Moonshot R&D MILLENNIA* Program

*Multifaceted investigation challenge for new normal initiatives program

” Research for the development of non-cellular microparticles capable of integrating animal and plant cells, and incorporating storage battery and sensor functions”

Initiative Report

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Brainstorming Team「Intelligent Living Cell」

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I. Concept

1. Proposed MS Goal

1.1 Proposed MS Goal title

By 2050, "iL-Cell", a fusion of cells and artificial materials, will enable a society where people can realize to tackle pre-diseases regardless of their location.

1.2 Vision for 2050 society

In the year 2050, the development of science will lead to personalized medicine, in which treatment policies are determined based on individual DNA and protein expression information. Molecular-level information on the onset mechanisms of diseases will be consolidated, and AI-based predictions will lead to not only treatment through molecular-level control, but also to detection of signs of disease and appropriate treatment based on predictions. As for therapeutic drugs, biopharmaceuticals such as antibodies, peptides, enzymes, and cells that are tailored to individual DNA information are becoming the mainstream. In addition, social services are moving online, and systems are being built to ensure the safety and convenience of sharing personal medical information in the cloud (Fig. 1).

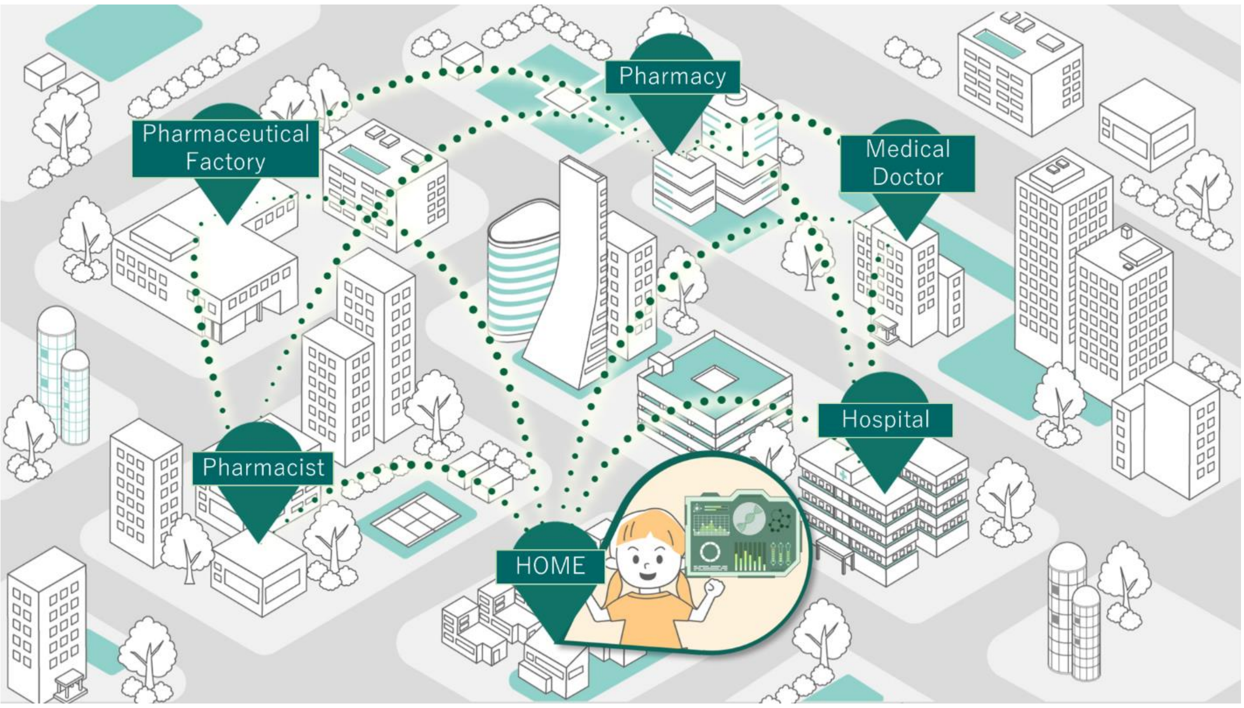


Figure 1: Vision of society in 2050
Medical services are moving online and to the home.

In order for people to enjoy the benefits of science, technology, and social systems in the medical field of such a society, a modality (called "Intelligent Living Cell (iL-Cell)" in this context) that combines the concepts of medical devices and therapeutics with sensing and tackling pre-diseases is needed. The iL-Cell needs to be able to (1) detect minute changes in biomolecules to detect signs of disease, (2) transmit the detected changes to the cloud, (3) emit therapeutic molecules proposed to improve physical condition. Then, (4) the iL-Cell should be almost comfortable to wear and not affect daily life, and (5) the iL-Cell can be used anywhere (Fig. 2).

In a society with iL-Cells, people can go about their daily lives and detect changes in their physical condition at an early stage, thereby leading a life in which they can maintain their health without being aware of illness. Accurate knowledge of the health status of infants and other children who have difficulty communicating will enable appropriate treatment. At the scene of a serious accident or disaster, it will be possible to accurately grasp the health status of people and take appropriate measures. A society in which everyone can maintain their health without being aware of illness, anytime, anywhere, will be realized.

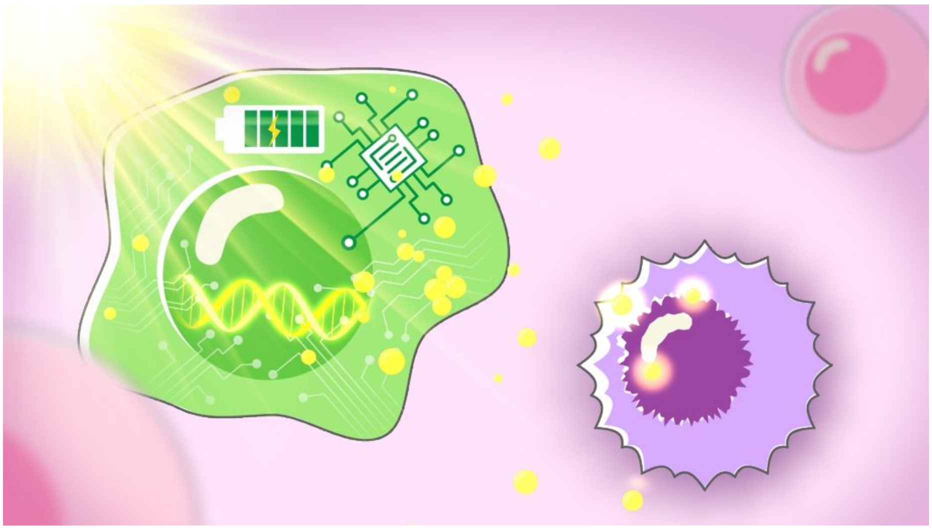


Fig. 2 Schematic diagram of Intelligent Living Cell (iL-Cell)

The iL-Cell, which does not require a power source due to its optical energy conversion and biological power generation, can detect changes in health status at the molecular level in the body and transmit the information outside the body. Based on this information, it will be possible to maintain health by releasing appropriate health condition improvement or treatment molecules.

2. Targets

By 2030

- Wearable devices will be equipped with therapeutic cells, and the integration of sensing and cellular medicine will enable the detection of physical conditions and the release of therapeutic agents in response to them.
- Bacteria-derived electron channels will be functioned in mammalian cells, enabling mammalian cells to generate electricity.
- Co-cultivation of mammalian and plant cells will enable continuous supply of energy to mammalian cells through photosynthesis.
- Energy can be produced in mammalian cells through light energy conversion using quantum dots.
- It will be possible to send and receive information through the cell membrane by fixing cells to the detector.

By 2050

- Miniaturization and water resistance of semiconductors with minimal communication functions will make it possible to attach semiconductors to cells or place them inside cells. This will make it possible to detect changes in the cell and transmit that information. In addition, it will be possible to remotely switch on the cells to release therapeutic molecules.
- The mammalian-derived power-generating cells will enable charger-free sensing in vivo.
- The combination of these technologies will lead to the realization of iL-Cells that can sense and transmit therapeutic molecules in vivo without the need for an energy source.

3. Background

3.1 Why now?

< Social Demands >

In the year 2050, the problem of a declining population will become more serious as the birthrate declines and the population ages. As the number of elderly people increases, the number of diseases increases, and the demand for medical care and nursing care increases, but as the working population decreases, the social infrastructure that supports this medical care and nursing care becomes weaker. In this context, if the problems of population concentration in urban areas and depopulation of rural areas are not corrected, it may become difficult to provide adequate medical care in rural areas with weak medical infrastructure. From a global perspective, environmental problems and the depletion of resources on a global scale will affect the production of pharmaceuticals, and the rise of emerging countries may lead to competition for limited resources.

On the other hand, the sophistication of medical care will also increase: the Human Genome

Project was completed in 2003, and the rapid development of genetic analysis technology since then has paved the way for personalized medicine based on it. In cancer treatment, personalized medicine based on genotype as well as histology is already in use. Genes related to lifestyle-related diseases such as obesity and hypertension have also been found in areas other than cancer, and genetic information may be used to prevent the onset of cardiovascular diseases in these diseases. Such advances in medical technology could lead to the realization of highly effective treatments with fewer side effects that are suitable for each individual, as well as more efficient efforts to tackle pre-diseases, which could greatly contribute to the promotion of the health of the entire nation.

Such new and advanced medical treatment is often accompanied by high medical costs, but as mentioned above, the social infrastructure that supports it is becoming weaker, and the resources needed to produce medicines are becoming depleted. In other words, although we have excellent medical technology, it is foreseeable that we will not be able to deliver it to a large number of people. There are also other factors that hinder the supply of medical care to the people. For example, as a result of the increasing number of married couples working together, there are cases where people are too busy to visit the hospital and their diseases progress. In addition, polypharmacy, in which patients take a large number of medications from multiple departments, is a cause of many adverse events, which is an ironic situation in which medical care undermines health. Medication compliance has also become a major therapeutic issue. As described above, the issue of how to deliver advanced medical care, as represented by personalized medicine, to the public is already becoming apparent, and it will become even more serious by 2050.

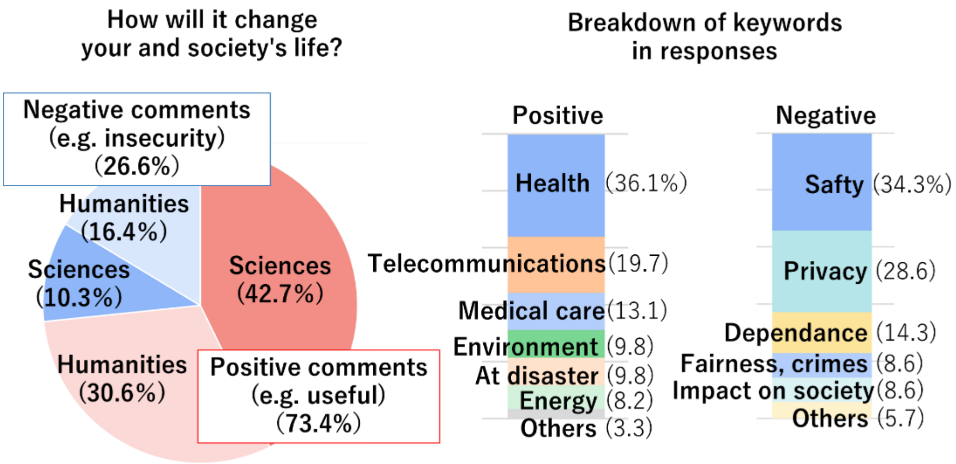
This issue will be difficult to overcome with the current medical research, which focuses only on improving the effectiveness and performance of drugs and medical devices. In this context, it is necessary to focus on how to deliver the most advanced personalized medicine and technologies to tackle pre-diseases to as many people as possible at low cost and in an environmentally sustainable manner. There are still many technical issues to be solved in such research, such as iL-Cell, as described below, and it is also necessary to establish a social framework for its practical use. Since this is a challenging and long-lasting issue, it should be tackled now that there are signs of social demands toward the year 2050.

< Scientific and Technological Requirements >

As a technology to respond to the social demands mentioned above, we propose iL-Cell, a cell-based device with advanced functions that can operate interactively with living cells. In order to obtain such functions, miniaturization of artificial cells, robots, and wearable devices have been studied as a methodology to assemble devices from parts in a bottom-up manner.

However, it is difficult to realize symbiosis and cooperation with living organisms using this method, and the functions obtained are limited compared to those of cells, which are the result of billions of years of evolution. In fact, cells express a variety of advanced functions in a very small space with high energy efficiency. On the other hand, regenerative medicine using iPS cells and other cells has been studied as a way to utilize cells. In this context, attempts have been made to improve the functions of cells by biologically modifying the cell functions and by using biomaterials in combination as appropriate. However, these methods, which rely only on the biological properties of cells, are insufficient for iL-Cells to express their intended functions, such as receiving information in vivo, acting autonomously, and producing therapeutic agents. In order to solve these problems, science and technology demand a new methodology to actively coexist with artifacts such as sensors and information communication devices in the cell.

In order to achieve this, it will be necessary to develop and integrate a variety of elemental technologies. For example, the detection of in vivo information and its transmission outside the body requires semiconductor chips for sensing and communication that function inside cells. The energy to be used in this process is assumed to be light energy, but it is necessary to consider how to make animal cells function with the photosynthesis of plant cells, the use of artificial materials such as quantum dots, the storage of electricity, and the use of energy. Furthermore, it is intended that the iL-Cell can be manufactured anywhere, including at home, but as cultivation and manufacturing technology for this purpose, home cultivation technology and cultivators must be developed and devices must be devised that do not affect the environment and ecosystem. Furthermore, the integration of these elemental technologies will also be a major issue, and development and research for symbiosis of cells and organisms with foreign materials will also be important. As described above, there are many scientific and technological demands that must be addressed now. In addition to the iL-Cell, the scientific and technological ripple effects that can be obtained from this project are extremely large. In a questionnaire survey of high school students, they expressed various wishes for the functions they would like to see in iL-Cells, indicating their high interest in the practical and safety aspects (Fig. 3).



What functions do you want iL-Cell to have in your life and the society you live in?

Category	Contents
Medical care	**Vaccines** **Telemedicine** (Administer personalized chemicals from a distance.) **Report** (Automatic notification in case of life threatening situations such as traffic accidents) **Medicine** (Eliminates the need to take medication) **Check our health status** (Medical devices that detect and treat health conditions)
Health	**keeping oneself awake** (It senses that I'm getting sleepy and sends out an electric current that's not harmful to my body.) **Alarm function** (I can wake up without disturbing the people I sleep with, I don't have to set an alarm and I won't oversleep, and I can adjust my sleep time by combining the alarm function with my health condition.) **Check our calorie intake** (Solution to overnutrition, prevention of diabetes) **Thermoregulation** (I don't like to be cold, so I want my body temperature to rise, and the cooling function to lower my body temperature.) **Child-rearing** (Knowing why my baby cries will help me raise my child.) **Others** (Improving the lives of people with physical deficiencies and other congenital disabilities)
Tele-communi-cations	**Payment** (Electronic money, train fares, store loyalty cards) **Personal identification** (Keys to coin-operated lockers, etc., and passwords for auto-locks) **GPS function** (Location information in case of lost, kidnapped, or in distress) **Timer** (Work time measurement and time management) **Robot** (Create robots that are as close as possible to humans, animals, and other living things.) **Interlocking with devices** (Sending messages in conjunction with my phone's functions)
Others	**AI, decision support** (I want it to be equipped with artificial intelligence.) **Safety device** (I'd like to see a feature that prevents runaway by switching it on and off.) **Environmental issues, photosynthesis** (It would be nice to be able to photosynthesize. It would be nice if we could produce oxygen like plants do.) **Biometric matching** (Top compatible with matching apps, personal compatibility matching from DNA information) **As material** (It would be nice to be able to change the shape and hardness freely. If it could be made hard or soft like steel, it could be used in many places.)

Fig. 3 Questionnaire on "Working cell" devices that produce energy from (solar) light, targeting second-year high school students (humanities and science majors) in various regions of Japan (continued in next section)

(Footnote to Figure 3 continued)
Interviews with second-year high school students in various regions of Japan, in separate groups for science and humanities, lasting about two hours. All conversations were transcribed and key words were extracted.

< Why a long-term approach is necessary? >

As mentioned above, there are many scientific and technological issues to be overcome. In addition, considerations other than science and technology are necessary for practical application. For example, the psychological resistance to implanting a new device into a living body can be mentioned. In fact, in a questionnaire survey of high school sophomores in various regions of Japan, while there were many positive opinions about iL-Cell, there were also many negative opinions about safety, privacy, dependency, fairness, etc., mainly from humanities students (Fig. 3). While safety can be overcome through the development of science and technology, other issues will require a lot of discussion involving society. In addition, infrastructure development, such as the development of a communication environment and the spread of incubators to households, is also necessary, and it is also important for everyone to be able to use them.

3.2 Social significance

Our goal is to create a society where everyone can maintain their health without being aware of their illness. When people go to the hospital, they are aware of their illness and feel a mental burden. The mental state of a person can also affect their medical condition, and there are many cases where people do not go to the hospital because they are afraid of knowing that they are sick. Furthermore, many elderly people are forced to take large amounts of medication every day. The greatest significance of this goal is to reduce the suffering of illness and medical treatment by maintaining good health without realizing that they are sick.

This goal will become more and more important to society as the birthrate declines and the population ages; as explained in detail in Section 3.1, Social Needs, the increasing number of elderly people will increase the burden of medical and nursing care, while the working population will decrease and the social infrastructure supporting medical care will become weaker. At the same time, the working population is declining, and the social infrastructure that supports medical care is becoming weaker. In addition, the working-age population is becoming increasingly busy, and there are concerns that health consciousness is declining. Under these circumstances, the tackling pre-diseases is important to prevent diseases before they occur, because serious complications caused by lifestyle-related diseases will require advanced and expensive medical care, as well as nursing care afterwards. On the other hand, as the depletion of natural resources becomes more and more serious around the world, the realization of sustainable medicine is strongly desired. The realization of iL-Cell, which aims to maintain health by maximizing the power of the living body, will not only address the issue of declining birthrate and aging population in Japan, but will also contribute greatly to the construction of a sustainable world.

Furthermore, concepts such as iL-Cell are also important for maintaining health in times of emergency such as disasters. When the supply of medicines is cut off due to a disaster, or when there is a risk of infection due to hospital visits, such as in the case of With Corona, it is desirable to have a system that can be implanted in the body and act autonomously to perform the functions necessary for the treatment and prevention of diseases. In other words, the development of this technology will make it possible to build a society that is resistant to disasters, pandemics, and other unusual events.

3.3 Action outline

The iL-Cell is a new concept in health care technology, and many efforts involving not only researchers but also society will be necessary to put it to practical use. First of all, it is necessary to consider the regulations and screening for transplanting cells containing foreign materials with advanced functions such as sensing and communication into humans. In addition, it is essential to establish robust communication security for this technology, in which biological information is communicated. In addition, it is necessary to build an infrastructure that allows anyone to easily use the communication and facilities for cultivating iL-Cells. In addition to the construction of such an environment, correct information and discussion on the usefulness and safety of iL-Cells will be necessary to counter the avoidance of foreign iL-Cells controlling the functions of living organisms.

4. Benefits for industry and society

Imports of pharmaceuticals have increased rapidly since 2000, and the current import value is about five times the value in 2000, resulting in a trade deficit of 2.347 trillion yen (2019). Japan is leading the world in the field of cell transplantation therapy, and creating and exporting new technologies in this field is of great industrial significance. Furthermore, the process of cell function control will have a significant ripple effect on other medical fields, and since the technology encompasses fields other than medicine, such as materials science, communications, and sensors, it will lead to the creation of industries in a wide range of fields. In society, this technology will help solve the problems of increasing medical costs, burden of nursing care, and medical depopulation in rural areas as mentioned above. In particular, this technology focuses not on the treatment of serious diseases, but on the tackling pre-disease and maintenance of health before anyone is aware of it. This is important not only for reducing the burden of medical and nursing care, but also for preventing the dwindling number of working-age people from dropping out of the workforce due to illness as the birthrate declines and the population ages.

II. Analysis

1. Essential scientific/social components

< Scientific and Technological Issues >

- Collaborative operation of cells and devices: Currently, genetic recombination technologies such as CRISPR-Cas9 have been developed, and molecular chemical modification of cells is well advanced. On the other hand, the symbiosis and cooperative operation of cells with artificial materials such as synthetic polymers, semiconductors, and metals is not yet fully developed. In order to realize medical devices and therapeutic cells, it is necessary to operate the cells through the intermediation of electrons, ions, and synthetic small-molecule compounds that connect them. However, at present, the concept of integrating medical devices with therapeutic cells has not even been established, and there is no research toward this end, despite the fact that research on elemental technologies that could be used is ongoing.
- Power supply: In current implantable medical devices, batteries are replaced, but this is a risky task because it requires a surgical procedure. Therefore, there is a need for measures that do not require a power source, such as longer battery life, contactless charging, or power generation using the body.
- Miniaturization of semiconductor chips: Currently, the size of semiconductor chips has been reduced to 1 mm square, which can be embedded in orally administered drugs, and to a size that can be mounted on an implanted microchip. In order to insert these chips into cells, they need to be reduced in size from several hundred nm to several micrometers.
- Safety of long-term use and impact on the living body: It is necessary to summarize the impact on the living body of long-term use of implantable medical devices and microchips that have already been implemented in society, and to evaluate the safety of new devices from a long-term perspective while avoiding the expected impact.

< Social Issues >

- Protection of privacy: Extremely personal information will be exchanged online. Protection of privacy: Extremely personal information will be exchanged online. It is necessary to establish the authority to access the collected information and establish a strict information management system.

- Security issues: Since all information will be exchanged online, measures must be taken to prevent cyber security vulnerabilities such as unauthorized access and attacks.
- Establishment of medical data transmission systems: Currently, the possibility of malfunctions in the use of implantable medical devices due to radio waves used in daily life, such as cell phones, PHS, wireless LAN devices, wireless card (contactless IC card) systems, electronic article surveillance (EAS) devices, and RFID (electronic tag) devices, remains an issue. In order to prevent this from happening, it is necessary to develop an implantable device in the body. In order to prevent these problems, dedicated frequencies have been allocated for implantable devices, telemetry, and specified low-power radio stations. However, it is necessary to establish technologies and social systems to avoid interference with radio systems that use the same or adjacent frequencies.
- Individual and social values, freedom of choice: It is assumed that public values will change in the balance between resistance to the attachment of iL-Cells, such as pasting or implantation, and new values of convenience and necessity for society and individuals. While only those who wish to use the system will be allowed to make choices based on their personal values, but if the system is to be integrated into the social medical system, it will be necessary to construct the system in a balance of personal and social values.
- Improving scientific education: COVID19 has approved mRNA vaccines at an unprecedented rate, and we are now in a situation where vaccination is being promoted from a public health perspective. In the absence of individual medical circumstances such as physical constitution and condition, we are now faced with a situation where vaccination is left to individual judgment. In the midst of this situation, there have been a number of cases of people refusing to be vaccinated due to wrong information, speculation, and false rumors. When iL-Cell, which is based on the new concept of fusion of medical devices and therapeutic cells, is implemented in society, it is obvious that the developers and implementers need to provide careful explanations, but in addition, education in basic science and information statistics needs to be enhanced so that people can make correct decisions.

2. Science and technology map

< The trend of Biopharmaceutical Development >

Until 2000, blockbuster drugs, mainly low-molecular-weight compounds, were mainly used to treat diseases with a large number of patients. Since then, molecular targeted drugs, which control the action of target molecules, have been attracting attention, and the number of approvals for nucleic acid drugs began to increase around 2010, and since 2015, there has been a series of approvals for cell-based drugs (Fig. 4). Specifically, there have been approvals for the transplantation of "Heart Sheet," a sheet-like culture of cells harvested from patients, for the treatment of ischemic heart disease (September 2015), for the intravenous infusion of “Temcell HS” Injection, mesenchymal stem cells harvested from the bone marrow of healthy adults, for the treatment of acute graft-versus-host disease (September 2015), for the intravenous infusion of “Stemirac” Injection, collected from patients, for the treatment of bone marrow injury (December 2018), for the intravenous infusion of “Kymriah” Injection, a patient-derived T cell expressing CAR that specifically recognizes CD19 using a lentiviral vector, for the treatment of acute lymphoma (March 2019), and by transplantation of “Nepic”, which cultivates corneal epithelial cells collected from patients into sheet form for the treatment of corneal epithelial exhaustion (March 2020).

In some cases, such as the "Heart Sheet" and "Nepic", the cells are cultured in a sheet form outside the body on a synthetic polymeric mesh-like artificial material, but even in those cases, the cell sheet is peeled off and transplanted into the heart or eye. Other cell-based drugs are simply injections of cell dispersions. The technology for expressing specific molecules by gene transfer and interacting with cells and molecules in the body to achieve therapeutic effects is well established, as in the case of intravenous infusion of “Kymriah”, but in the future, the control and expansion of cell functions through the cooperative operation of artificial materials and cells is expected.

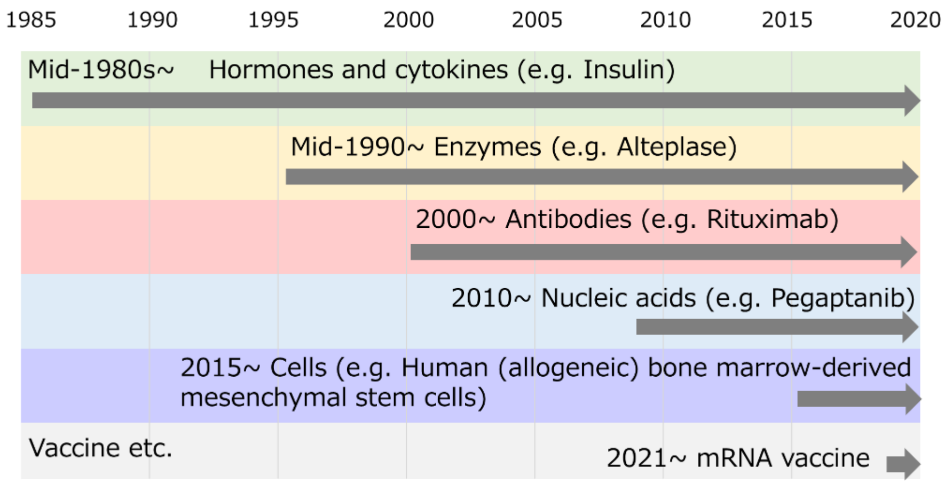


Figure 4: Transition of biopharmaceutical development and approval items in Japan
Until the mid-1980s, small molecule compounds were the mainstream, but since then the development of biopharmaceuticals has grown rapidly.

< Current Trends in Implantable Medical Devices and Implantable Devices >

Implantable medical devices include cardiac pacemakers, defibrillators, deep brain stimulators, spinal cord stimulators, sacral nerve stimulators, vagus nerve stimulators, infusion pumps, and ECG data recorders, which are classified as active implants. In the case of active implants, the problem of malfunction caused by radio waves, which are frequently used in daily life, remains. In addition, there are issues such as reducing life risks associated with battery replacement, reducing the size and weight of medical devices in line with the promotion of home medical care, and improving the QOL of patients.

In Sweden and the U.S., microchip implant technology, which was developed for individual identification of livestock, has been applied to humans since around 2017, although it has not been put to practical use in Japan. In Sweden, chips developed by Biohax began to be used in 2017 for internal ticket inspection and fare collection on the state-run railroad, SJ. In the U.S., Three Square Market began implanting Biohax microchips in the hands of employees who wish to use them for internal operations and product purchases in 2017. Stockholm's public transportation company SL and Scandinavian Airlines are also considering launching similar services. Medihome has formed a business alliance with Swedish company Biohax to develop a solution, although it has not yet been put to practical use in Japan. Biohax's microchip uses RFID (radio frequency identification) technology that uses short-range wireless communication, and does not require recharging.

In 2017, the FDA approved "Abilify MyCite", a digital medicine developed by Otsuka Pharmaceutical and Proteus Inc. in the U.S. The tablet contains a 1 mm square chip that emits a weak signal when it reacts with gastric juices and is placed on the patient's abdomen. A sensor patch affixed to the patient's abdomen captures the signal and sends it to a smartphone app, which records that the patient has taken the medication. "Abilify" is a psychotropic drug that helps patients and their caregivers who have difficulty managing their medication due to symptoms of illness. It is expected to help prevent patients from forgetting to take their medication and reduce social security costs due to missed doses.

< Trends in Wearable Device Development >

Currently, there are three types of wearable devices: the first is an optical sensor that measures vital data without being worn directly, using an optical camera or similar device; the second is a biopotential sensor that uses electrodes to measure electrocardiogram, muscle activity, eye movement, brain activity, and so on. This type is often used in combination with wearable and implantable devices, such as patches applied to the skin or straps on the chest. The third type is a chemical biosensor that analyzes proteins contained in blood and sweat. The third is a chemical biosensor that analyzes proteins in blood and sweat, which can be detected by implantable devices, needles, patches, etc. Remote monitoring is very difficult, and there are few examples of practical applications. There are other devices that measure body temperature, blood pressure, and stress levels.

However, in any case, the wearing comfort of the device is an issue, and "contactless monitoring" has been set as a future goal. In addition, there are some electrode-based sensors that are expected to have a therapeutic effect by activating nerves through electrode stimulation, but other than these devices, they specialize in sensing functions and are not yet therapeutic.

The above is a summary of the current trends in biopharmaceutical development, wearable devices, and implantable medical devices (implants). If we check these related research fields on the science map, we find that they are quite distant from each other, and there are few results of collaborative research at present (Fig. 5). In view of the changes in pharmaceutical modalities and the progress of the information society, this is an area where we should focus on the fusion of fields, and it could become a major innovation for the first time in Japan if we take the lead in the world in integrating these fields as soon as possible.

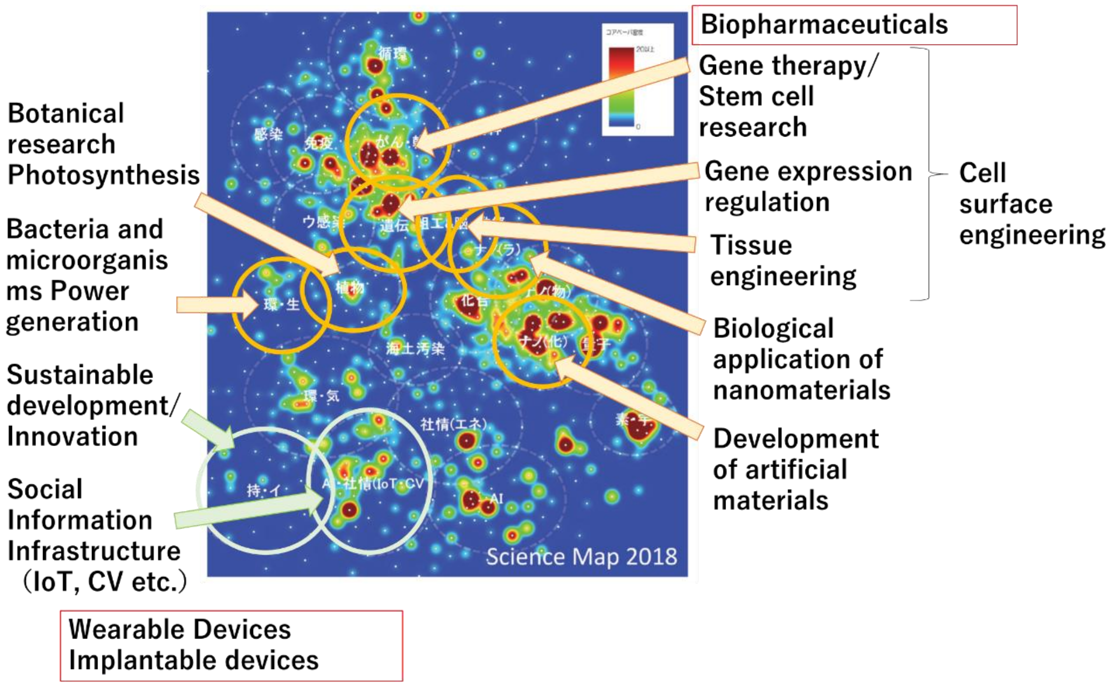


Figure 5 Structure of related research fields.
Relevant fields are plotted on the Science Map 2018. Yellow is the existing research fields related to iL-Cell development, and green is the fields in which the existing fields will participate and strengthen their collaboration through iL-Cell development.

3. Japan’s position in overseas trends

The individual technologies listed below could be important elemental technologies in the realization of iL-Cell, which aims at the cooperative operation of therapeutic cells and medical devices, but they are not currently being pursued from that perspective. In the future, it is necessary to establish a research platform that integrates each research area toward the goal of realizing iL-Cell (Table 1).

- Cell therapy: In 2012, the world's first mesenchymal stem cell therapy, "Prochymal" from Osiris Therapeutics of the U.S., was approved in Canada. In Japan, "Temcell HS" was approved in 2015 through the alliance between JCR Pharma and Osiris Therapeutics. With the discovery of iPS by Professor Shinya Yamanaka and his Nobel Prize, Japan is leading the world in cell therapy.
- Cell Surface Engineering: A technology to equip conventional cells with new functions by modifying cell membranes with proteins or synthetic polymers. Cell surface engineering is a technology to equip conventional cells with new functions by modifying cell membranes with proteins or synthetic polymers. Yeast, yeast, koji mold, bifidobacteria, human and animal therapeutic cells, etc. are being studied for this technology. It has been applied in the fields of energy and environmental purification, such as biofuel development and energy recovery of heavy metals, environmental hormones, and rare metal earths. It has also been applied in the field of immunotherapy and medicine, such as oral vaccines and CAR-T therapy.
- Artificial cells: Molecules that constitute cells, such as proteins, DNA, RNA, and lipids, are used as parts to assemble particles that function like cells. The outer membrane is covered with a lipid bilayer, similar to the cell membrane, into which a system for expressing proteins in aqueous solution is inserted. Globally, the Genome Project-write (USA), Buid-a-Cell (USA), fabriCELL (UK), BaSyC (Netherlands), MaxSynBio (Germany), Minimal Biology (Max Planck & (Germany), MaxSynBio (Germany), Minimal Biology (Max Planck & Bristor), etc., and there is a movement to form a consortium of projects in each country. In Japan, ImPACT "Artificial Cell Reactors for a Prosperous and Safe Society and New Biomanufacturing" (2013-2018) (Representative: Hiroyuki Noji) was implemented. In the U.S., the International Biomolecular Design Competition (BIOMOD), organized by Harvard University and the University of California, San Francisco, has been held since 2011 as a mechanism to foster young researchers (students) in this research field. Since 2011, Harvard University and the University of California, San Francisco have hosted the BIOMOD (International Biomolecular Design Competition). As a national project, Japan seems to be lagging behind the rest of the world.
- Cell function control by artificial materials: Synthetic polymers are used to control the function of therapeutic cells in cell surface engineering as mentioned above. In addition,

thermo-responsive polymers are used for cell culture in sheet form in the treatment of transplantation of cells cultured in sheet form. In recent years, membrane-free organelles generated by phase separation in cells and the cause of disease development have been clarified and have attracted much attention. Molecules that control the formation and destruction of membrane-less organelles in cells have been developed, and are attracting attention as a new method of controlling cell functions using artificial materials. This is part of the field of nanotechnology in which Japan excels, and in which Japan has an advantage over the rest of the world.

- Co-culture of mammalian and plant cells: Plant cells have the ability of photosynthesis to obtain energy from sunlight, while mammalian cells do not have this ability. One of the attempts to utilize this photosynthetic ability of plants is to supply oxygen to the transplanted organs from algae by circulating the culture medium or co-culturing with plants, which has been shown to preserve the organs in a better condition. Also, in Moonshot Goal 5, "Bioeconomical cultured food production system using circular cell culture with algae and animal and plant cells" is underway. With regard to the possibility of photosynthesis in mammalian cells, research on Kleptoplasty of Nudibranch is progressing, and in May 2021 the genome information of Nudibranch was decoded, indicating the possibility that Nudibranch maintain photosynthetic proteins made by algae for a long time. Japan is one of the world leaders in photosynthesis research, and in particular, Nudibranch research is one of the few in the world, and Japan is at the forefront of this field. In particular, Nudibranch research is one of the few in the world, and Japan is at the forefront of this field. Co-cultivation of mammalian and plant cells is a field in which there are still few examples, and Japan should take the lead in the future.
- Microorganisms and bacteria power generation: In recent years, the development of microbial fuel cell systems has led to the development of self-sustaining sensors that measure the concentration of carbon dioxide (Takami Kosako, National Institute of Agrobiological Sciences, Asahi Kasei Electronics Corporation). In addition, there are bacteria that generate electricity in the soil, in the ocean, and in living organisms. It has recently been revealed that one of them, an electric bacterium, has channels that allow electrons to pass through, and can generate electricity using the electron transfer (Akihiro Okamoto, National Institute for Materials Science). The possibility that these mechanisms can be implemented in mammalian cells in the near future has also come into view. This field has been actively researched in Japan as an extracellular electron transfer pathway and bio-electron transfer reaction. As a big project, the use of microorganisms for photoenergy conversion was promoted in the ERATO "Photoenergy Conversion System Project" (Representative: Kazuhito Hashimoto) from 2006 to 2012.

- Molecular robotics and DNA computers: These are small robots that use biomolecules such as DNA and proteins. It is constructed of a power source, controller and sensor. It includes DNA nanostructures, such as DNA cube, DNA origami, and a computer which convert or store information based on DNA sequences. In 2019, the University of Washington and Microsoft Corporation collaborated and succeeded in developing a device that converts digital data into DNA and stores it, and has also successfully converted it into text. Although the long-time requirement for DNA synthesis remains a challenge, Microsoft has calculated that 1 g of DNA can store 1 billion terabytes of data. Therefore, comparing with current storage medias, DNA is expected to be a better storage device, which can store a larger digital data for longer period. Recently, DNA nanorobot succeeded in delivering anti-tumor drugs to tumor cells. And, DNA robot with the body (Microtubules, which is driven by Kinesin), a motor (Kinesin, which get energy from ATP) and a sensor (DNA that is structurally transformed by light) could move in a straight line or rotate(Akira Kakugo, Hokkaido University). As for molecular robotics, the DNA Robotics Project was launched in Europe in 2018 under the Horizon 2020 framework, coordinated by Aarhus University in the Netherlands, with Ludwig-Maximilians University in Germany, Technical University of Munich, Oxford University in the UK, Microsoft Corporation, and others. University of Oxford, and Microsoft Corporation in the UK are participating in the project. In the U.S., the Wyss Institute at Harvard University, Massachusetts Institute of Technology, and California Institute of Technology are planning to launch a research area on Molecular Robotics. In Japan, the National Institutes of Natural Sciences (NINS) will launch the Center for Life Innovation and Research in 2018, and the National Institute of Advanced Industrial Science and Technology (AIST) will launch a project on Smart Active Materials in 2017.
- New battery: By changing the electrolyte that facilitates the movement of lithium ions between the electrodes of a lithium-ion battery from a conventional liquid to a solid, the structure can be made thinner, the capacity can be increased by layering, durability can be improved, and high-speed charging and discharging can be achieved. This is called an all-solid-state battery, and Ilike (UK) has developed an all-solid-state battery that enables wireless charging and has a lifespan of 10 years with once-a-day charging and discharging. As for miniaturization of solar cells, the development of dumbbell-shaped quantum dots has opened up the possibility of light energy conversion with a single particle (Tsukasa Torimoto, Nagoya University).
- Biological power generation: Based on battery technology that suppresses the natural discharge of energy, the aforementioned British company Ilike has developed technology to generate electricity from the beating of the heart and the movement of the lungs due

to respiration, and to secure drive energy, and is implementing this technology in an all-solid-state battery, with the aim of developing a battery that can generate electricity from living organisms. In addition, a contact lens equipped with a sensor that generates electricity using the sugar contained in tears makes it possible to measure the concentration of sugar in tears and transmit the data (Kiichi Niitsu, Nagoya University).

- Remote medicine: In recent years, the aging of society and home healthcare have been advancing, and the construction of a comprehensive community care system based on multidisciplinary cooperation among doctors, pharmacists, helpers, and care managers has been promoted. In particular, in remote islands such as the Goto Islands in Nagasaki, where the aging of the population and the shortage of medical personnel are remarkable, telemedicine using drones and avatars has been implemented on an experimental basis with the cooperation of the local government, mainly at Nagasaki University Hospital, and is worthy of attention (Takahiro Maeda, Nagasaki University Hospital). It is necessary to select the functions required for iL-Cell from the voices of such actual sites.

	Global Trends	Japan's Position
Therapeutic cells	Mesenchymal stem cells, Car-T cells, and other therapies are being vigorously pursued.	The company is a world leader in iPS research. It was among the first in the world to approve mesenchymal stem cell therapeutics.
Implantable microchip	It has been socially implemented in the United States and Sweden.	It has not been implemented in society yet.
Artificial cells	Large national projects have been launched, including Genome Project-write (USA), Buid-a-Cell (USA), fabriCELL (UK), BaSyC (Netherlands), MaxSynBio (Germany), and Minimal Biology (Max Planck & Bristor).	ImPACT, "Artificial Cell Reactors for a Prosperous and Safe Society and New Biomanufacturing" (2013-2018) Somewhat late to the party.
Molecular Robotics and DNA Computers	DNA computer: University of Washington and Microsoft in 2019 to jointly develop a device that converts and stores digital data into DNA, and also converts it into text Molecular Robotics: Europe, DNA Robotics project from 2018 (Aarhus University in the Netherlands, Ludwig-Maximilians University in Germany, Technical University of Munich, Oxford University in the UK, Microsoft, etc.); USA, the launch of Molecular Robotics research area is planned at Wyss Institute at Harvard University, Massachusetts Institute of Technology, and California Institute of Technology.	DNA computers: somewhat delayed. Molecular robots: Smart Active materials project at the National Institute of Advanced Industrial Science and Technology (AIST) in 2017, and the Center for Life Innovation and Exploration at the National Institutes of Natural Sciences (NINS) in 2018.
Fusion of mammalian and plant cells	The use of optogenetics, a group of molecules related to photosynthesis, is being studied. Algae-derived proteins have been applied to humans, and vision has been restored (José-Alain Sahel et al.(Nature Medicine, May 24, 2021).	This is one of the few studies in the world on Kleptoplasty from Nudibranch. We have succeeded in preserving transplanted organs by supplying oxygen from algae. Moonshot Objective 5: "Bioeconomical cultured food production system using circular cell culture with algae and animal and plant cells.
Microbial and bacterial power generation	It is attracting attention as an alternative energy source.	Succeeded in power generation and bioreactor using microorganisms and bacteria. ERATO "Photo Energy Conversion System Project" from 2006 to 2012.
Biological power generation	Power generation using physical movements such as heartbeats, breathing, and lung movements as driving force, and the use of all-solid-state batteries are progressing.	For the first time in the world, sugar content could be transmitted from a chip attached to a contact lens using sugar in tears as an energy source.
Cell surface engineering Regulation of cell function by artificial materials	It is still a relatively new field.	This is still a relatively new field. It is closely related to the fields of nanomaterials and biomaterials, where Japan's strengths can be utilized.

Table 1 Global trends in each research area and Japan's position

III. Plan for Realization

1. Area and field of challenging R&D, research subject for realization of the Goals

(1) Area and field to promote challenging R&D

It is necessary to establish a research area that integrates the following research fields: cell therapy, cell surface engineering, nanomaterials, biological power generation, bacterial and microbial power generation, photosynthesis, and microsensors (semiconductor chips). Of these, cell therapy, cell surface engineering, and nanomaterials are still relatively close to each other, and collaboration is progressing. Biological power generation and microsensors (semiconductor chips) are also in relatively close proximity. However, the aforementioned two groups, bacterial and microbial power generation, and photosynthesis have almost no contact. Therefore, the fusion research of these four groups will be quite challenging, but it is expected that great innovation will occur through collaboration with a single goal (Fig. 6).

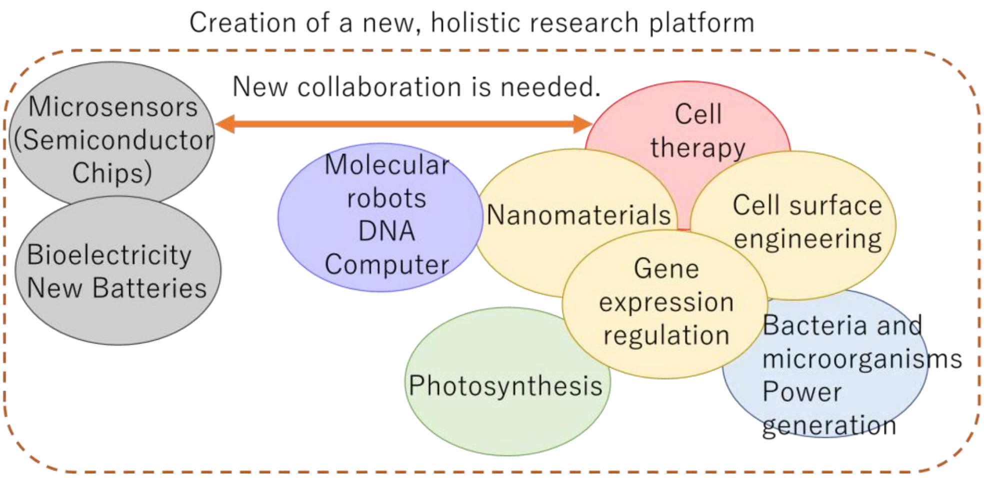


Fig. 6 Current relationship of research fields to be promoted

The circles of the research fields that are currently in contact with each other are shown. The circles of the research fields that are currently in contact are adjacent to each other.

(2) Research subject for realization of MS Goal

- Fixation of cells on microsensors (semiconductor chips) and signal transmission between sensors and cells.
- Establishment of a power generation function in mammalian cells based on research on bacterial and microbial power generation
- Light energy conversion in mammalian cells by using photosynthesis and quantum dots.
- Construction of cell blocks by combining cells based on cell surface engineering.
- Functional expansion of mammalian cells using nanomaterials and molecular robotics

2. Direction of R&D for realization of goals

(1) Specific goals (milestones) to be achieved and expected to be achieved in 2030, 2040, and 2050

2030: Integration of sensors and therapeutic cells

2040: Development of iL-Cell precursors using cell blocks

2040: Development of iL-Cell precursors using cell blocks

(2) Specific R&D themes that should be addressed to achieve the milestones and the effects that achieving the milestones will have on society.

2030: Integration of sensors and therapeutic cells

Establish a mechanism to fix cells on sensors and send signals from the sensors to the cells to initiate specific gene expression, and a mechanism to detect secretions from the cells and send signals. Using cell surface engineering and artificial cell construction technologies, we will construct signal-sensitive cells for light, heat, and electricity, and fix them on the sensor. We will also implement power generation by microbes and bacteria in mammalian cells for the next goal.

At this point, we can expect to establish a new therapeutic device by fixing a glucose sensor and insulin-expressing cells for diabetes, for which sensing technology has been established and the therapeutic mechanism is relatively clear. The implantation of this device will eliminate the need to measure blood glucose levels and self-injections, and is expected to improve the QOL of patients.

2040: Development of iL-Cell precursors using cell blocks

Mammalian cells with various functions such as photo-energy conversion, sensing, and production of therapeutic cells will be combined and fixed on a substrate like Lego blocks to construct a cell block that can perform sensing to therapy with as few artificial materials as possible. Here, we need to integrate the fields of cell surface engineering, molecular robotics, nanomaterials, and biological power generation.

If implantable devices do not require a power source, it is expected to improve the quality of life of patients by reducing the risk of surgical procedures. In addition, it will be possible to use the device in disaster areas and areas where electricity is not available. The range of applications will expand in conjunction with ex vivo organ construction, which is the goal of design cells.

2050: Development of iL-Cells with all functions in a cell

Gathering the technologies up to 2040, we aim to combine all functions into one. This is expected to improve convenience and stability. It is expected to reduce the impact on the body and invasiveness through long-term use. This will make it easier to expand the use of the system not only for treatment, but also in daily life, such as for tackling pre-disease, personal recognition, and payment. As the scope of use expands, it will be necessary to establish rules for use that balance social values and individual values, and to solve social problems such as privacy and information protection issues at the same time.

The above flow is shown in Figure 7.

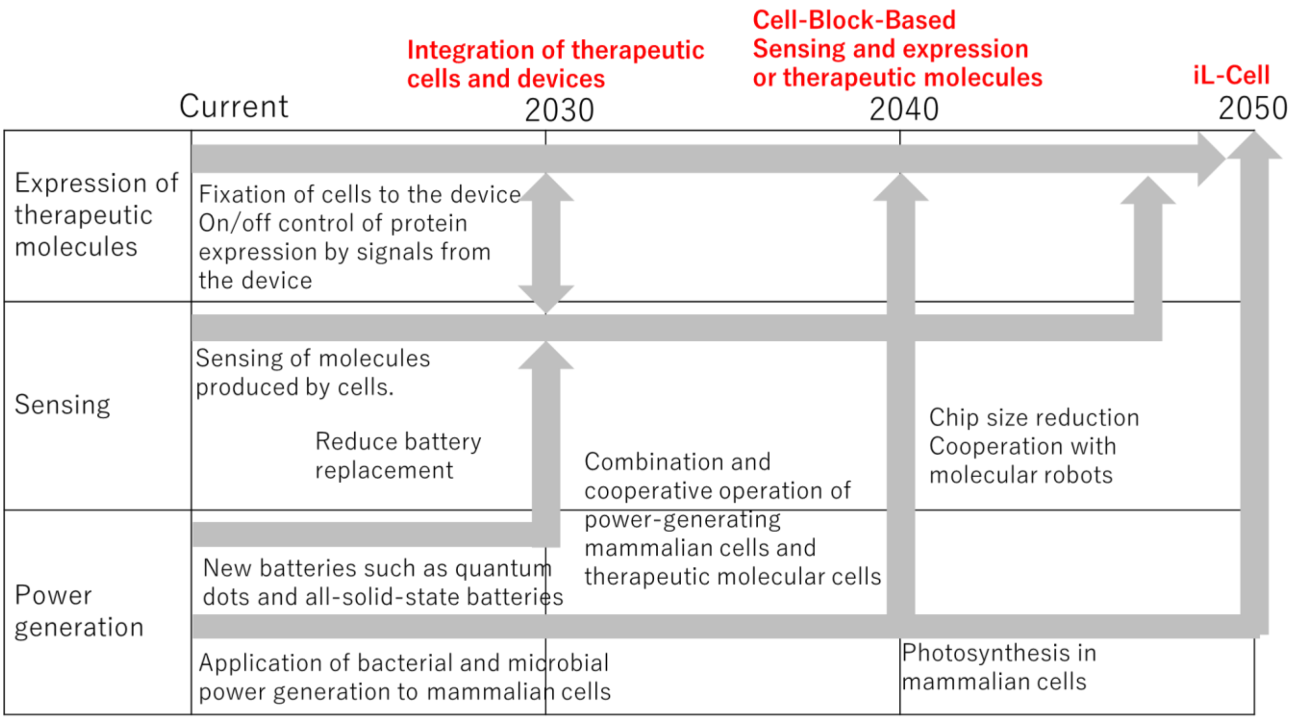


Fig. 7 Research scheme for the development and realization of iL-Cell in 2050

3. International cooperation

Although the elemental technologies have matured in a disparate manner, they are not working toward the goal of iL-Cell, and there is a lack of collaboration worldwide. Japan has strengths in cell-based therapies, such as Professor Shinya Yamanaka's discovery of iPS, Professor Tasuku Honjo's discovery that led to immune checkpoint inhibitor therapy for cancer, and the subsequent Car-T cell therapy. On the other hand, there is no denying that the company is a bit behind the curve when it comes to artificial cells. In addition, in terms of taking advantage of the complex information processing capabilities and biocompatibility of cells, it is more efficient to integrate cells with artificial materials, and therefore, research should be conducted based on cells to achieve cooperative operation with artificial materials. First of all, I think it is important to establish a research platform aiming at the cooperative operation of cells and artificial materials (iL-Cell development) in Japan, and to promote cooperation among various research fields toward this goal. After establishing Japan's first research field, we will collaborate with national projects and trans-national consortiums in various countries for artificial cells and molecular robots.

4. Interdisciplinary cooperation

In terms of scientific and technological collaboration, as mentioned above, elemental technologies have matured in a disparate manner, but by establishing a research platform with the single goal of establishing the cooperative operation of cells and artificial materials (iL-Cell), great innovation can be expected. At the same time, based on the examples of online medical care and cloud computing in remote areas, such as the case of the Goto Islands in Nagasaki, I think it is important to extract the elements and issues that are needed in a super aging society with a low birthrate and medical depopulation, and to promote research with specific applications in mind. In the U.S. and Sweden, microchips implanted in the body have been used for individual recognition, payment, and other social applications, and the social and personal convenience, values, and safety resulting from these applications have been clarified. It is necessary to prepare for the social issues that will arise when iL-Cell is implemented in Japan from both ethical and legal perspectives.

5. ELSI (Ethical, Legal, Social Issues)

When iL-Cells are used as a therapeutic modality, the cost of treatment is likely to be higher than that of conventional drugs. Although scientific and technological efforts to reduce the cost are necessary, there are limits. In the calculation of drug prices, research is needed on the balance between the high cost of treatment and the value obtained from it, and on the social security system.

It is expected that there will be resistance to attaching iL-Cell to the body or implanting it. Scientific and technological research on safety for application to the body and long-term use is necessary, but at the same time, research needs to be conducted from the perspective of medical ethics, balance between social values and individual values, balance between social convenience and personal convenience, and cost effectiveness. In addition, it is necessary to establish an educational system to avoid being misled in the generation of new values and choices by individuals.

Research on legal regulations and social systems from the perspective of privacy protection and information management is necessary to prepare for the actual implementation of iL-Cell in society. In addition, it is necessary to establish a social mechanism to prevent malfunctions and radio interference caused by radio waves used in daily life, which is an issue in the use of implantable medical devices.

IV. Conclusion

In the year 2050, medical services will be online and home-based, and modalities (iL-Cells) based on the concept of integrating medical devices and therapeutic agents will be required, such as sensing the physical condition of individuals at home, proposing improvement programs based on the obtained data, and administering improvement and therapeutic molecules. However, at present, there is no similar concept. However, there is nothing similar to this concept at present. Therefore, we proceeded with the research in the setting of fusion of wearable devices and therapeutic cells, which seems to be relatively close. The current issues of wearable devices are that they are uncomfortable to wear in daily life, and especially in the case of implantable devices, there is a risk of surgical procedure when replacing the device due to battery life, and malfunction caused by radio waves in daily life. In addition, at present, the system is specialized in sensing except for treatment by electrical stimulation, and does not have any therapeutic function. The current issue with cell therapy is that it is still a new field, and although the combined use of genetic modification technology (Car-T cells) has finally been approved in recent years, other innovations such as the production of therapeutic cells and the internal dynamics of cells are still at the level of basic research. In the future, in addition to genetic modification, the control of expression of therapeutic molecules by concerted operation with artificial materials is eagerly awaited. The fusion of these two concepts will lead to a new concept of therapeutic and health maintenance devices that seamlessly connect sensing to expression of therapeutic molecules.

The elemental technologies required to realize this, such as cell therapy, cell surface engineering, nanomaterials, biological power generation, bacterial and microbial power generation, photosynthesis, microsensors (semiconductor chips), molecular robotics, and DNA computers, are developing independently, although some of them are in contact with each other. . In particular. Sensors and cells are not even in contact. In the field of cell-healing nanomaterials, Japan is in a leading position in the world, and Japan has also achieved leading results in research on bacteria/microbial power generation and photosynthesis. Therefore, the creation of a platform to promote joint research with a single goal by linking these research fields ahead of the rest of the world is an opportunity to create innovation and to be one step ahead of the rest of the world.

In addition, when iL-Cells are implemented in society, they will create new values in society, and in turn, research on the balance between the convenience of society and the values of individuals is necessary. The actual situation in the U.S. and Sweden, where implantable chips have already been implemented in society, will be helpful. In addition, since personal information is sent and received, it is necessary to study the laws, regulations, and institutional settings for privacy protection and information management.

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