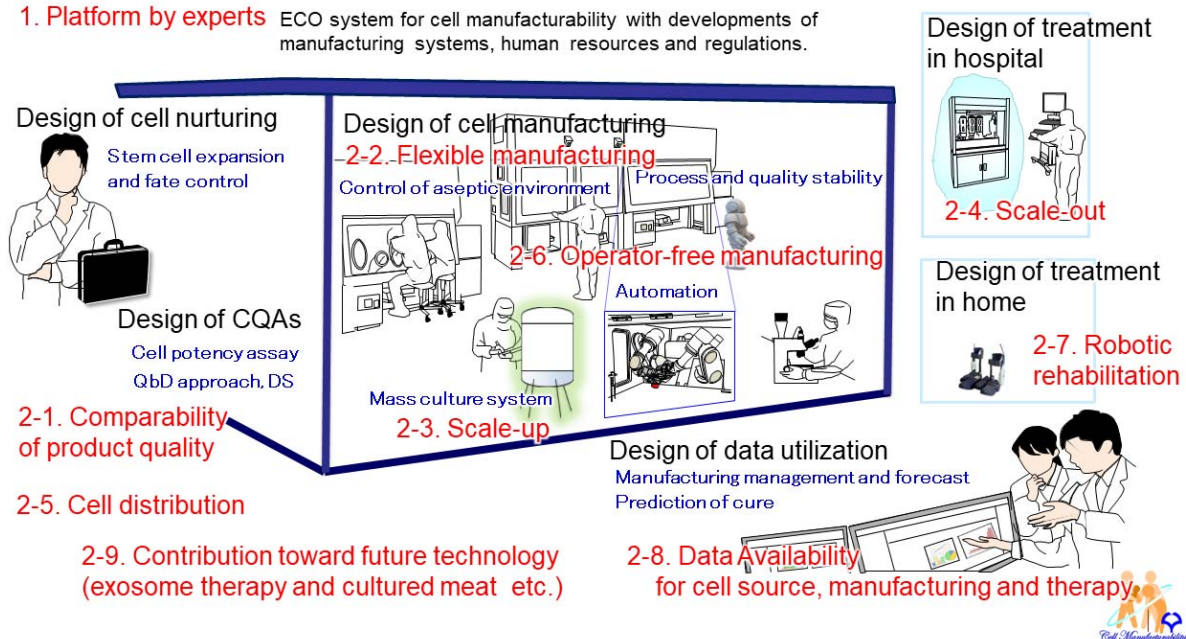
- (1) Forming a core group of brainpowers: To form a group of brainpowers that contributes to social implementation, to spread the concept of Koto-Zukuri, which consists of Mono-Zukuri, Hito-Zukuri, and Rule-Zukuri, and to make the significance of the realization of Core Japan known at universities, society, and overseas.
- (2) Accomplishing Koto-Zukuri: Implement Koto-Zukuri through collaboration among social implementation sites (eco-system) to build a Core Japan. Furthermore, efforts should be made to form Global Japan, an activity that includes overseas development.
- (3) Communicating to the next generation: To pass on our experience to those who aim to become Core Japan in the next generation of industries, and support new Koto-Zukuri in other fields.

2. Development of manufacturing technology (Mono-Zukuri)

As a core technology initiative, we aim to achieve the following nine goals, which we hope to accomplish together as a group of brains.

- (1) Clarification of comparability of cell-based products: Clarification of methods to prove comparability of quality in accordance with manufacturing changes, such as mechanization and mass production, and simplification of automation and scale-up.
- (2) Development of flexible manufacturing design: It is possible to understand and express process stability and instability, and to suppress intrinsic disorder. Furthermore, it is possible to construct a novel QbD concept and to implement manufacturing changes relatively easily.
- (3) Scale-up: Cost reduction is possible in large-scale manufacturing facilities for mass production (more than 100 L of culture, more than 10^{11} cells), which consists of the culture process, pipetting,

1. Platform by experts ECO system for cell manufacturability with developments of manufacturing systems, human resources and regulations.



freezing, and storage processes. In addition, the development of scale-down technology is critical to realize the scale-up of cell manufacturing.

- (4) Scale-out: The technical construction for simple and small-scale cell preparation facilities (a room in a hospital, etc.) will enable the reduction of the cost under closed system operation.
- (5) Cell distribution: Easy procurement of cell sources to achieve optimal product quality.
- (6) Operator-free manufacturing: Cell manufacturing without operators can be realized by robotics and automation technology (operator-free technology + cleaning regulation).
- (7) Robotic rehabilitation: Understanding of rehabilitation unique to regenerative medicine and data management of treatment prognosis at home and in clinics, etc., should be made possible by constructing technologies such as robotic rehabilitation.
- (8) Data availability: DX technology will speed up manufacturing approval and change procedures by linking data at the time of development with manufacturing management data. In addition, the data from manufacturing management (raw material procurement, manufacturing process, product distribution, human resources), treatment management, and prognosis management (rehabilitation) should be linked to clarify the therapeutic effect. Construction of a system that realizes treatment prediction and cost reduction by linking data from research and development, clinical trials, and manufacturing.
- (9) Contribution to future technology: We would like to contribute to the industrialization of newly emerging technologies such as exosome therapy and cultured meat technology.

3. Human resource development (Hito-Zukuri)

The following educational activities will be conducted in academic fields for which there are no textbooks.

- (1) Training of experts: We will hold seminars (about 40 times/year) for company persons and students to broaden and deepen the know-how of the technologies and ideas developed in the center.
- (2) Training of experts for working people: As recurrent education for company persons, we will offer courses in cell manufacturing and design (currently two courses: cell manufacturing design course and cell processing design course) to train experts who understand the concept of process design and cell culture in cell manufacturing. Furthermore, in collaboration with the Global Medical Engineering Information Center (MEI Center) at Osaka University, we will offer courses that provide education on a wide range of knowledge, including regulatory, non-clinical, clinical, and manufacturing knowledge (Cell Manufacturing Design Expert Development Course).
- (3) Training and practical education in collaboration with companies and within the university; opening of training courses (e.g., hygiene management) as part of recurrent education for working people. In this case, the courses should be offered in cooperation with companies (e.g., Earth Environmental Service, Cooperative Research Institute, and joint research courses), by creating training contents and utilizing in-house training facilities (currently two courses, beginner's course and advanced course (training) for cell manufacturing design experts by MEI Center). In addition, the Center's know-how will be imparted through joint research and academic consultations tailored to the needs of each company, and through the promotion of practical research by company personnel at the Center.
- (4) Student education: The current "Cell Manufacturability" class for graduate students should be enhanced as a part of student education. In addition, some contents of recurrent education for company persons should be utilized as a voluntary participation type class that does not depend on class credits. We will demonstrate the value of education for social implementation through research on cell manufacturing and increase the number of experts who will lead the next generation (including active recruitment of doctoral students who are company persons).
- (5) Education for government; Utilize the above contents to enhance the contents for government

officials such as inspectors.

4. Rule development (Rule-Zukuri)

In cooperation with academic societies, associations, and government, we will promote industrialization by constructing guidelines and instruction manuals as follows.

- (1) Investigation of the needs of government, universities, and companies: Investigation of requests for guidelines and guidelines from various positions in industry, government, academia, and the private sector.
- (2) Construction of guidelines for the government: construction of various guideline proposals based on the needs of the government.
- (3) Guidelines for the practitioners: The Center will prepare various guideline drafts based on the needs of the practitioners of cell production.
- (iv) Development of documents for international standardization: The Center should develop various guideline proposals based on the needs of the practitioners, collaborating with ISO organizations (especially TC198/WG9 (aseptic processing), TC276/WG3 (analysis) and WG4 (bioprocessing)) to prepare documents for international standardization.

5. Formation of social implementation sites and seed chains

Together with the group of brainpowers, we will draw up a vision of what social implementation sites should be and form practical sites together with those who need them. In addition, we will also use our experience to "good OSEKKAI" in other new technology industry fields.

- (1) Formation of a place for social implementation: Together with practitioners (International Center for Future Medical Care in Osaka, etc.), we collaborate with local organizations (Organization for Promotion of Future Medical Science, BioCommunity Kansai, etc.) and academic societies (Japanese Society for Regenerative Medicine, Japanese Society for Regenerative Medicine and Rehabilitation Science, Japanese Society for Biotechnology, Society for Chemical Engineering, etc.) to realize a place for social implementation.
- (2) Achievement of social implementation: Transfer and implementation of the technology developed with the brain group.
- (3) Establishment of a "Seeds Chain": To develop next-generation seeds at the group of brainpowers, and to develop them into next-generation technology industries (exosome therapy technology, cultured meat technology, etc.) in addition to this implementation site.

6. Outreach and efforts to maintain the research base

Report and publicize the activities of Core Japan, hold public symposiums, and raise funds for new industry-academia collaboration.

- (1) Activity reports: Report on the results and activities of the center through the symposium (about 2 times/year).
- (2) Utilization of new communication venues: Utilize the Consortium Kansai (Biok) and other communication venues to disseminate the activities of the research base both domestically and internationally.
- (3) To make new friends and to be independent: To survey guidelines, guidelines, and requests for technological development from various positions in industry, government, academia, and the private sector, and to gain new friends. In addition, to build a system that can be sustainable through the Mono-Zukuri supports from private companies and national projects, and by earning profits through Hito-Zukuri and Rule-Zukuri.