

# Pharmaceuticals, Bio CDMO and Regenerative Medicine Business



## **FUJIFILM Holdings Corporation**

January 15th, 2019

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Director, Corporate Vice President, General Manager of  
Corporate Planning Division and Group Company Managing Division

Junji Okada

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FUJIFILM Corporation Director, Senior Vice President  
General Manager of Bio CDMO Division

Takatoshi Ishikawa

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FUJIFILM Corporation General Manager of  
Regenerative Medicine Business Division

Masataka Akiyama

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FUJIFILM Corporation Director, Corporate Vice President,  
General Manager of Pharmaceutical Products Division

Junji Okada

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# 1. Fujifilm's Pharmaceuticals, Bio CDMO and Regenerative Medicine Business

Director, Corporate Vice President,  
General Manager of Corporate Planning Division

Junji Okada

# 1. Fujifilm's Healthcare business field

## Sustainable Value Plan 2030



### Health

Create a healthy society through the process of prevention, diagnosis and treatment in healthcare.

#### Priority Issue

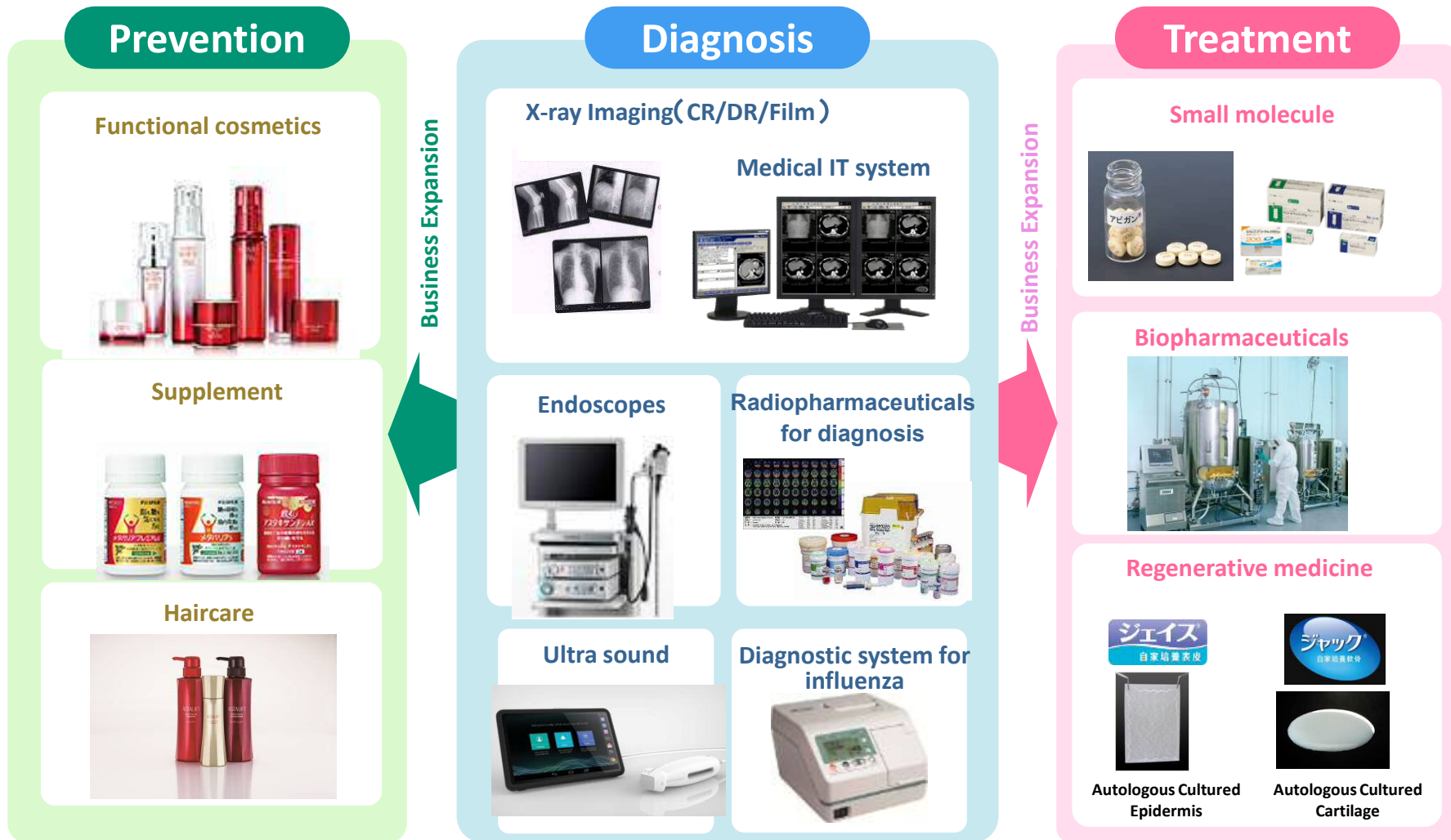
1. Fulfill unmet medical needs.
2. Improve accessibilities to medical services.
3. Contribute to identifying diseases at an early stage.
4. Contribute to health promotion and beauty.
5. Promote management of a healthy workplace.



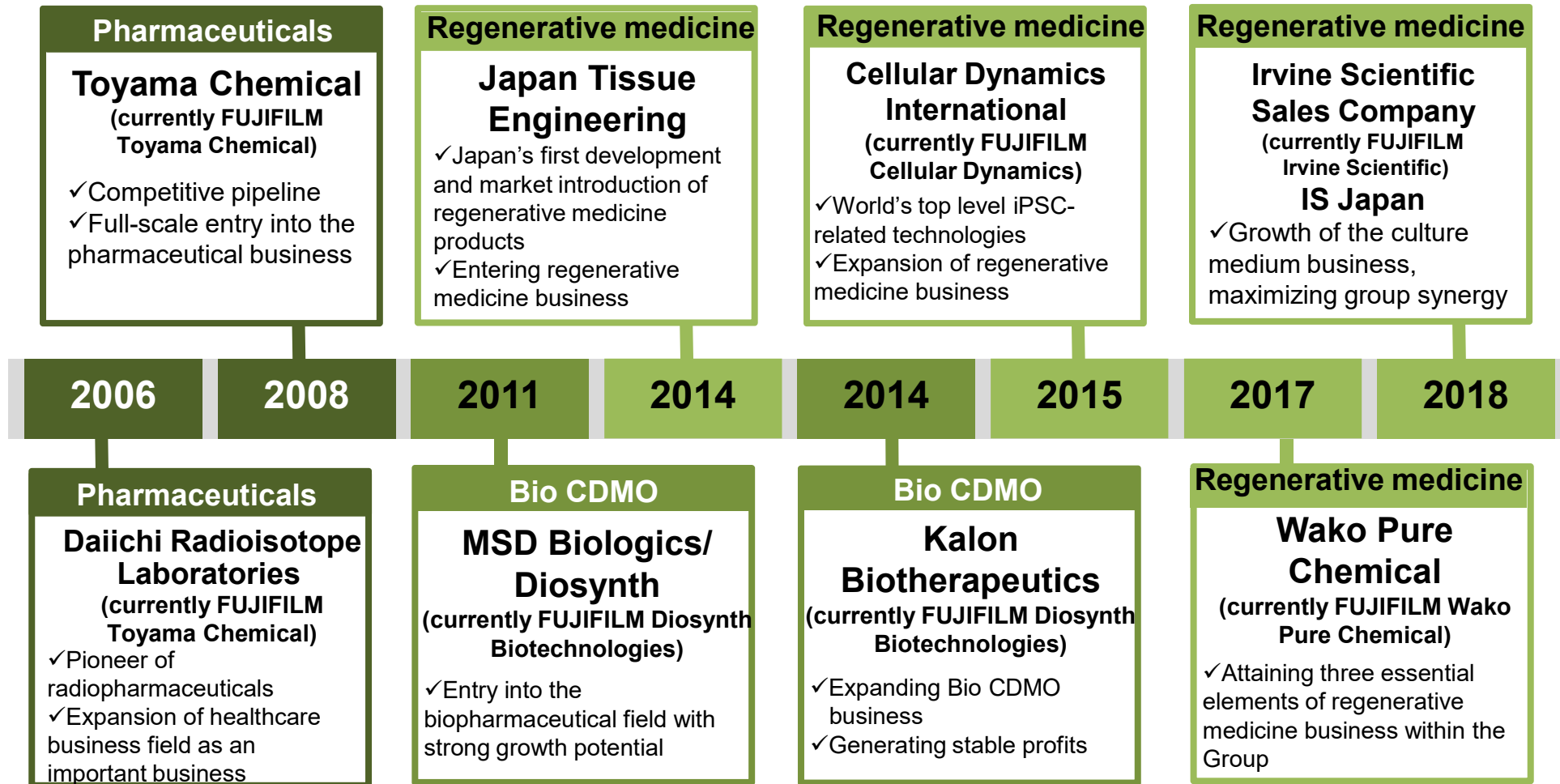
Contribution for SDGs

- ✓ Positioning “health” as one of the priority areas in the CSR plan
- ✓ Working on solving social issues through business operations

# 1. Fujifilm's Healthcare business field



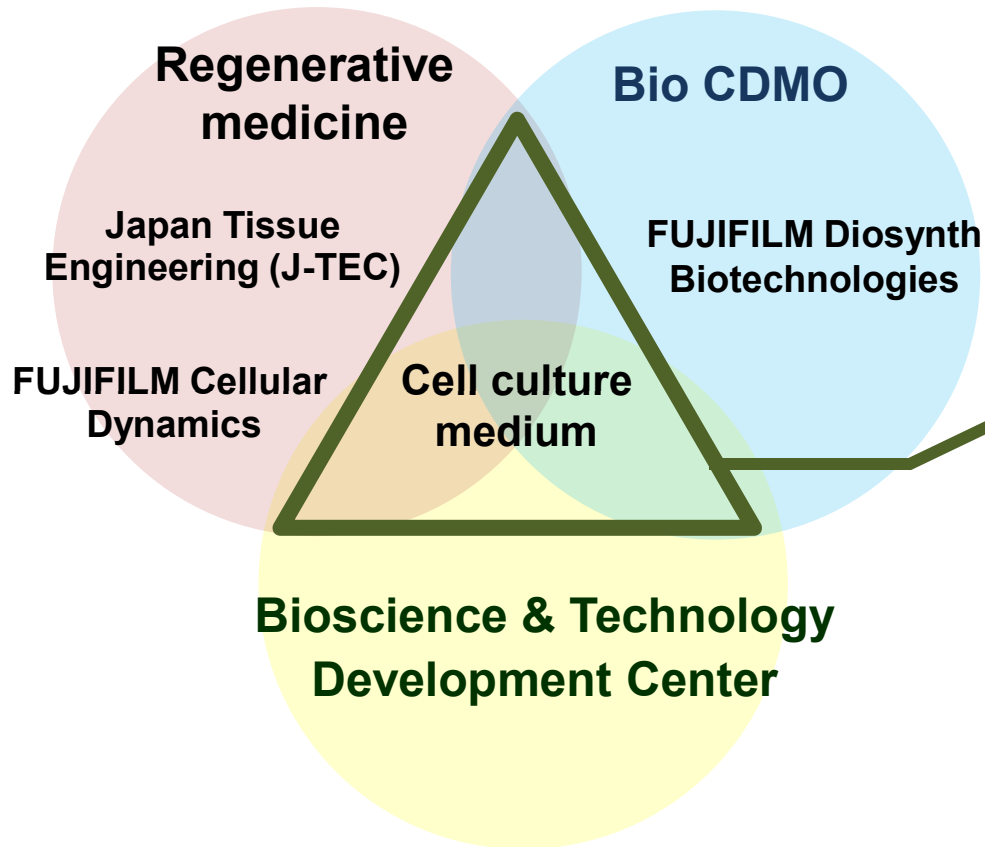
## 2. From entering to pharmaceuticals and Regenerative medicine business to date



**Actively undertaking M&A to create new business and expand growth fields**



## 2. From entering to pharmaceuticals and Regenerative medicine business to date – culture medium business



### Cell culture medium

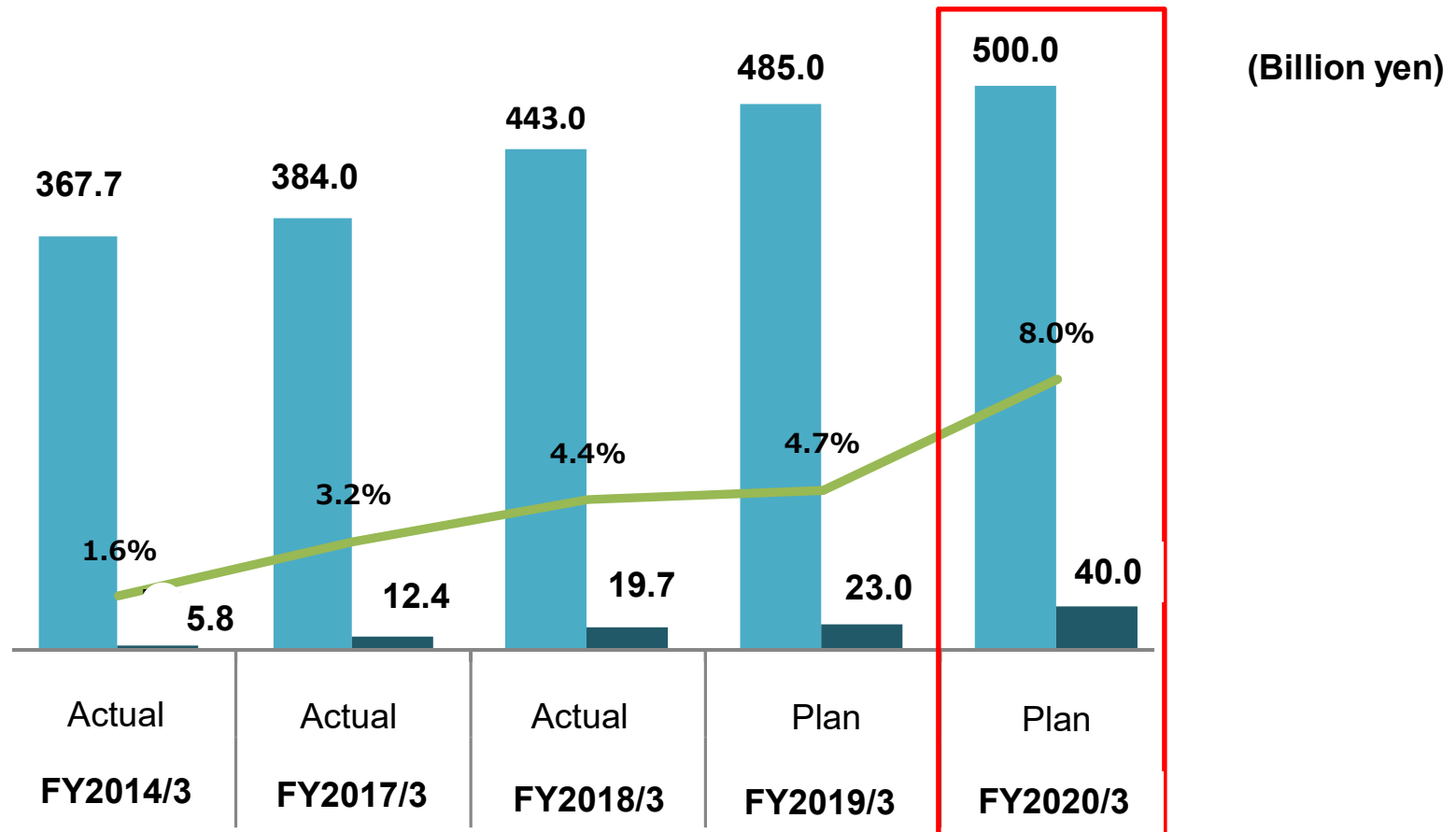
Annual growth rate of culture medium market : about 10%

	<b>FUJIFILM Wako Pure Chemical</b>
	<b>FUJIFILM Irvine Scientific (FISI) IS Japan (FISJ)</b>

- ✓ Offering wide product lineup through each of the sales channels
- ✓ Developing high-quality, high-functional culture medium by creating group synergies with regenerative medicine business and bio CDMO business.

**Accelerating the expansion of culture medium business and business of bio medical field, maximizing the Group synergy**

### 3. Healthcare business targets in the Mid-term management plan “VISION2019”



**Achieving the net sales of 500 billion yen and operating income of 40 billion yen under the mid-term management plan “VISION2019”**



## 4. Environment surrounding the pharmaceutical product related business

### Changes in medical needs and environment

- Changes in diseases due to progress of aging population
- Spread of informed consent
- Pursuit for QOL
- Growing national medical expenditure
- Increased difficulty in drug discovery

- Expectations for healthy life expectancy extension
- Necessity for significant change in healthcare system

### **Requiring new business models and innovation amidst changing business environment**

- ✓ New drug development for personalized medicine
- ✓ Acceleration of initiatives toward practical application of gene therapy and cell therapy
- ✓ Open innovation and use of external functions such as CRO and CMO

## 5. Growth strategies of Bio CDMO, Regenerative medicine, Pharmaceuticals business

### Bio CDMO

- ✓ Securing stable profits
- ✓ Engaging in capital investments and technological development to expand production capacity, thereby accelerating business growth

### Regenerative medicine

- ✓ Driving industrial applications as a leading company in regenerative medicine
- ✓ Collaborating with partners to reduce risks and promote pipeline development
- ✓ Taking advantage of iPSC production technology to work on CDMO business

### Pharmaceuticals

- ✓ Developing pipeline to seek marketing approval for multiple drugs in 2019
- ✓ Focusing on developing the technology for a drug delivery system that enhances efficacy of existing drugs

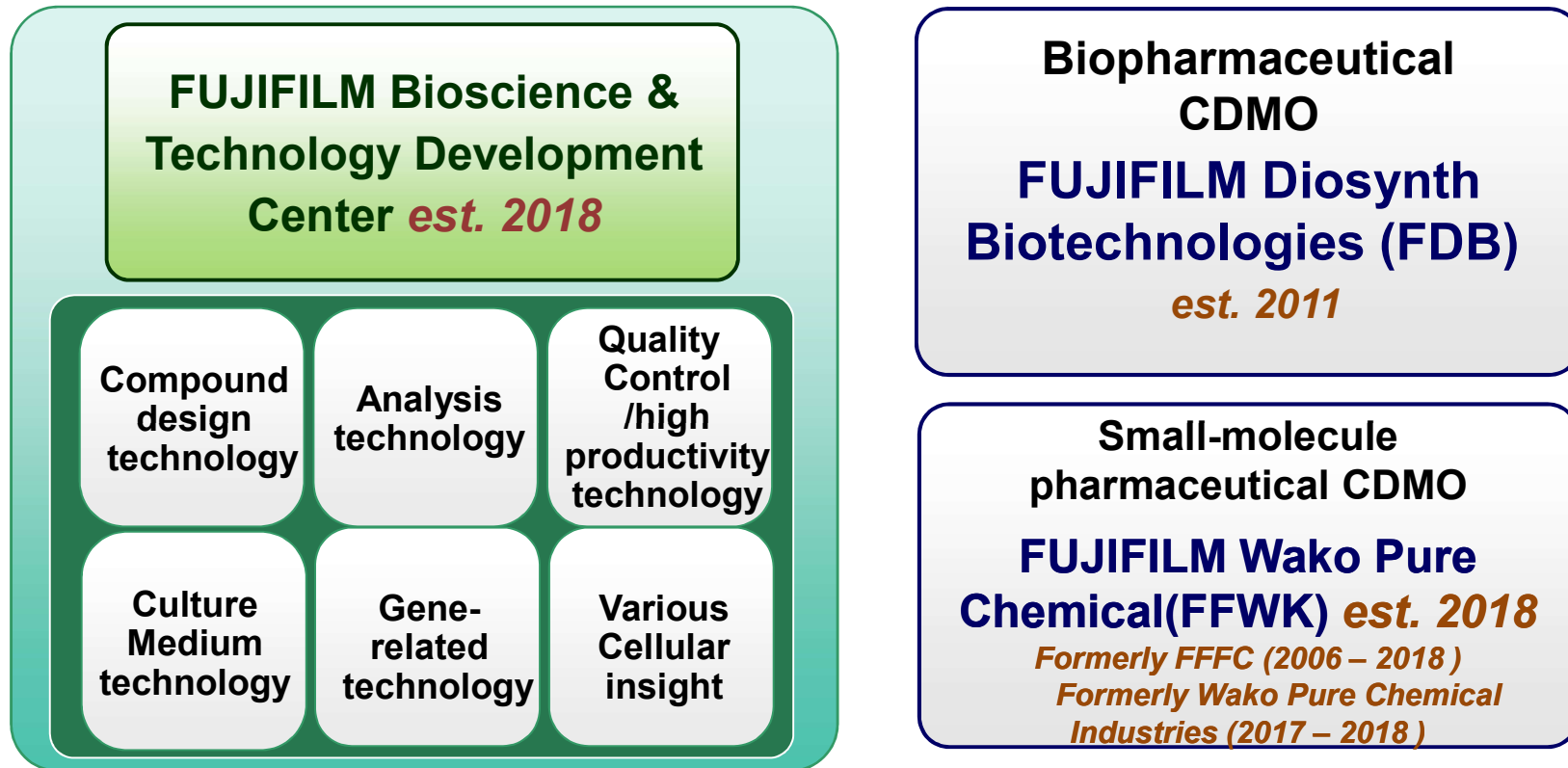
Through business operations, we will provide technologies, products and services that respond to unmet medical needs in order to contribute to solve social issues.

## **2. Bio CDMO Business**

FUJIFILM Corporation  
Director, Senior Vice President  
General Manager of Bio CDMO Division

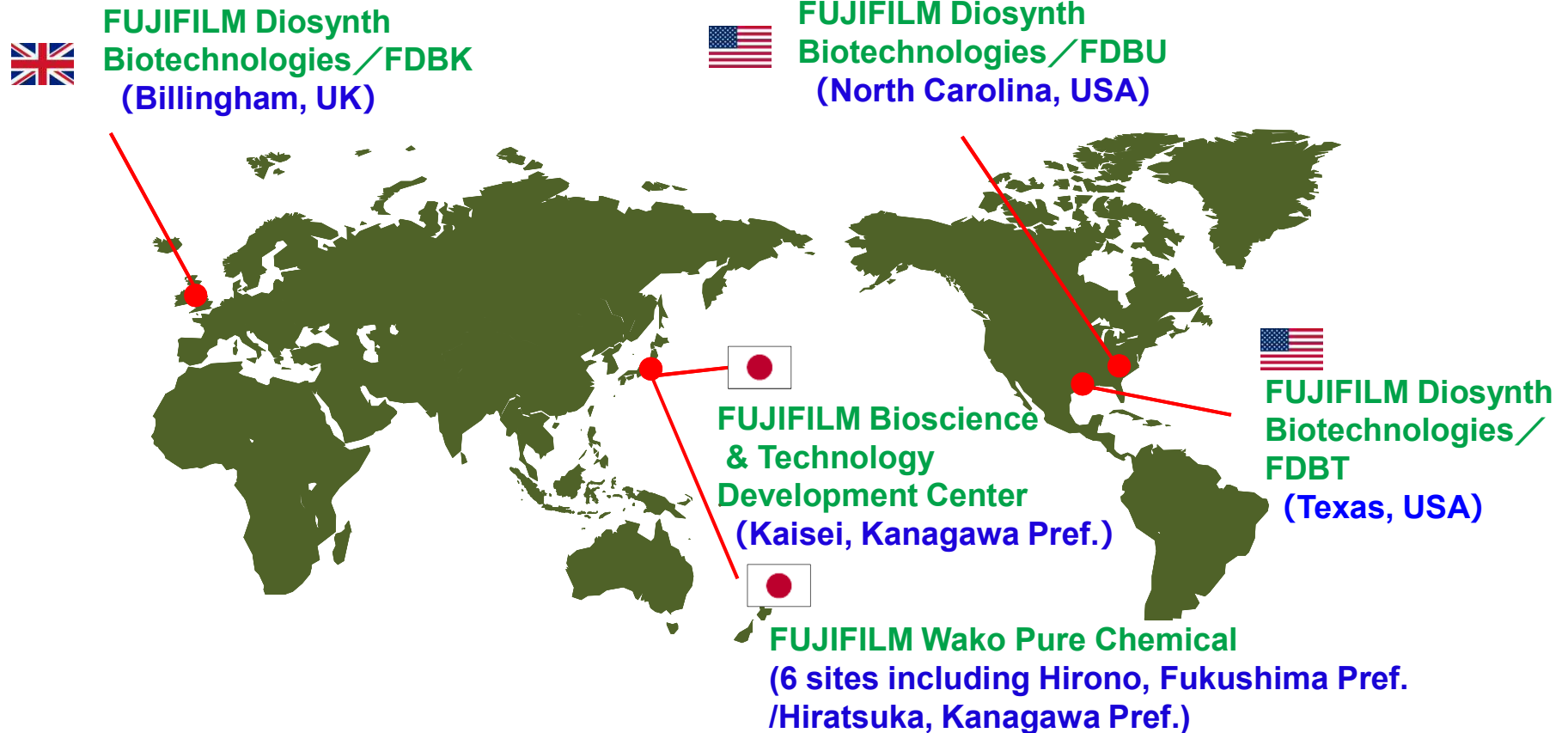
**Takatoshi Ishikawa**

# 1. Bio CDMO Division (1) Structure



- The CDMO business for biopharmaceuticals is handled by FDB, while CDMO for small-molecule drugs are carried out by FFWK.
- The Bioscience & Technology Development Center was established in 2018 as a specialized R&D unit to carry out foundation and application research for cell development, culture medium development and productivity enhancement.

# 1. Bio CDMO Division (2) Sites



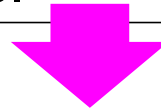
The sites are based in the United States and Europe, where the market size is large.

## 2. Fast-growing bio CDMO market

### < Background of market growth >

#### ◆ **Biopharmaceuticals as a whole**

- The biopharmaceutical market is expected to continue to grow at the **CAGR rate of approx. 8% (worth approx. 27 trillion yen in 2018)**, due to biopharmaceuticals' advanced therapeutic effects on intractable diseases and limited side effects.



#### ◆ **Bio CDMO market**

- Manufacturing active ingredients for biopharmaceuticals requires advanced manufacturing / quality control technology, large-scale production facilities and accumulated know-how. This is why manufacturing is increasingly contracted to CDMOs.

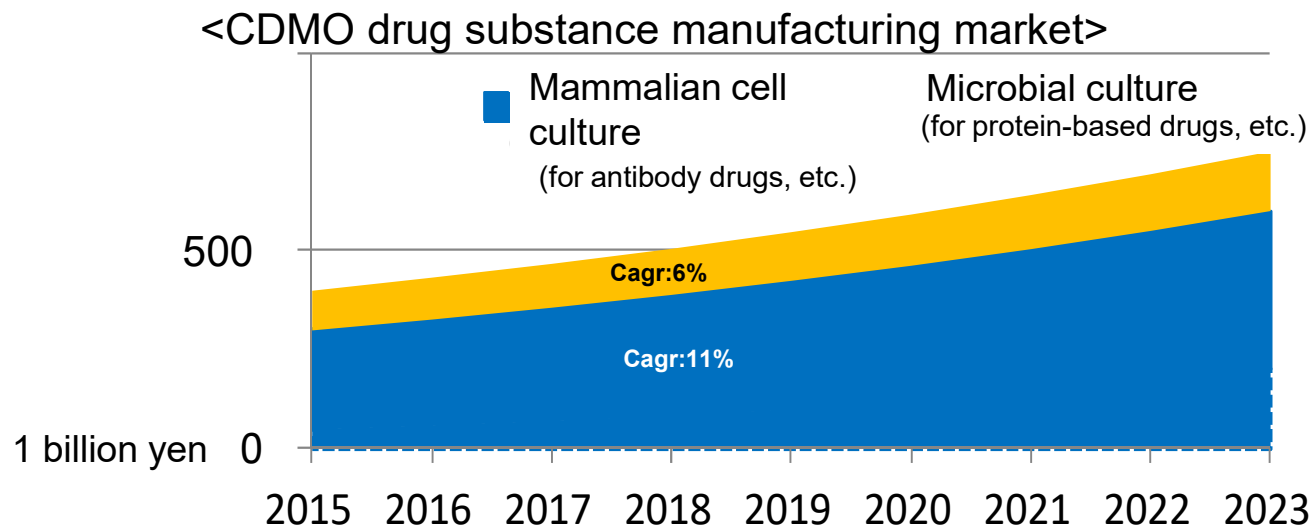
**The bio CDMO market\* is expected to maintain strong growth outstripping the expansion of biopharmaceutical business as a whole. (Market size: Approx. 500 billion yen in 2018)**

\* Excluding gene therapies

## 2. Fast-growing bio CDMO market

### <Trends in Bio CDMOs>

- (1) The manufacturing of active pharmaceutical ingredients for new drugs is shifting from low-variety / high-volume production to high-variety / low-volume production as each ingredient's scope of indications becomes increasingly narrower. At the same time, biosimilars' market penetration has steadily increased the needs for high-volume production.
- (2) With the expansion of demand for antibody drugs, **mammalian culture is becoming increasingly popular** as culturing method for manufacturing drug substance.





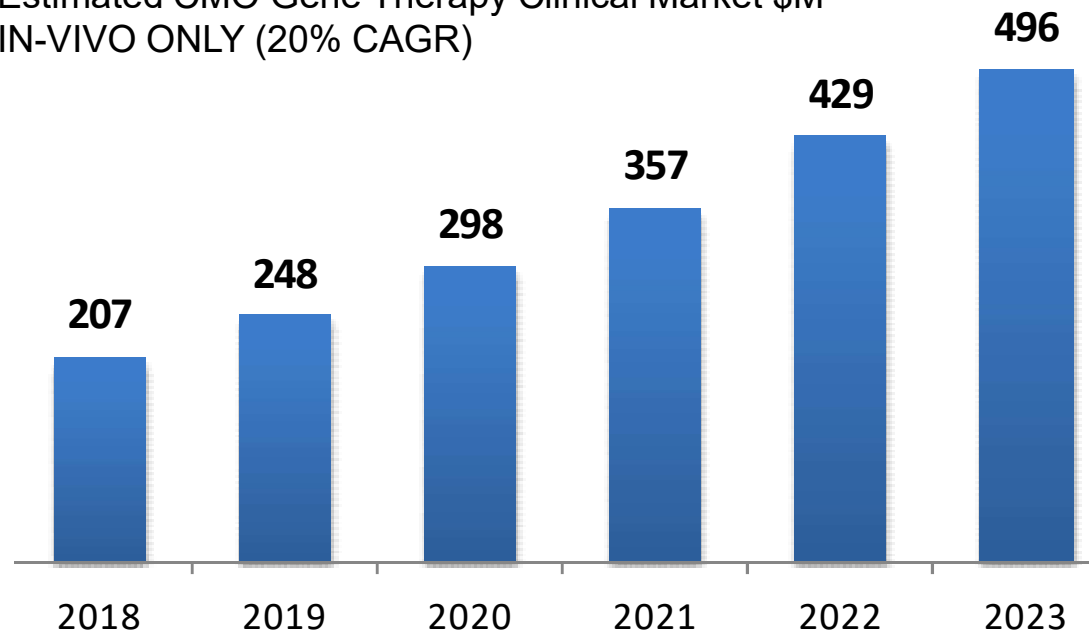
## 2. Fast-growing bio CDMO market

### < Recent Trend in Bio CDMOs >

Rapid expansion is seen in advanced medical fields such as gene therapy drugs in addition to the existing markets including antibody drugs

(20% CAGR growth for gene therapy drugs)

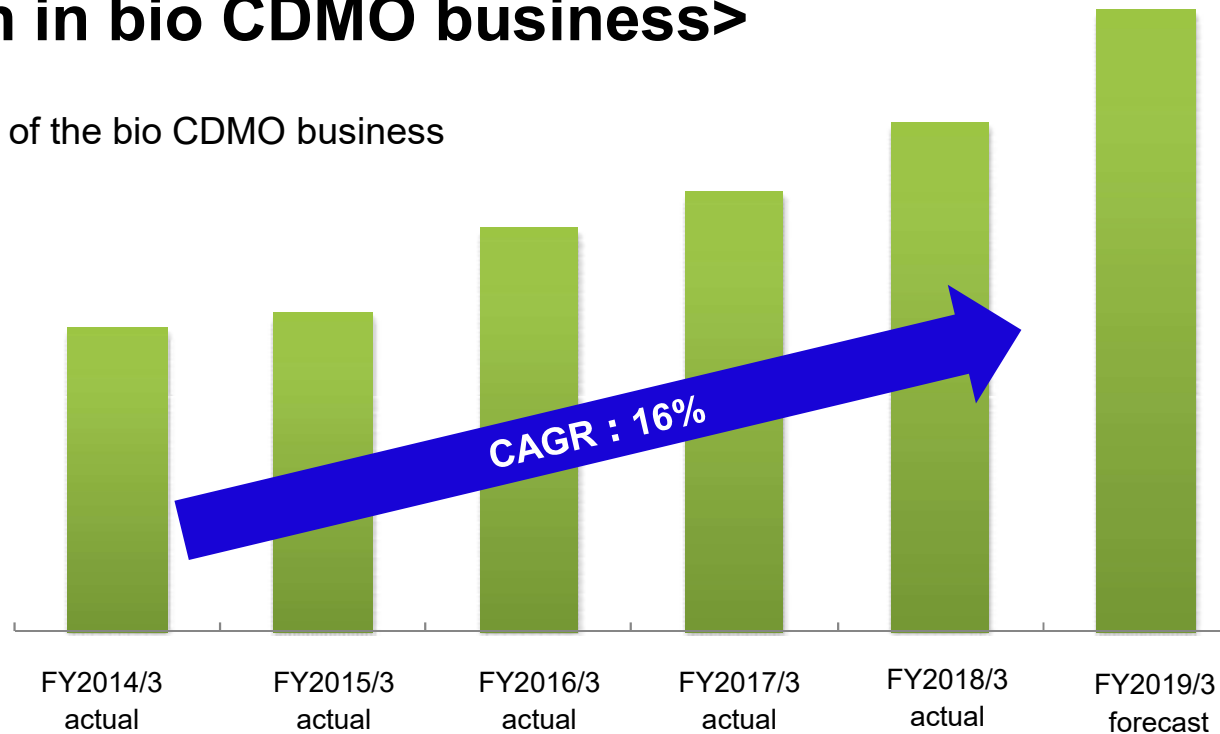
Estimated CMO Gene Therapy Clinical Market \$M  
IN-VIVO ONLY (20% CAGR)



# 3. Fujifilm's strong business growth (~2018)

## <Growth in bio CDMO business>

Sales trend of the bio CDMO business



**Fujifilm's CDMO business has steadily expanded at a rate outstripping the growth of overall demand.**

## 4. Reasons of strong growth

### (1) Active investment for reinforced capability

**(Cumulative total of 31 billion yen)**

=> Concentrated capital investment in growth areas and advanced facilities

- 2000-liter single-use bioreactors for mammalian cell culture, suitable for high-variety / low-volume production (FDBT)
- Gene therapy drug production facility (FDBT)

### (2) Industry-leading advanced culture technology

=> Introducing the high-productivity antibody production technology “Apollo™” in 2014. (Delivering 5g/L, the world top level\*) It offers a streamlined total solution covering cell line development to process development and manufacturing of drug substance.

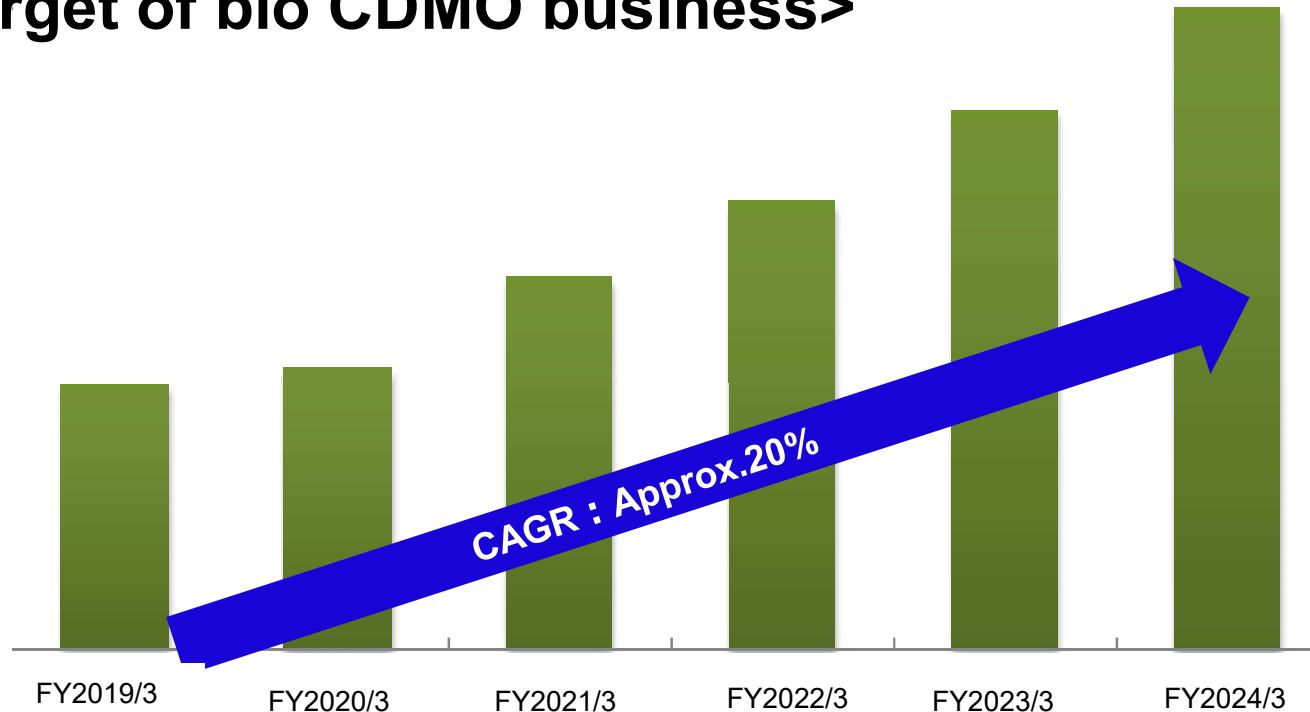
(\*Other companies' productivity as of 2017; 2.5g-5.0g/L)

### (3) Significantly improved manufacturing yield

=> Applying the technologies to manufacture under constant conditions and superior quality control, nurtured through the manufacturing and development of photographic films, following FDB acquisition to improve manufacturing yield by approx. 20% while reducing manufacturing costs and maximizing manufacturing capacity

## 5. Further business growth in the future (2019-)

### <Target of bio CDMO business>



**Achieving the sales of 100 billion yen in FY2024/3  
The CAGR growth target of approx. 20%, which is above past  
achievements**

## 5. Further business growth in the future (2019-)

### <Growth strategies>

#### (1) Further productivity enhancement

=>Introducing the high-productivity antibody production technology “Apollo™X,” which delivers more than double the level of antibody production with the existing “Apollo™” technology, and over 10g/L, industry highest level.

#### (2) Continuous production capacity reinforcement

=>Making further capital investments

#### (3) Full-scale entry into new fields

=>Entering into the contract drug product business.  
Strengthening business in the gene therapeutics field

## 5. Further business growth in the future (2019-)

### (1) Further Productivity Enhancement

- **Apollo™ X introduction**

Apollo™ has evolved to be introduced as X in January 2019.

Delivering industrial leading level\* of high productivity of antibody (5g/L => Over 10g/L,) which is more than double of the current level. In addition, shortening the cell production period (70% of the current level: 25 weeks => 18 weeks)

=> Further-streamlined production in all processes from cell line development to process development and manufacturing of drug substance.

(\*Other companies' productivity as of Jan. 2019; 2.5g/L-8.0g/L)

< Improvements from Apollo™ >

- Fujifilm's gene analysis technology and FDB's biotechnologies (cell culture technology and cell evaluation technology) have been used to achieve high productivity by the combination of below.

#### Created high-efficient DG44 cells

Designed to promote the transfer of genetic information from DNA to mRNA and encourage the conversion of proteins, generated based on genetic information on mRNA, into antibodies with higher-order structure.

+

#### The use of original culture medium for optimized cultivation

Providing quality stability and safety that ensure no change in DG44 cell properties even after repeated multiplication.  
Achieved high-performance protein productivity

## 5. Further business growth in the future (2019-)

### (2) Continuous production capacity reinforcement

**Jan. 2019 : Decision to make additional capital investments worth 10 billion yen in total**  
(announced on Jan. 7, 2019)

<Schedule of operation commencement>

**2019 at FDBT** (announced on January 18, 2018)

- 2000L single-use bioreactors for mammalian cell culture  
(adding 4 units)

**2020 at FDBU** (announced on January 7, 2019)

- 2000L single-use bioreactors for mammalian cell culture  
(adding 1 unit)
- Equipment reinforcement for the refining process in both  
processes of antibody drugs and protein-based drugs

**=> When the above facilities go operational, FDB's overall capacity to manufacture drug substance will increase by 1.8 times in antibody pharmaceuticals, 1.1 times in protein-based drugs.**



## 5. Further business growth in the future (2019-)

### (3) Full-scale entry into new fields

#### • Entering into the contract drug product business

Newly setting up a drug product manufacturing line at FDBT to go operational in 2021

Offering one-site, one-stop-shop services in contract development and manufacturing to meet customer needs, covering operations from process development to drug substance manufacturing and preparation of drug product

### One-Site, One-Stop CDMO

Process development



Manufacturing drug substance



Drug product



## 5. Further business growth in the future (2019-)

### (3) Full-scale entry into new fields

- **Strengthening business in the gene therapeutics field**
- **World's top-level advanced containment technology** to contain viruses, required for manufacturing gene therapeutics, within manufacturing processes (possible to conform to Biosafety Level 3) and **mobile clean rooms**
- Using the research support structure for cutting-edge fields as well as the global sales network to win manufacturing contracts at a pace outstripping the **rate of market growth (CAGR20%)**



FDBT's mobile clean rooms

## 6. Conclusion

**Fujifilm is striving to become a comprehensive healthcare company covering prevention, diagnosing and treatment.**

**In the treatment field in particular, Fujifilm, aims to achieve business growth and help enhance people's quality of life through exploring its comprehensive capabilities associated with biomedicine and contributing to the further development of advanced healthcare.**



# 3. Regenerative Medicine Business

FUJIFILM Corporation General Manager of  
Regenerative Medicine Business Division

**Masataka Akiyama**

# 1. What is regenerative medicine?

## Regenerative medicine

Regenerative medicine refers to new medical technology that uses cells and tissues cultured outside a patient's body to repair, regenerate or complement the functionality of human tissues and organs that are lost, damaged or compromised functionality due to illnesses, injuries, aging or for congenital reasons.

There is high expectations for regenerative medicine (cell therapy, tissue regeneration, organ regeneration) as an effective option to treat conditions that conventional medicine cannot cure or only provides a low level of therapeutic satisfaction (unmet medical needs).

<Categories of regenerative medicine>

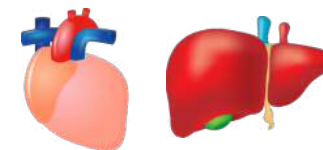
- **Cell therapy**



- **Tissue regeneration**



- **Organ regeneration**



# 1.Environment surrounding regenerative medicine

## Japan

◆ **Regenerative Medicine Promotion Act (enacted in May 2013)**  
The government basic philosophy for a comprehensive approach to promoting and spreading R&D on regenerative medicine

◆ **Amended Pharmaceutical Affairs Act (enacted in November 2014)**  
① Setting up a new “Regenerative medicine products” category  
② Introducing an approval system in line with the characteristics of regenerative medicine

◆ **Regenerative Medicine Safety Act (enacted in November 2014)**  
① Allowing the outsourcing of cell culture operation  
② Approval / reporting system according to the level of risks

## Overseas

◆ **21st Century Cures Act of the United States (signed into law in December 2016)**  
Based on this law, the designed system of RMAT (Regenerative Medicine Advanced Therapy) was newly established aimed at speeding up the approval process for regenerative medicine

**Regenerative medicine products approved in Japan**  
(products enclosed in red box are Fujifilm’s products)

2007	Japan Tissue Engineering Autologous cultured epidermis “JACE”
2012	Japan Tissue Engineering Autologous cultured cartilage “JACC”
2015	JCR Pharma Allogeneic mesenchymal stem cell “TEMCELL”
2015	Terumo Autologous skeletal myoblast preparation “HeartSheet”
2018	Nipro Autologous cell preparation “Stemirac injection” for spinal cord injuries treatment

**Legal frameworks for regenerative medicine are actively developed to promote applications in business and industries**



# 1. Activities of each company and development status related regenerative medicine

## ■ Activity of each company

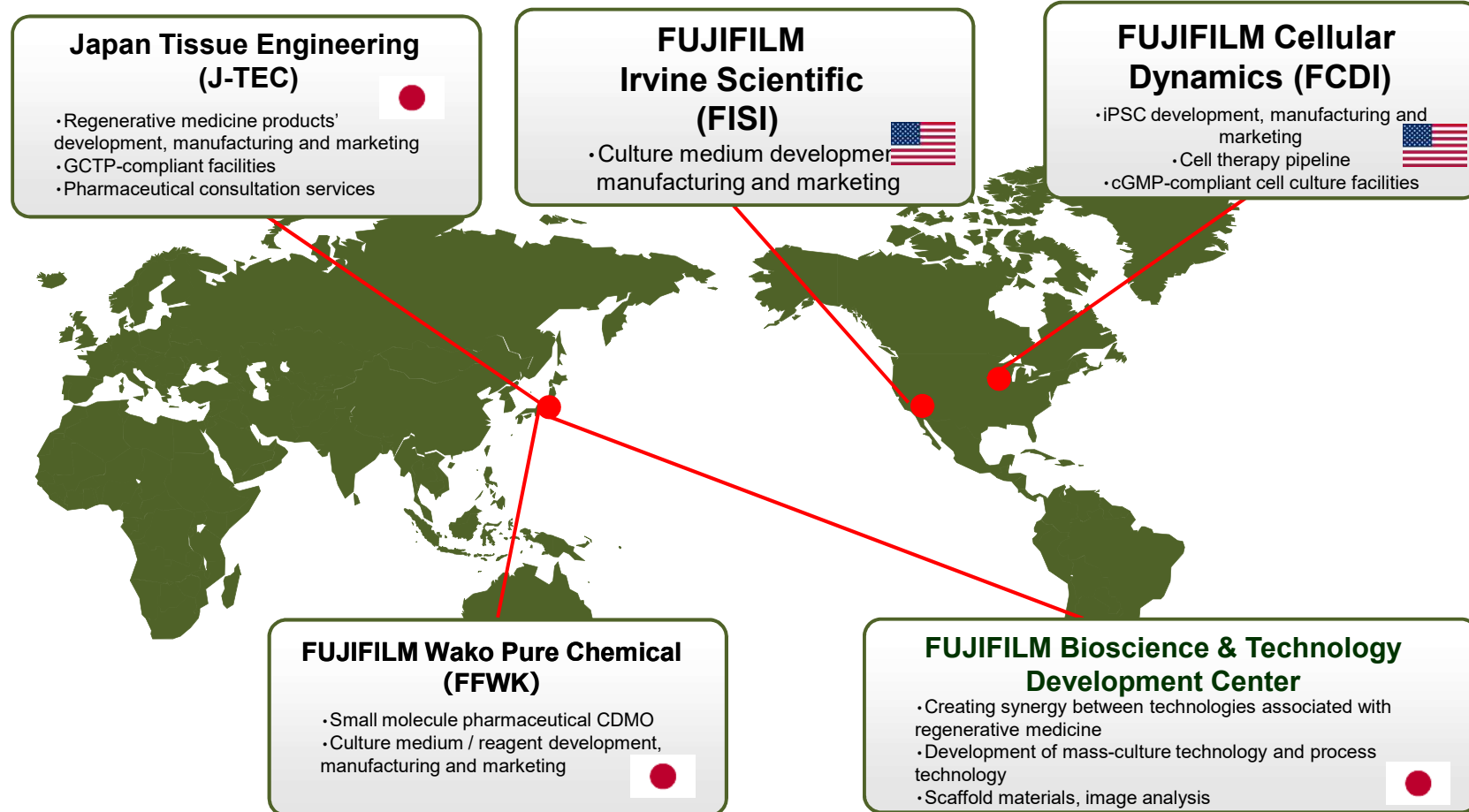
Year	Company	Description
2016	Bayer /Versant	Jointly funding the establishment of BlueRock Therapeutics with a Series A financing of US\$225 million
2016	Astellas	Acquiring Ocata (today's AIRM) to obtain critical stem cell technology
2017	Megakaryon	Establishing a method for manufacturing iPSC-derived platelet preparations
2018	Astellas	Acquiring Universal Cells to obtain the Universal Donor Cell technology
2018	Eli Lilly	Business alliance with Sigilon in development of encapsulation cell therapy products for type I diabetes
2019	Bristol-Myers Squibb	Released acquisition of Celgene on Jan. 3, 2019 for US\$74.0 billion

## ■ Cell therapies using CAR-T (oncology)

Year	Indication	Main body	Remarks
2017	B-cell acute lymphoblastic leukemia	NOVARTIS	Product name "Kymriah" FDA approved in the U.S. In 2018, applied an application for a manufacturing and marketing approval of regenerative products in Japan
2017	Diffuse large B-cell lymphoma	Gilead Sciences	Product name "Yescarta" Gilead Sciences acquired Kite in 2017 for US\$11.9 billion.
2018	Non-Hodgkin's lymphoma	Celgene	Development code "JCAR017" Celgene acquired Juno in 2018 for US\$9 billion

**Regenerative medicine companies are actively conducting business, especially cell therapies using CAR-T cells are promoted practical applications.**

## 2. Fujifilm's regenerative medicine business structure



**Fujifilm group holds three main technological elements in regenerative medicine, e.g. cells, culture medium / cytokines and scaffolds. Creating synergy between the group.**

## 2. Initiatives in regenerative medicine business

### Accelerating the use of cell therapy pipeline in actual treatments

As a leading company, accelerating the realization of treatments using iPSC.

⇒ Widely spreading iPSC for therapeutic use through our own sales networks and partners

- ✓ Maximizing the use of iPSC related technologies including cell reprogramming, extended culture, differentiation induction and the resources of the group.
- ✓ Partnering with companies that have technologies of strong potential to accelerate development

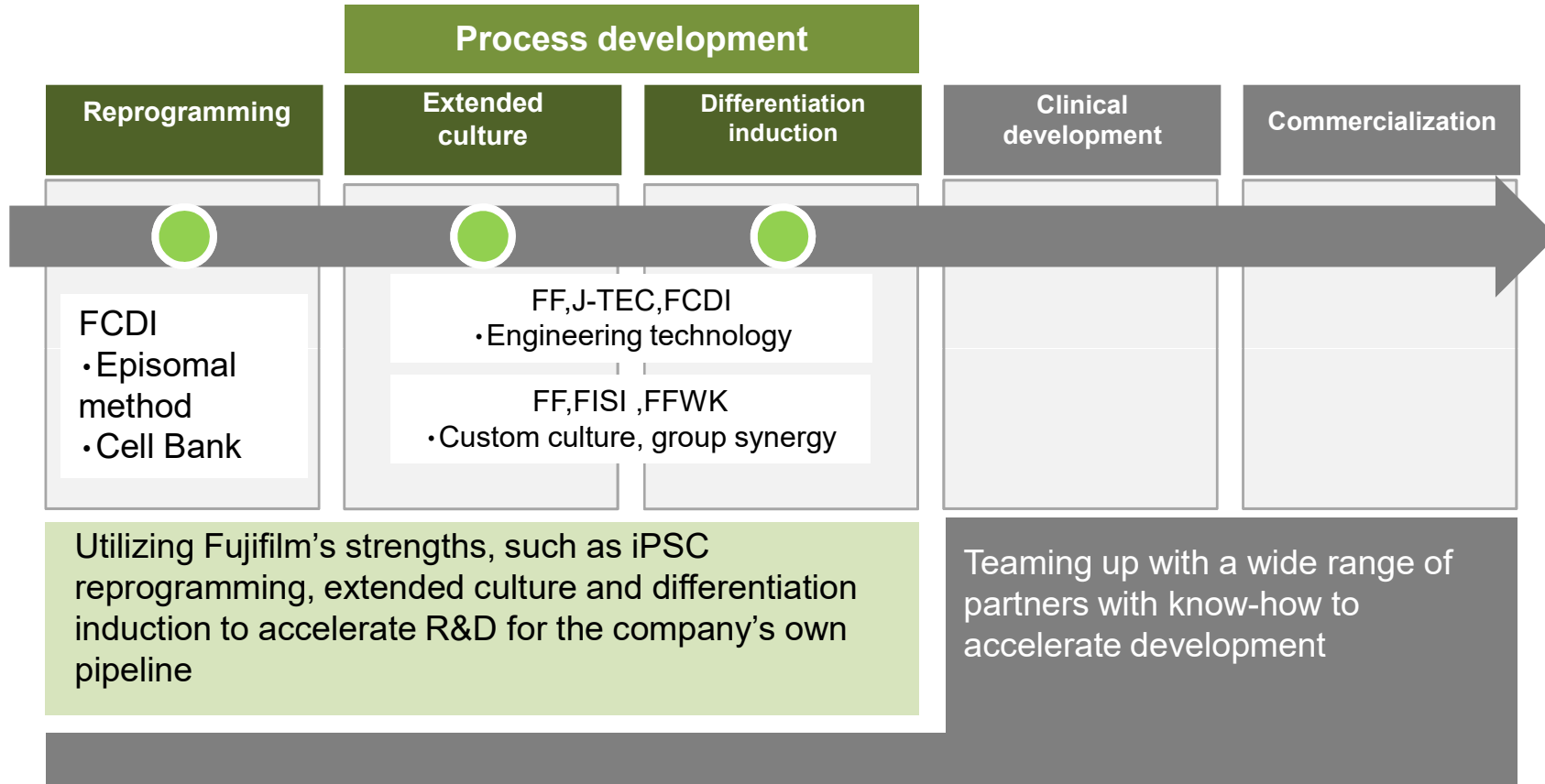
### CDMO business Accepting contract development and manufacturing for regenerative medicine / cell therapy products

- ✓ Capturing demand with GMP-compliant facilities in Japan / USA and technologies for cell reprogramming, extended culture, and differentiation induction

**Contributing to profits by accelerating the realization of cell therapy and the expansion of CDMO business as a leading company, Fujifilm promotes industrialization of regenerative medicine**

## 2. Fujifilm's technologies that support the strategy

### ■ Flow of regenerative medicine product development using iPSC



**Making full use of Fujifilm's strengths and teaming up with partners. Realizing regenerative medicine, especially cell therapy, to promote industrial applications.**

### 3. Accelerating the use of cell therapy pipeline in actual treatments

#### Accelerating the use of cell therapy pipeline in actual treatments

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**CDMO business**  
Accepting contract development and manufacturing for regenerative medicine / cell therapy products

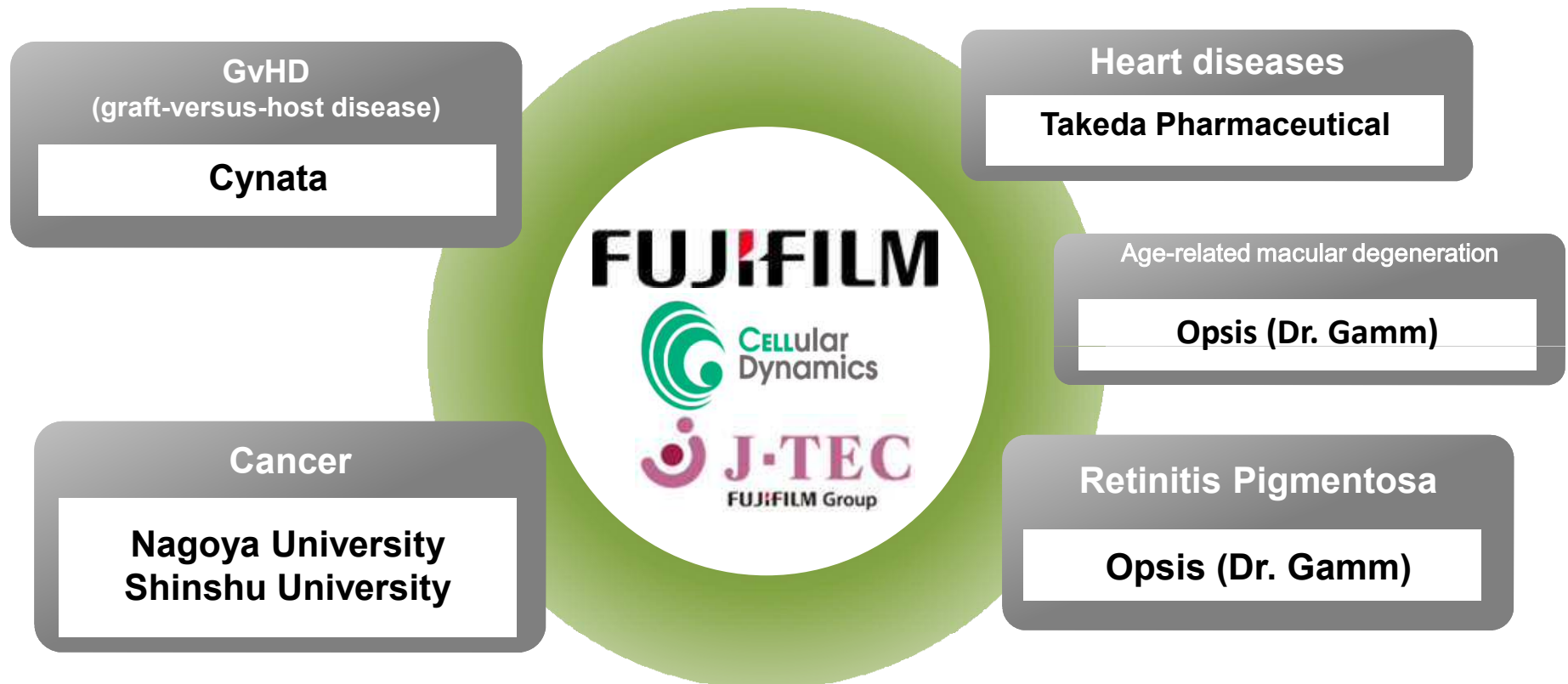
- ✓ Capturing demand with GMP-compliant facilities in Japan / USA and technologies for cell reprogramming, extended culture, and differentiation induction

### 3. Priority areas for the pipeline for iPSC-based therapies

Cell	Target disease	Partner	Development progress			Remarks	Potential market size (Fujifilm estimation) trillion yen
			Pre-clinical	Clinical			
				P1	P2		
Mesenchymal stem cell	GvHD (graft-versus-host disease)	Cynata				P1 completed with cells supplied by FCDI (UK)	0.2
Gene-transduced CAR T cell	Cancer	TBD					1.4
RPE (retinal pigment epithelium) + PRP (photo receptor)	Age-related macular degeneration	Dr.Gamm				JV "Opis Therapeutics" established with Dr.Gamm	1.7
PRP (photo receptor)	Retinitis Pigmentosa	Dr.Gamm					
Myocardial cell	Heart diseases	Takeda Pharmaceutical					1.0
Dopamine neuron	Parkinson's Disease	TBD					1.3

**Aiming to establish iPSC therapy business with a focus on areas with unmet medical needs**

### 3. Collaboration with partners



**Collaborating with partners that have technologies of strong potential and know-how, utilizing Fujifilm's business base of the iPSC, cell therapy as a platform  
=> Accelerating development while reducing risks**



## 3. Collaboration with Cynata

- ✓ **Making US\$3 million capital participation in Cynata Therapeutics Limited (Australia) in January 2017**
- ✓ **Fujifilm has acquired an option to a license to develop, manufacture and commercialize Cynata's product in Japan, the United States and the United Kingdom in the field of treating graft-versus-host disease (GvHD).**

### **Cynata**

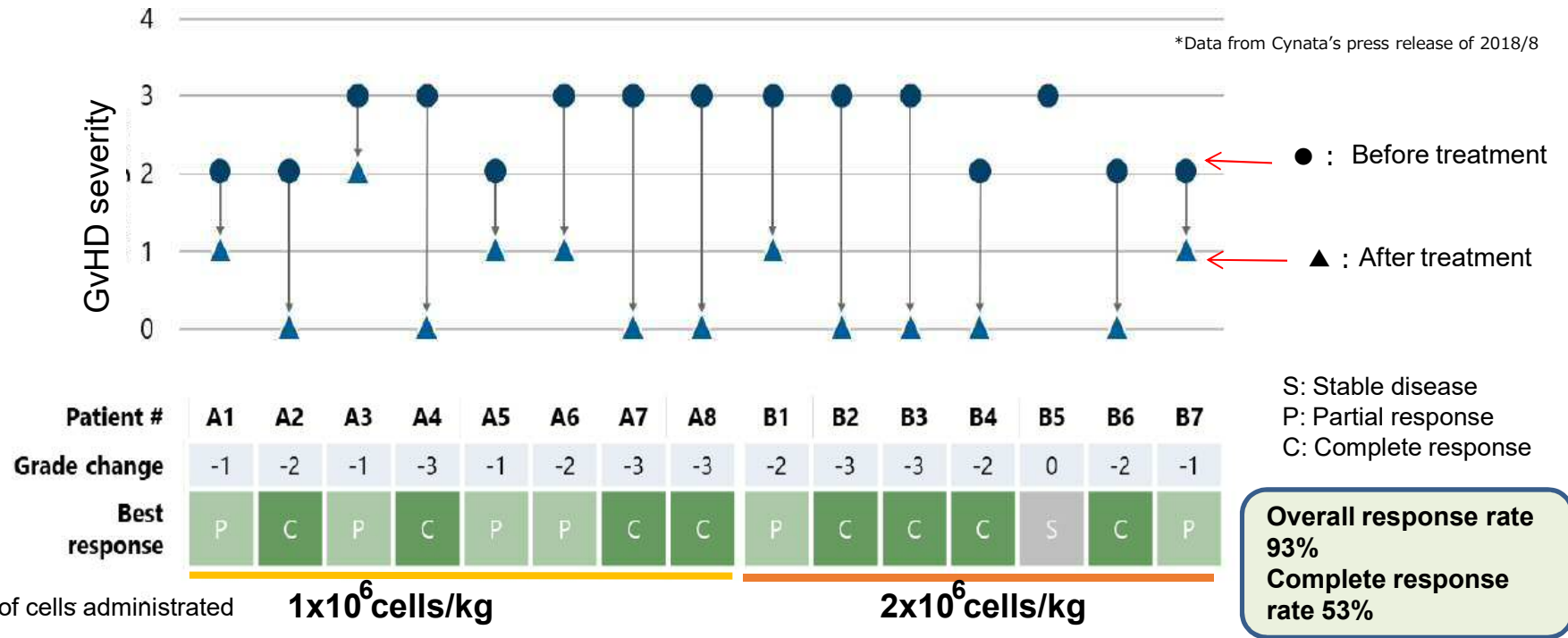
- ✓ Australian bio-venture established in 2013
- ✓ Built a technology for efficient mass production of iPSC-derived mesenchymal stem cells

#### ✓ **May 2017**

#### **Commenced clinical trial on GvHD patients in UK**

- ✓ This trial is using allogeneic iPSC supplied by FUJIFILM Cellular Dynamics of the United States, a leading company in iPSC development and manufacturing.

### 3. World's first clinical trial data using iPSC for the treatment of GvHD

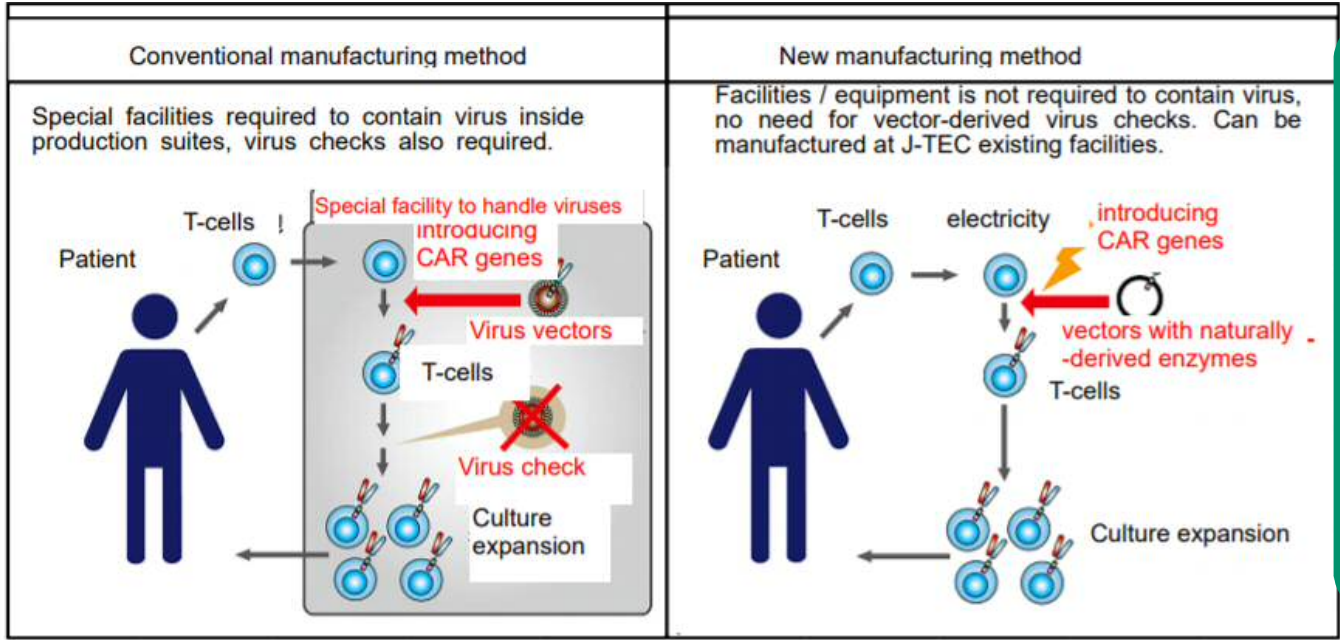


Product	Status	Indication	Country	Number of patients	Post-treatment results	
<b>CYP-001</b>	Phase1 completed	GvHD (graft-versus-host disease)	UK	15	Complete response: 8 Partial response: 6 Stable disease: 1	No hazardous event reported

**The world's first clinical trial on allogeneic iPSC-derived cell therapy product for GvHD was executed in May 2017**

### 3. Collaboration with Nagoya University and Shinshu University in the field of oncology

- ✓ J-TEC, Nagoya University and Shinshu University signed patent license agreement for a low-cost manufacturing technology for antologous CAR-T cell therapy against CD19-positive acute lymphoblastic leukemia (ALL) in June 2018.
- ✓ J-TEC acquired the exclusive rights to manufacture, develop, and commercialize the therapies using this technology in Japan.



Using low-cost vectors with naturally-derived enzymes instead of virus vectors. It is expected to reduce manufacturing cost as neither equipment for containing virus nor vector-derived virus checks are required.

### 3. Business expansion through capital participation and partnerships

Timing	Company	Country	Amount	Objectives
May 2017	RegCell	Japan	JPY170 million	<ul style="list-style-type: none"> <li>• Accessing to immuno-cell therapy technology</li> <li>• Expanding contract development and manufacturing</li> </ul>
September 2017	NC Medical	Japan	JPY 430 million	<ul style="list-style-type: none"> <li>• Accessing to know-how on mesenchymal stem cells' therapeutic applications</li> <li>• Expanding contract development and manufacturing</li> </ul>
November 2017	Cyfuse	Japan	JPY 390 million	<ul style="list-style-type: none"> <li>• Accessing to cell lamination technology</li> <li>• Expanding contract development and manufacturing</li> </ul>
November 2017	Tokiwa Bio	Japan	JPY 170 million	<ul style="list-style-type: none"> <li>• Accessing to transgenic technology (stealth RNA vector)</li> </ul>

## 4. CDMO business in regenerative medicine

### Accelerating the use of cell therapy pipeline in actual treatments

As a leading company, accelerating the realization of treatments using iPSC.

⇒ Widely spreading iPSC for therapeutic use through our own sales networks and partners

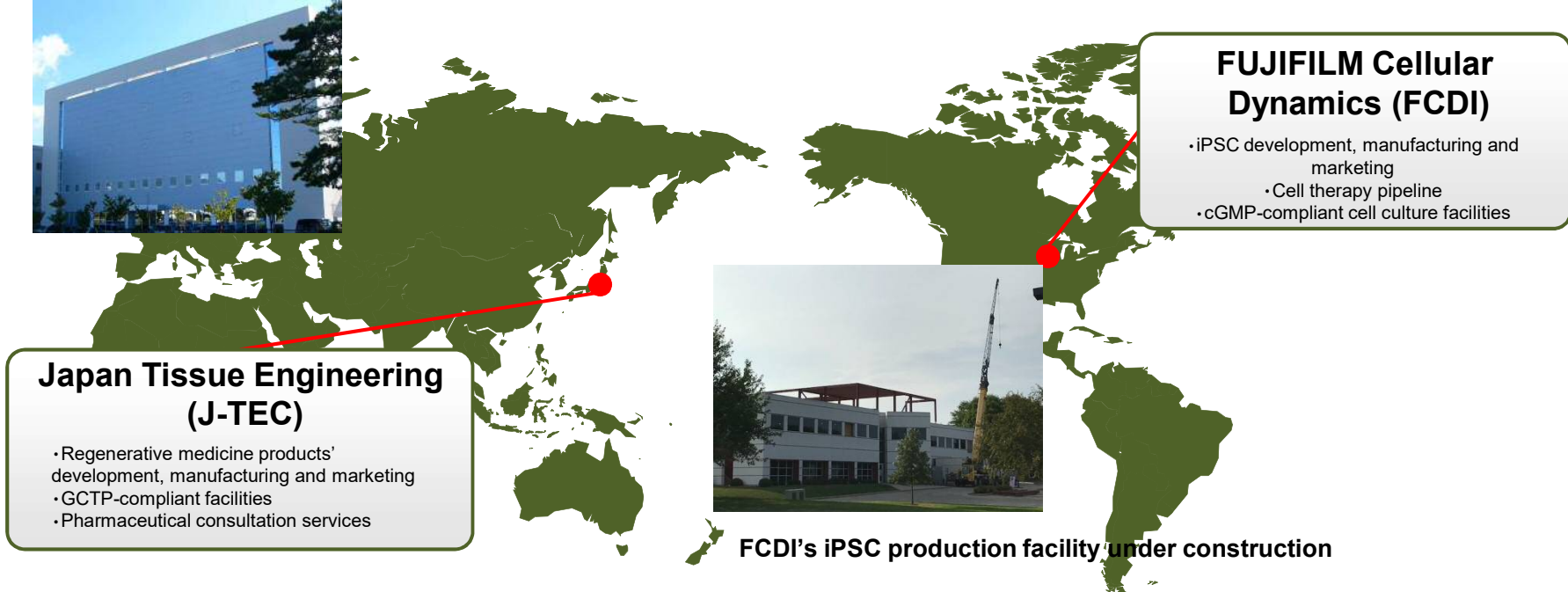
- ✓ Maximizing the use of iPSC related technologies including cell reprogramming, extended culture, differentiation induction and the resources of the group.
- ✓ Partnering with companies that have technologies of strong potential to accelerate development

### **CDMO business** Accepting contract development and manufacturing for regenerative medicine / cell therapy products

- ✓ Capturing demand with GMP-compliant facilities in Japan / USA and technologies for cell reprogramming, extended culture, and differentiation induction

## 4. Establishing the production system

In December 2018, announced approx. 2.5 billion yen investment in U.S. FCDI to build a new production facility for therapeutic cells derived from iPSC (Operation start in FY2020/3)



The image features a world map with two callout boxes. A red line connects the J-TEC callout in Japan to the FCDI callout in the United States. The J-TEC callout includes a photo of a modern building. The FCDI callout includes a photo of a building under construction with a crane.

**Japan Tissue Engineering (J-TEC)**

- Regenerative medicine products' development, manufacturing and marketing
- GCTP-compliant facilities
- Pharmaceutical consultation services

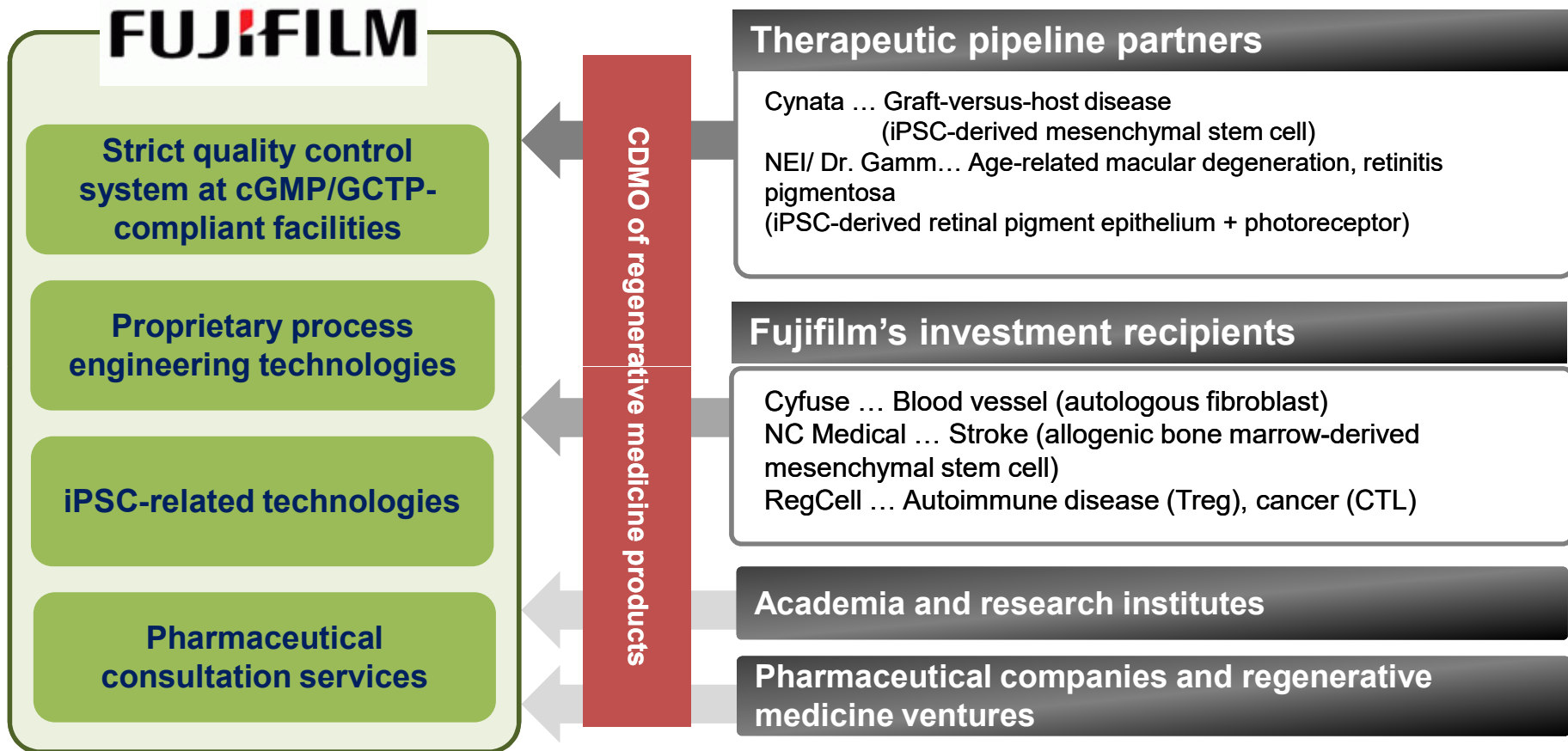
**FUJIFILM Cellular Dynamics (FCDI)**

- iPSC development, manufacturing and marketing
- Cell therapy pipeline
- cGMP-compliant cell culture facilities

FCDI's iPSC production facility under construction

**Establishing a structure to achieve highly efficient production of high-quality regenerative medicine products at two sites in Japan and the United States**

# 4. Fujifilm's strength in CDMO business

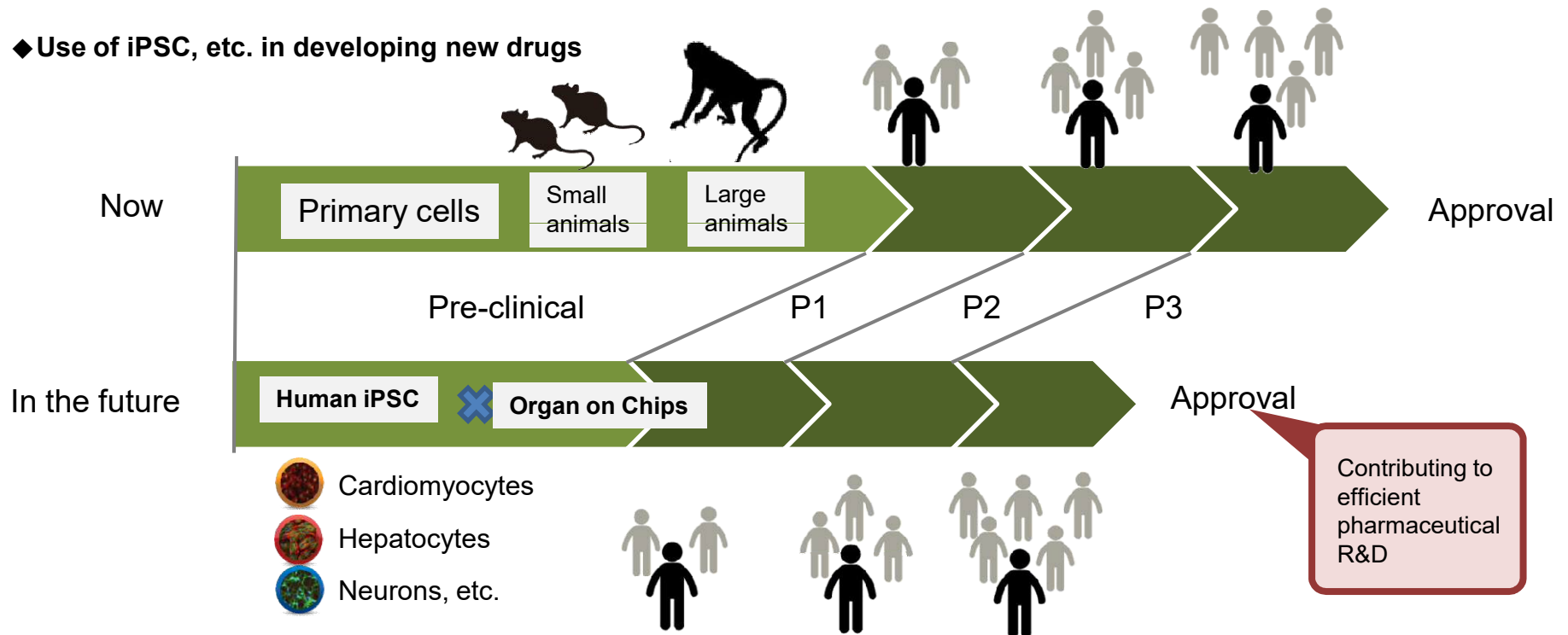


**Utilizing Fujifilm Group's foundation technologies to accept contract development and manufacturing of various regenerative medicine products in order to accelerate the establishment of industry**

# 5. What is drug discovery support?

✓ Providing diverse lineup of human iPSC including “iCell<sup>®</sup> (iPSC-derived differentiated cells)” and “MyCell<sup>®</sup> (custom-made differentiated and induced cells” and cell-used Organ on Chips to contribute to more efficient pharmaceutical R&D

◆ Use of iPSC, etc. in developing new drugs



◆ What are Organ on Chips?

Chips and other devices that carry various organ-specific cells

High expectations as a new foundation of technology that facilitates the assessment of drug-candidate compounds' safety, pharmacokinetics, etc.



## 5. Fujifilm's initiatives in drug discovery support

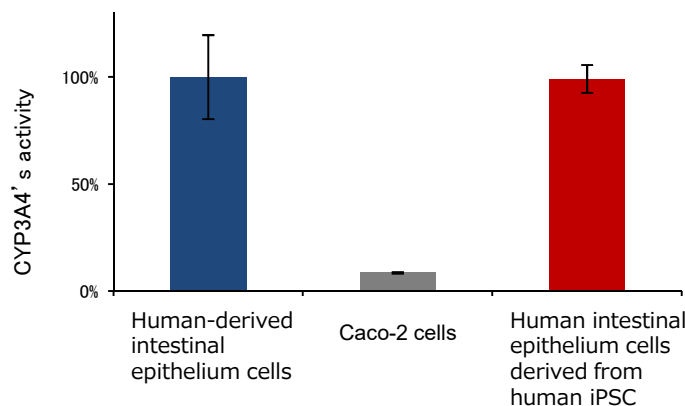
### 1. Launch of "iCell® Microglia," differentiated cells derived from iPSC for drug discovery support (January 2019)

- Microglia are known to be involved in the development of neurological disorders such as Alzheimer's Disease and Parkinson's Disease.
- This product is expected to contribute to boosting efficiency in R&D of new drugs as this enables to develop new evaluation method in the condition similar to the human central nervous system when it is used for new drug development for neurological disorders.

### 2. Successfully developing intestinal epithelium cells derived from iPSC suitable for drug absorption assessment (September 2018)

- Co-development of Nagoya City University and Fujifilm.
- The cells have been confirmed to have properties similar to epithelial cells of the small intestine that play an important role in drug absorption.
- It is expected to significant contribute in streamlining the development of oral preparation.

<Comparison of the activity of CYP3A4, a main drug metabolizing enzyme found in intestinal epithelium cells>



This graph compares the activity level of CYP3A4, a drug metabolism enzyme that plays the most important function when intestinal epithelium cells absorb a drug.

If the enzyme's activity level in human-derived intestinal epithelium cells is set at 100%, Caco-2 cells' activity level was as low as around 10%. In contrast, the newly-developed intestinal epithelium cells derived from human iPSC demonstrated the level of activity equivalent to that of human-derived intestinal epithelium cells.

## 6. Animal regenerative medicine

### ✓ **Celltrust Animal Therapeutics Co., Ltd**

Established by Anicom Holdings, Inc. and Fujifilm

By combining each company's technologies and products, developing and providing advanced and reliable medical technologies and services with the focus on regenerative medicine / cell therapy in the field of cutting-edge veterinary medicine.

#### < **Business overview** >

- (1) Development and practice of cutting-edge medical care
- (2) Provide cutting-edge medical solutions
- (3) Provide medical information services

### ✓ **Animal Regenerative Medicine Center Hospital**

Established by Celltrust Animal Therapeutics.

The operational base for regenerative medicine / cell therapy in veterinary medicine, which possesses following 3 features;

- (1) Highly managed cell culture facilities and quality assurance system
- (2) Laboratories and medical equipments for clinical development
- (3) Medical equipments for own practical initiatives of cutting-edge diagnosis

#### <**Diseases adopted cell therapy**>

##### ◆ **Kerato Conjunctivitis Sicca (KCS)**

Target: dogs

The route of administration of MSC

: Local administration



##### ◆ **Chronic Enteropathy (CE)**

Target: dogs

The route of administration of MSC

: Intravenous dosage



Realization of cutting-edge medical care with a focus on regenerative medicine and cell therapy to contribute to veterinary medicine.

## 7. Establishing a distribution system for regenerative medicine products

Cell transportation technology and know-how nurtured in the drug discovery support business

- Delivering regenerative medicine products safely to patients under strict quality control

Providing the management network built around the cell transportation equipment "TS500-TSF" which can keep constant temperature

- Highly accurate temperature control within the non-freezing temperature range
- Advanced traceability and diverse security functions

## 8. Conclusion

✓ **Accelerating the use of cell therapy pipeline in actual treatments**

In addition to utilizing Fujifilm's proprietary engineering technology and the synergy of each group company's technology / resource, by collaborating with partners to accelerate the development to realize cell therapy in actual treatments.

✓ **Expanding CDMO business**

Expanding CDMO business by supporting development and production of regenerative medicine / cell therapy products, utilizing each group company's technological resource and facility as a platform.

✓ **Drug discovery support business**

Contributing to more efficient development of new drugs through providing human iPSC etc, to expand drug discovery support business.

**Accelerating the realization of regenerative medicine to establish new treatments which meet the expectation from patients who have unmet medical needs.**

# 4. Pharmaceutical Products Business

FUJIFILM Corporation  
Director, Corporate Vice President  
General Manager of Pharmaceutical Products Division

**Junji Okada**

## 1-1. Business areas focused by Fujifilm

- Concentrating on development of existing pipeline to address unmet medical needs

**Existing  
pipeline**

- Establishing practical application of Drug Delivery System (DDS)
- Actualizing pharmaceutical IoT services

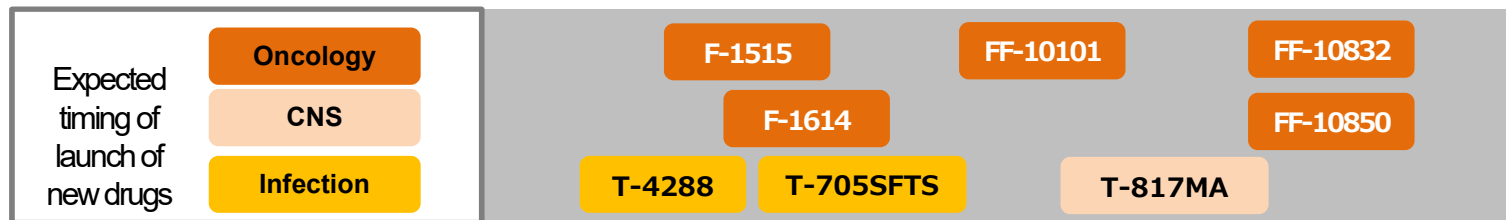
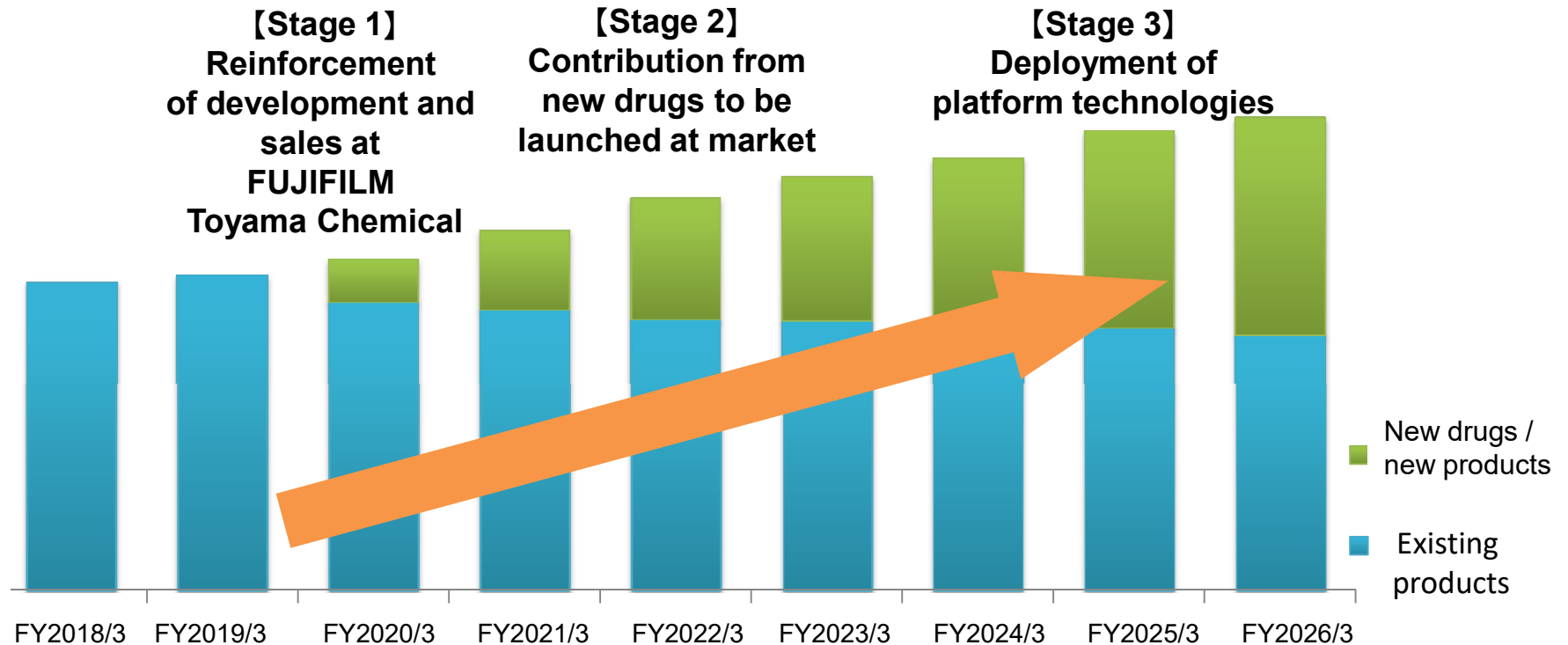
**Solutions using  
Fujifilm  
technologies**

- Promoting the establishment of regenerative medicine as an industry
- Accelerating R&D of current pipeline
- Establishing CDMO business in regenerative medicine

**Cell therapy  
(Regenerative medicine  
business)**

**Concentrating business resources to the areas above, in which Fujifilm has a “competitive edge” and is capable of “leading the market”**

# 1-2. Mid- and long-term sales outlook

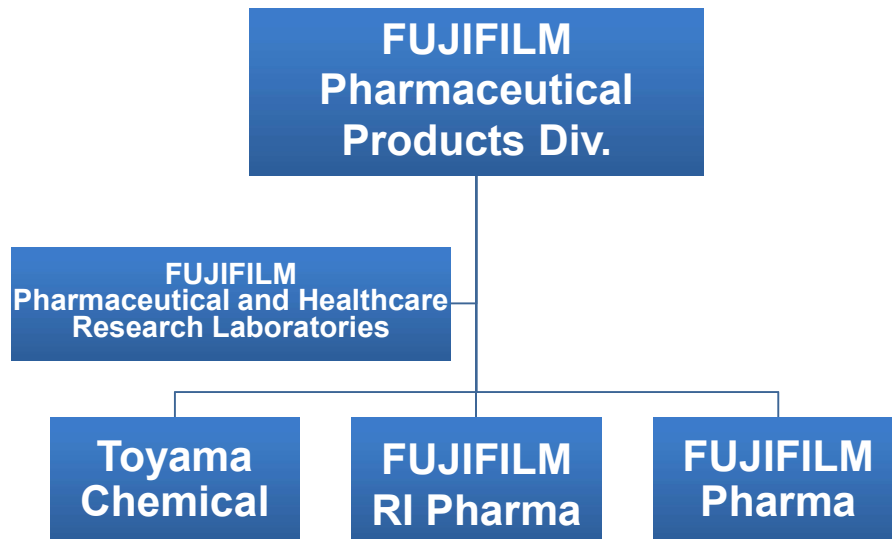


**Concentrating on R&D in prioritized areas to accelerate launch of new drugs**

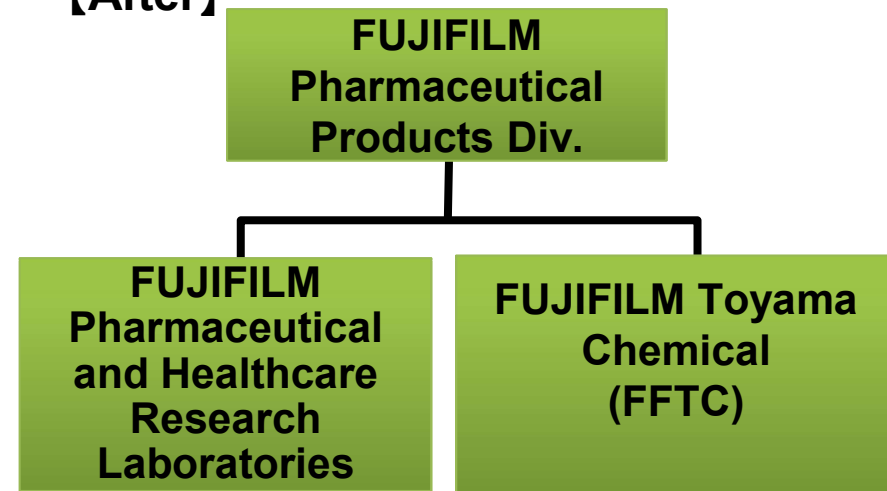
# 1-3. Challenge for New Growth : Purpose of establishing FUJIFILM Toyama Chemical

Transforming the business structure and organization to ensure early launch of new drugs

**【Before】**



**【After】**



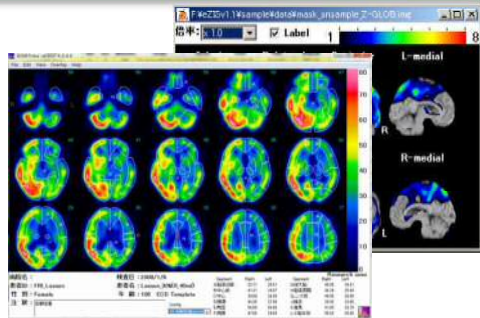
**Integrated group management**

- Making quick decisions by integrated group management
- Accelerating the mutual utilization of each company's function, know-how, and technologies
- Combining diagnosis and treatment to provide new values
- Strategic investment of resources in focused areas where Fujifilm can utilize own strength



# 1-4. Business overview of FUJIFILM Toyama Chemical

## Radiopharmaceuticals (for Diagnosis and Therapy)



### Transfer of marketing rights from Taisho Toyama Pharmaceutical

(Since 4/2019)

#### Mainly antimicrobials



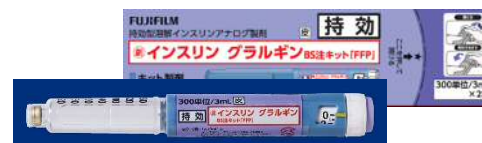
### Succeeded from FUJIFILM Pharma

(Since 1/2019)



**“Sanorex”**  
Appetite suppressant for severely obese patients

**“Oravi”** for oropharyngeal candidiasis licensed from Sosei approved in September 2018 and  
※To be launched in February 2019



Insulin glargine biosimilar

### Pharmaceutical IoT

(Since 10/2018)

Medication verification system

**PROFIT**



Constant-temperature transportation system, blood transportation system



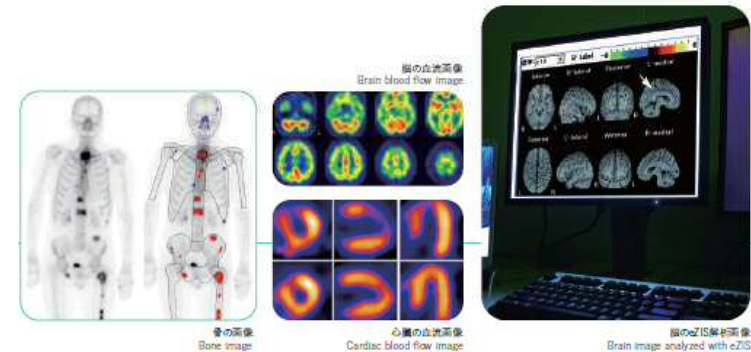
# 1-5. FUJIFILM Toyama Chemical - Radiopharmaceuticals

## Diagnostic Radiopharmaceuticals

This type of radiopharmaceuticals combines a radioisotope (RI) with a compound that targets a specific organ or lesions. A small amount is administered intravenously. Radiation emitted from the RI is visualized as images with a special camera.

## SPECT scan

Imaging RI that emits gamma rays



## Therapeutic Radiopharmaceuticals

This type of radiopharmaceuticals is used for “internal radiation therapy”, which utilizes beta rays emitted from RI bound to a compound to destroy specific cells, e.g. tumor cells.

## PET scan

Imaging RI that emits positrons



## 1-6. Comprehensive solution with diagnostic and therapeutic radiopharmaceuticals

### ■ Theranostics :

**Concept of conducting diagnosis and treatment with the same compound. Lesions can be localized with the compound labeled with diagnostic RI first, then be treated with the same compound labeled with therapeutic RI.**

Diagnosis: Visualize physiological and functional information of organs / tissues

Therapy: Minimum invasiveness with fewer side effects

Indication	RI diagnostic	RI therapy
Neuroendocrine tumor	Octreoscan	F-1515( <sup>177</sup> Lu : Lutathera)
Refractory pheochromocytoma	MyoMIBG-I123	F-1614 ( <sup>131</sup> I)
B-cell non-Hodgkin lymphoma	Zevalin indium	Zevalin yttrium
Advanced / metastatic solid cancer	FF-21101( <sup>111</sup> In)	FF-21101( <sup>90</sup> Y)
Glioblastoma	FF-10158※	FF-10158※

Red text :launched

※Overseas development rights licensed out to AAA

## 2-1. Business areas focused by Fujifilm

- Concentrating on development of existing pipeline to address unmet medical needs

**Existing pipeline**

- Establishing practical application of Drug Delivery System (DDS)
- Actualizing pharmaceutical IoT services

**Solutions using Fujifilm technologies**

- Promoting the establishment of regenerative medicine as an industry
- Accelerating R&D of current pipeline
- Establishing CDMO business in regenerative medicine

**Cell therapy**  
(Regenerative medicine business)

## 2-2. Main existing pipeline

- ✓ **Focusing on oncology, central nervous system and infection as priority areas**
- ✓ **Planning to establish proof of concept for new drugs developed in-house in the stage of market introduction (reaping phase)**

Development number	Efficacy and indication	Region	Development stage	2019	2020	2021
—	Oropharyngeal candidiasis	Japan	Included in the NHI drug price list	Release		
T-3811	Synthetic quinolone antibacterial drug	China	Application filed	Approval		
T-4288	New fluoro-ketolide antibacterial drug	Japan	Ph III	Application	Approval	
T-705	Severe fever with thrombocytopenia syndrome (SFTS) treatment drug	Japan	Ph III		Application	Approval
F-1515	【RI】 Neuroendocrine tumor treatment drug	Japan	Ph I / II	Application	Approval	
F-1614	【RI】 Refractory pheochromocytoma treatment drug	Japan	Ph II		Application	Approval
T-817MA	Mild cognitive impairment (MCI) (Europe)	Europe	Preparing for Ph II			POC
	Promoting the recovery of motor functions during recovery from stroke (Japan)	Japan	Preparing for Ph II		POC	
FF-10101	Acute myelogenous leukemia treatment drug (FLT3-ITD inhibitor)	USA	Ph I	POC		
FF-21101	【RI】 Advanced / metastatic solid cancer treatment drug (Anti-P-Cadherin antibodies)	USA / Japan	Ph I		POC	
FF-10832	【DDS】 Solid cancer treatment drug (Gemcitabine liposome)	USA	Ph I			POC
FF-10850	【DDS】 Solid cancer treatment drug (Topotecan liposome)	USA	Preparing for Ph I			POC

**ORAVI** **[Oravi]**

**[Indication]** Oropharyngeal candidiasis caused by the genus *Candida*

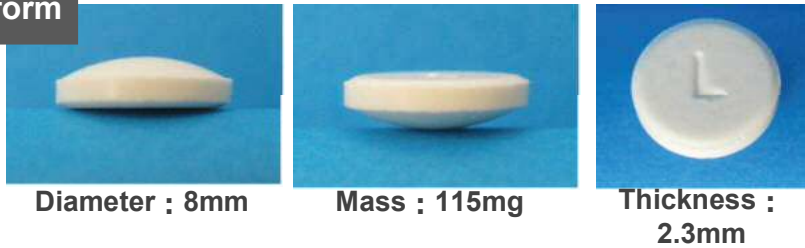
**[Market size]** 2 billion yen (Japan)

**[Features]**

**Effective ingredient**

Miconazole (same as the existing fluoride gel)

**Dosage form**



**Usage**

Attach one table to the gum of maxilla (canine fossa) once a day.

Attachment method (guide)



Listed in the NHI drug price list in November 2018

↓  
To be launched in February 2019

- 1** **Tablet form**  
(Readily accepted in Japan)
- 2** **Easy to use**  
(Attaching one table to the gum once a day)
- 3** **Administration**  
(No food effect)

Oropharyngeal candidiasis is often seen in people with compromised immune system, e.g. those treated by cancer therapy. Synergistic effect with anti-cancer drugs in the pipeline is expected in the future.

## **[T-4288 (Solithromycin) ]**

### **[Indication]**

Respiratory (e.g. pneumonia) and  
Otolaryngology (e.g. sinusitis)

### **[Market size]**

100 billion yen (Japan: respiratory and otolaryngology, adults and children)

### **[Characteristics]**

Strong antibacterial activity against pneumococci resistant to macrolide antibiotics and mycoplasma pneumoniae

Application being prepared in Japan



Application due to be filed in 2019

**Solithromycin is not only effective for antimicrobial-resistant bacteria that cause infectious diseases, but could also be a new option with a different mechanism of action. It could contribute to the efforts to prevent the increase of antimicrobial resistant to existing drugs.**



**Consistent with countermeasures to antimicrobial resistance (AMR) led by the WHO and the Japanese government**



## **[F-1515 (Lutathera): Radiopharmaceutical]**

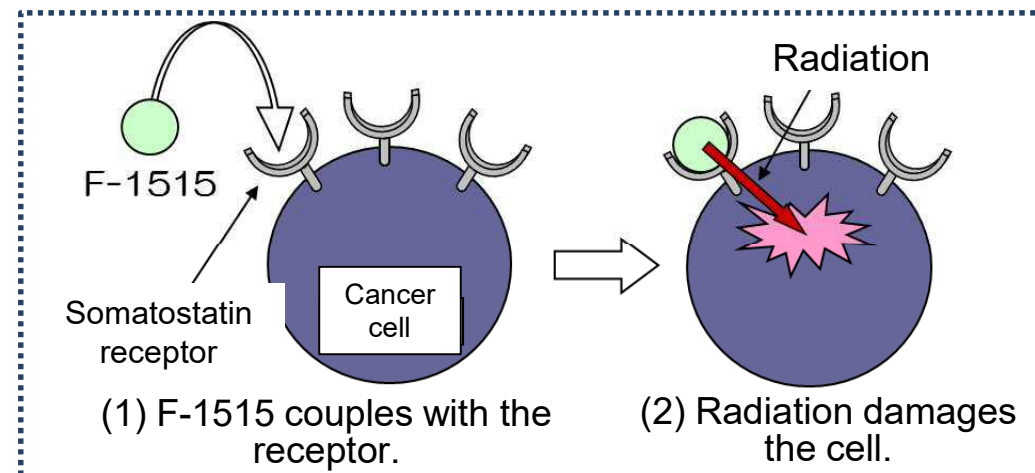
**[Indication]**  
Neuroendocrine tumor

**[Market size]**  
8 billion yen (Japan)

**[ Characteristics]**  
A radiolabeled somatostatin analog peptide for PRRT (Peptide Receptor Radionuclide Therapy), which binds to the receptor on the surface of cancer cells to deliver the radioactive component directly to the tumor and kill the cancer cells

Ph I / II underway in Japan

↓  
Application due to be filed in 2019



**In US and Europe, AAA has acquired manufacturing and marketing approval.**

- ✓ Progression-free survival period in Ph III  
Lutathera = 40 months, comparator (Sandostatin) = 8.4 months
- ✓ Manufacturing and marketing approval obtained in September 2017 in Europe and January 2018 in the United States  
(List price per dose: €24,000 in Germany and \$ 47,500 in the United States)
- ✓ RRRT is a recommended treatment option for inoperable advanced neuroendocrine tumor, prompting many Japanese patients to travel overseas to receive this treatment.



# 【T-817MA】

## Initiation of clinical trials for efficacy on MCI and recovery promotion during and after stroke

### (1) MCI (mild cognitive impairment)

#### Results of T-817MA's PhII (mild – moderate AD patients) in US

- ✓ Reduced phospho-tau in cerebrospinal fluid
- ✓ Significant difference in cognitive function score for patients who have been diagnosed for 2.6 years or less

Expected the best efficacy of T-817MA in MCI and earlier stage of Alzheimer's Disease

Clinical testing for MCI is to be initiated this spring in Europe, assessing p-tau reduction and improvement of cognitive function

### (2) Functional recovery after stroke

(Promoting the effect of rehabilitation)

Evidence by the collaboration research with Yokohama City University, National Institute of Advanced Industrial Science and Technology and National Institute of Biomedical Innovation

- ✓ Dramatic improvement in recovery of motor function from rehabilitation after brain damage (primate model, rodents)
- ✓ New mechanism of promoting brain changes in the process of functional recovery

Clinical testing to be initiated in Japan by the end of this fiscal year, covering patients recovering from stroke for 4 – 6 weeks to assess the recovery of motor functions in combination with rehabilitation

# 【T-705】

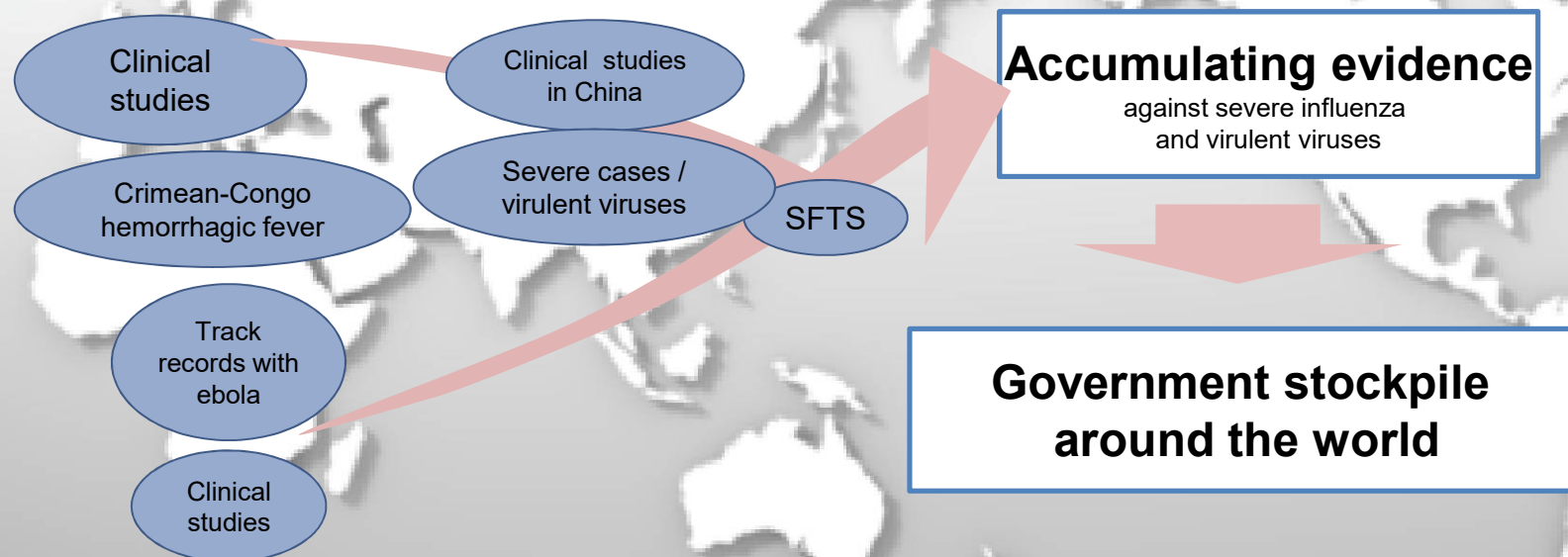
## 【Characteristics】 Indicated for emerging and re-emerging influenza, and expected efficacy against virulent non-influenza viruses\*

\* Single-stranded RNA (-) viruses including ebola virus, rabies virus, Marburg virus and SFTS (severe fever with thrombocytopenia syndrome) virus

➤ **Japan: Stockpiled to treat 2 million people in preparedness against Pandemic**  
(completed supply in the first half of FY2019/3)  
**Phase III underway in Japan to expand indication for SFTS**

➤ **WW: Conducting clinical study in various countries around the world to accumulate clinical evidence on its efficacy against severe influenza and virulent viruses so as to promote stockpiling**

\* China: Clinical study underway on patients hospitalized for severe influenza at the China – Japan Friendship Hospital



## 3-1. Business areas focused by Fujifilm

- Concentrating on development of existing pipeline to address unmet medical needs

Existing pipeline

- Establishing practical application of Drug Delivery System (DDS)
- Actualizing pharmaceutical IoT services

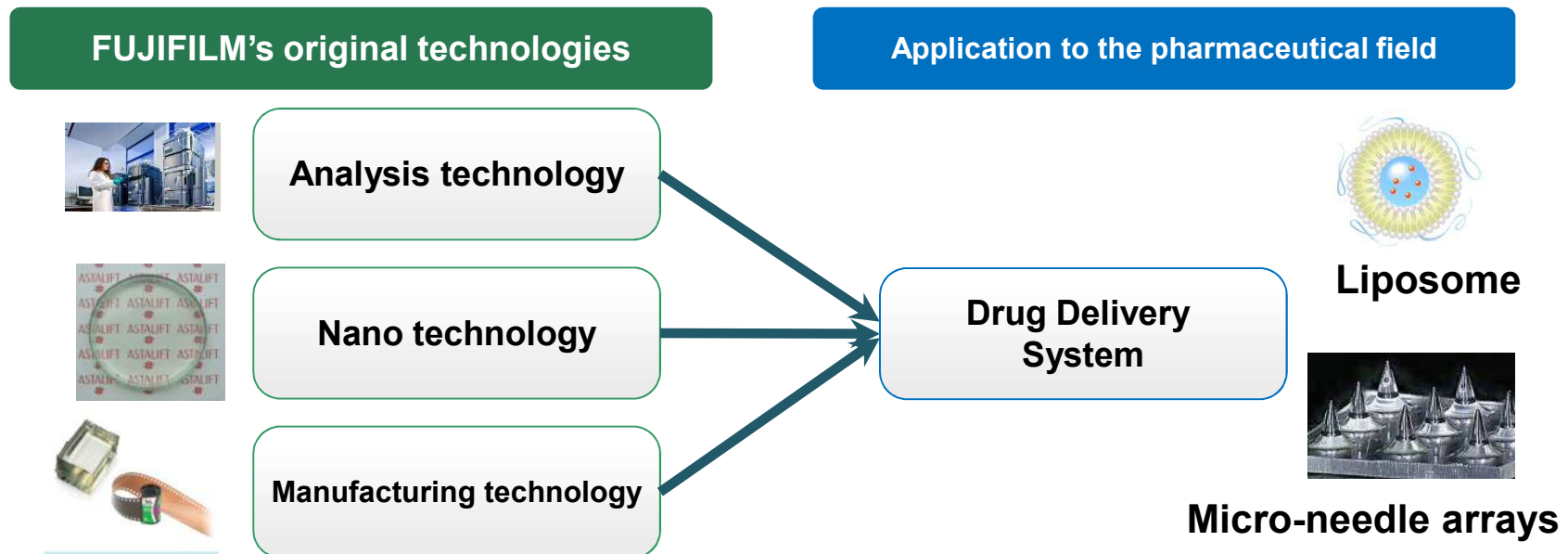
Solutions using Fujifilm technologies

- Promoting the establishment of regenerative medicine as an industry
- Accelerating R&D of current pipeline
- Establishing CDMO business in regenerative medicine

Cell therapy  
(Regenerative medicine business)

## 3-2. Establishing practical application of the DDS

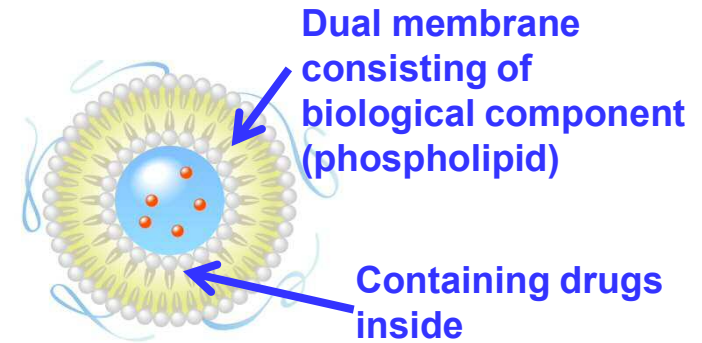
Applying Fujifilm original technologies, created through the R&D and manufacturing of photographic films, to the development of DDS



- ✓ Developing a DDS based on Fujifilm original technologies to provide innovative drugs with improved efficacy and safety over existing products
- ✓ Promoting the application of DDS technology to nucleic acid therapeutics, gene therapeutics, etc.
- ✓ Pursuing collaboration with pharmaceutical companies that own effective drugs to become a DDS platformer

## 3-3. What are liposome drugs?

- A type of DDS
- Nanoparticle consisting of organic phospholipids and other components of cell membranes and biological membranes
- Liposome containing drugs



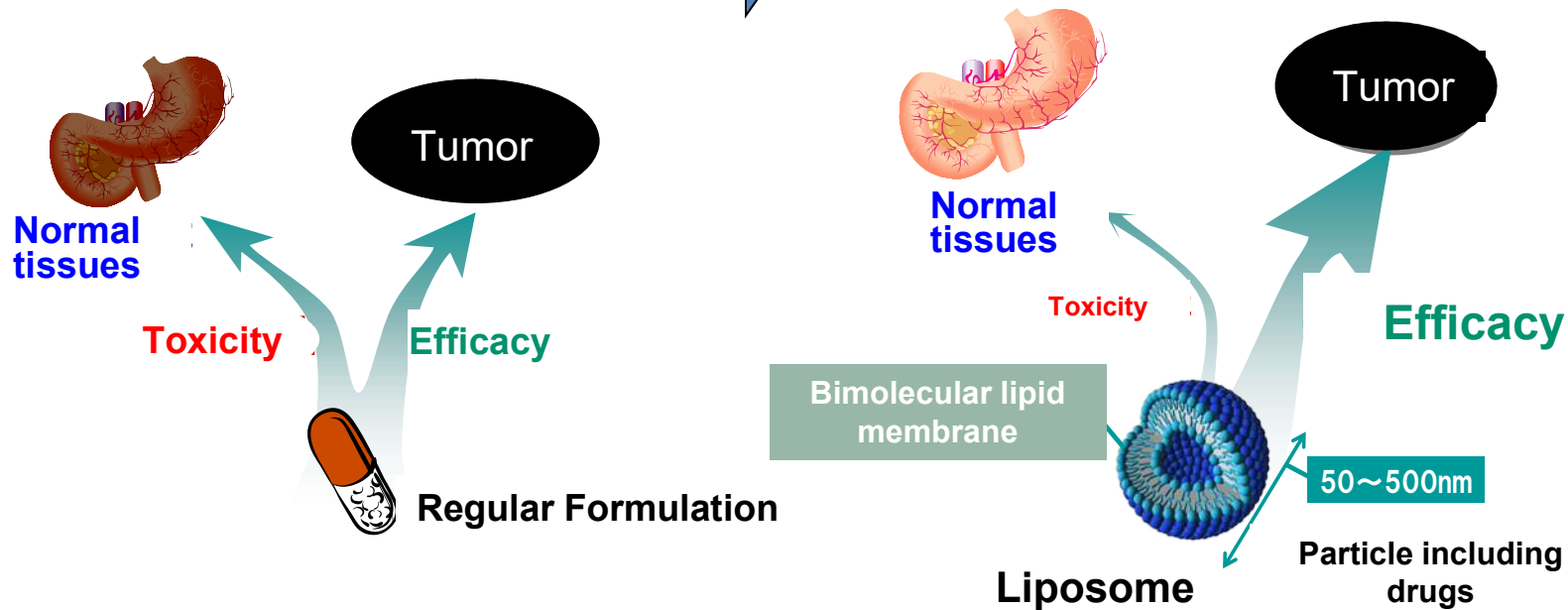
### ■ Mechanism of the drugs targeted to tumor

**[Regular formulation]**

Delivery also to normal tissues to cause a side effect

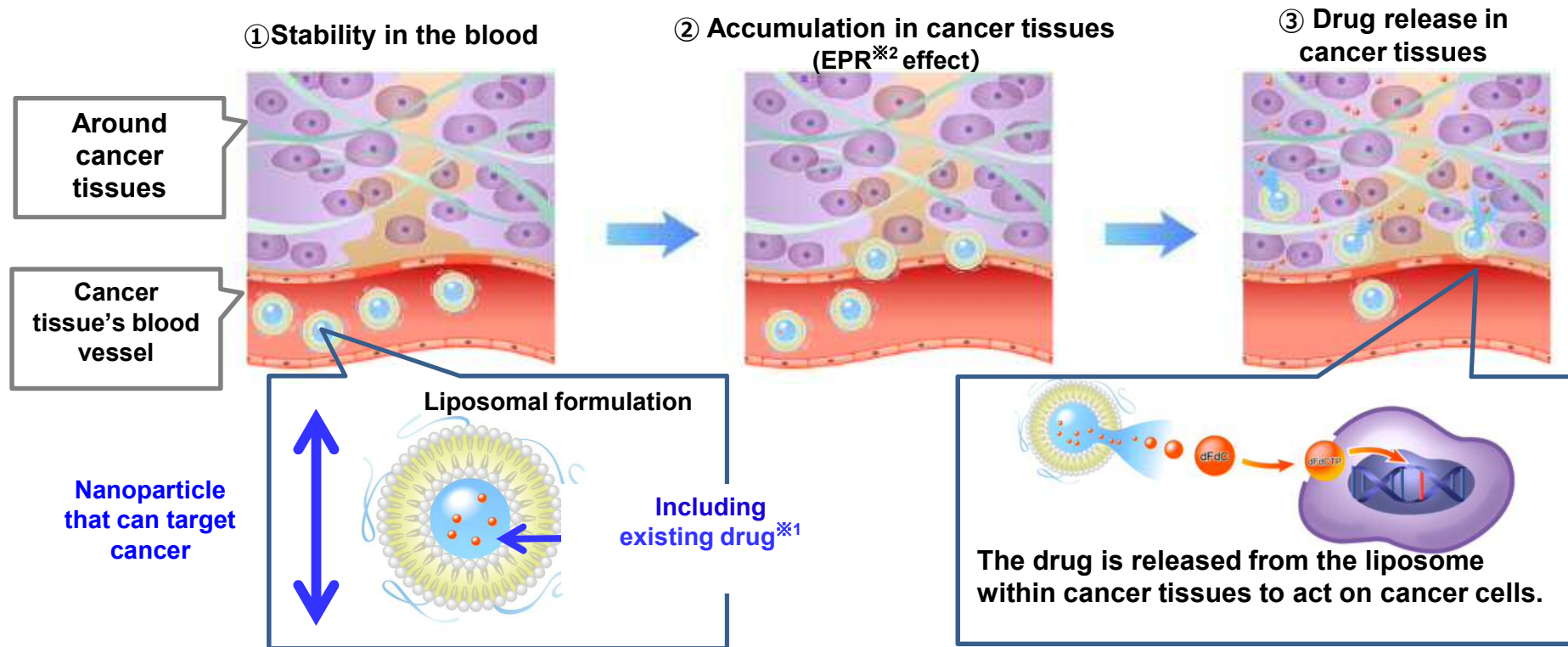
**[Liposomal formulation]**

Continuous efficacy due to effective delivery to tumors



## 3-4. FF-10832 Mechanism of liposome drug

### Image of delivering and releasing the anti-cancer drug “FF-10832” in cancerous tissues



◆ **EPR effect, a Nobel Prize-class discovery by Dr. Yasuhiro Matsumura and Dr. Hiroshi Maeda<sup>※2</sup>**

※1 An anti-cancer drug developed by Eli Lilly and Company (Gemcitabine, or the brand name “Gemzar”). It is used as a first-line drug for treating pancreatic cancer, and also to treat a wide variety of cancers (including lung cancer and ovarian cancer).

※2 Cancerous tissues grow new blood vessels to receive nutrients. These blood vessels are immature and have gaps on their walls, which are not seen in normal blood vessels. Liposomes and macromolecules in the blood cannot pass through the wall of normal blood vessels with no gaps, and only permeate through vascular walls around cancerous tissues. Also, cancerous tissues have immature lymph tissues, therefore cannot readily discharge liposomes and macromolecules that pass through. As a result, they accumulate within cancerous tissues. This is called the EPR (Enhanced Permeability and Retention) effect. Its discovery was announced in the report, “A New Concept for Macromolecular Therapeutics in Cancer Chemotherapy: Mechanism of Tumorotropic Accumulation of Proteins and the Antitumor Agent Smancs” (1986) by Hiroshi Maeda, special professor of the DDS Research Institute, Sojo University and professor emeritus of Kumamoto University, and Yasuhiro Matsumura, head of Developmental Therapeutics, Exploratory Oncology Research and Clinical Trial Center, National Cancer Center. In 2016, for the paper and its citation analysis, they were included in Thomson Reuters Citation Laureates, a list of candidates considered likely to win the Nobel Prize.

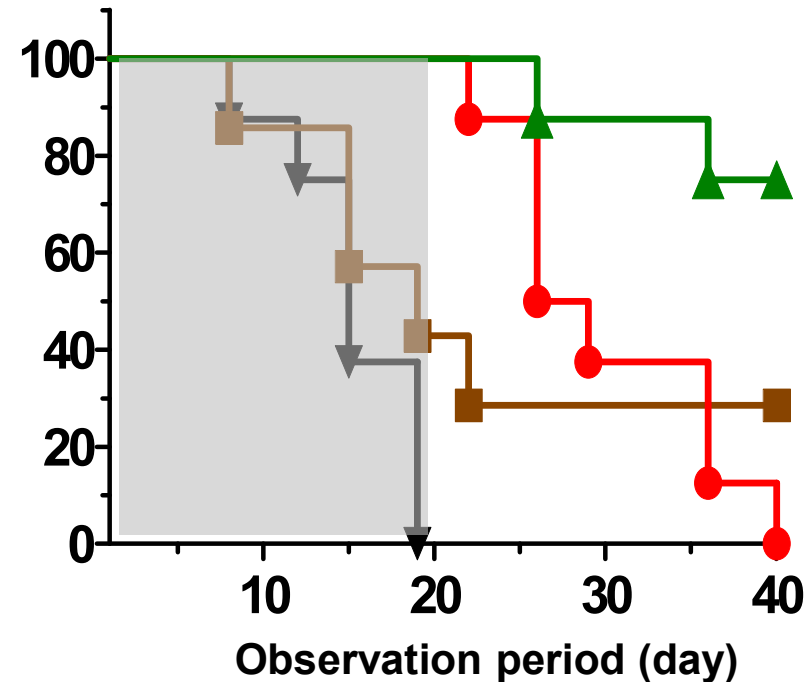
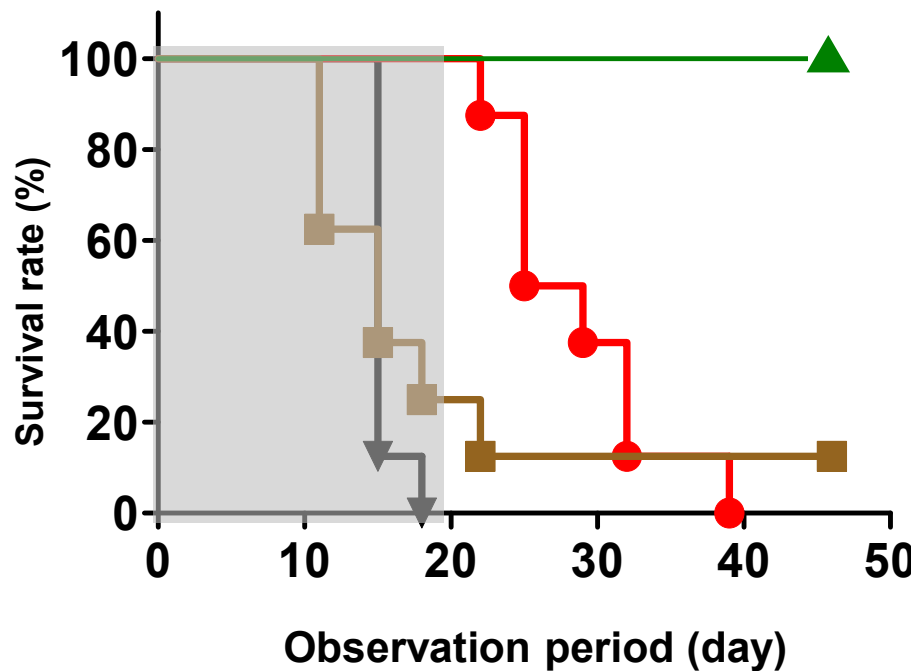
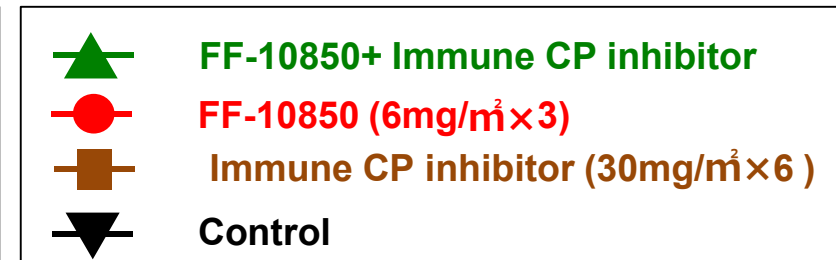
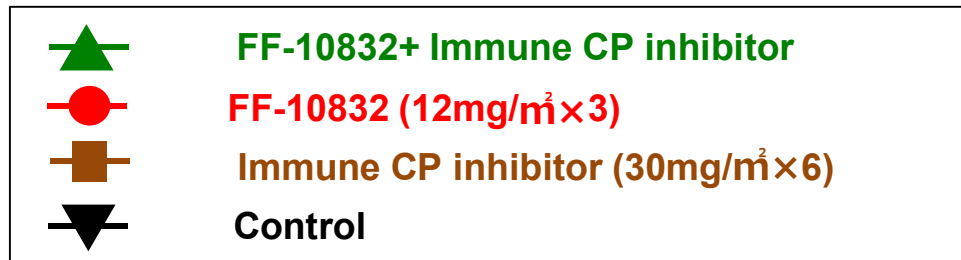
### 3-5. FF-10832, FF-10850 Synergistic efficacy with immune checkpoint inhibitors

#### Confirming prolonged mouse survival in combined use

■ Drug administration period

Survival rate of animal models transplanted with mouse-derived breast cancer cells

Survival rate of animal models transplanted with mouse-derived colorectal cancer cells





## 3-6. Overview of the liposome drug manufacturing facility

- ✓ **Location :** Toyama-shi, Toyama Prefecture (within the site of FUJIFILM Toyama Chemical)
- ✓ **Production description:** Manufacturing and commercial production of liposome products for clinical trials
- ✓ **Investment:** Approx. 4 billion yen
- ✓ **Total area:** Approx. 3,359m<sup>2</sup>  
(steel-framed two-story structure)
- ✓ **Start of Construction :** September 2018
- ✓ **Start of Operation:** February 2020



### Concept

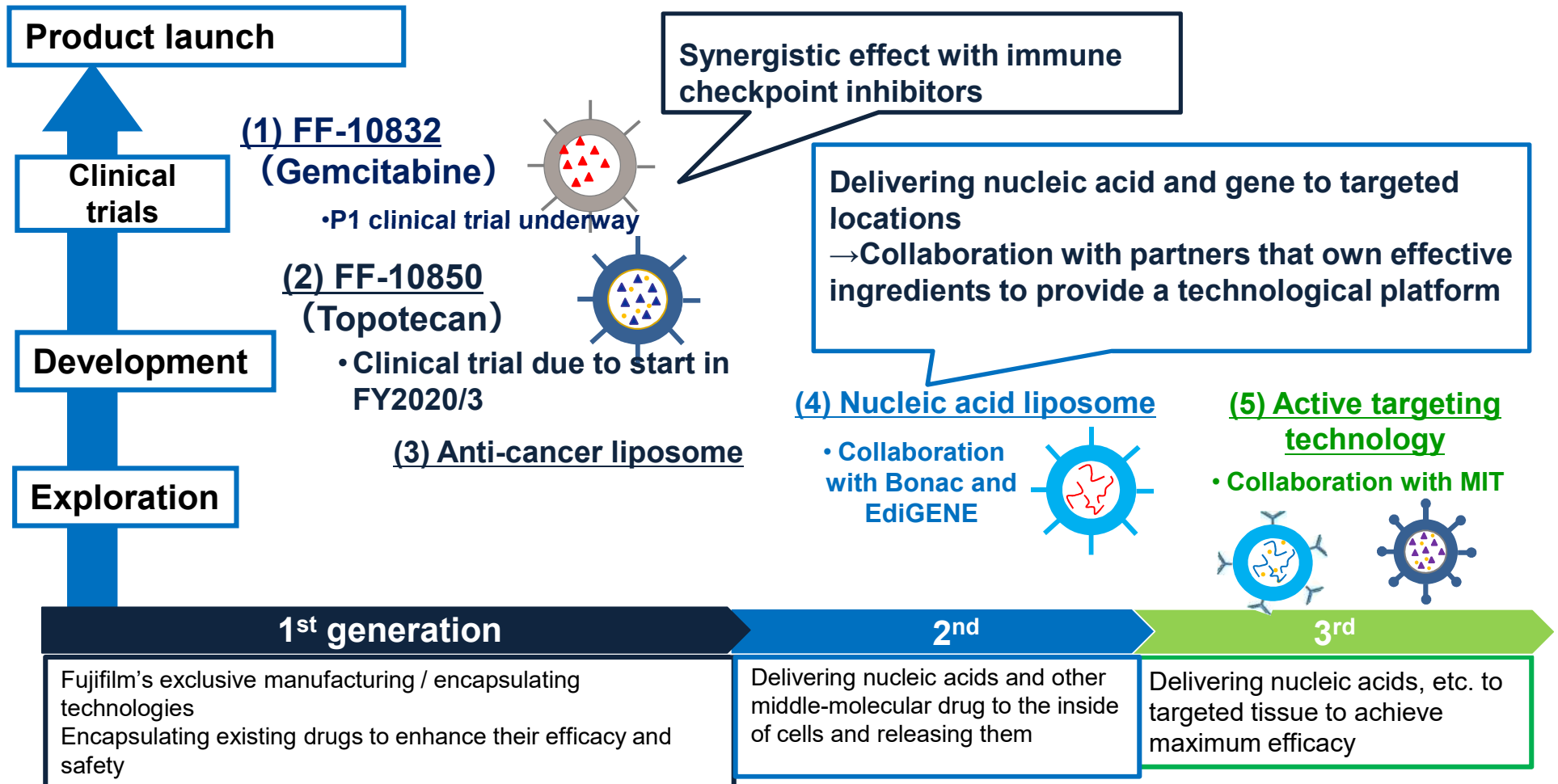
- (1) Designing under Japanese, U.S. and European GMP\* standards
- (2) Actualizing large scale production equipment and containment equipment designed and developed by FUJIFILM
- (3) Applying Toyama Chemical's production know-how, accumulated skills through aseptic manufacturing of injections, for stable production
- (4) Achieving advanced manufacturing system using cutting-edge ICT technology



## 3-7. Strategy for liposome technologies

Starting from encapsulating existing drugs and expanding to nucleic acid therapeutics and gene therapeutics

Pursuing to initiate clinical trial for at least one product per year

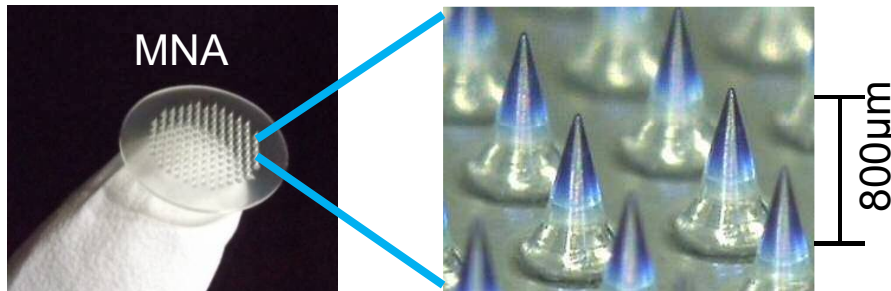


# 3-8. Micro-needle array (MNA)

## MNA formulation

- “Injection patch” to create new values
- Exploring MNA’s potential since the 1990s in response to strong market needs, but failing to put the technology to practical use due to difficulty in (automated) aseptic mass-production and the issue of high costs.

## MNA formulation and its administration

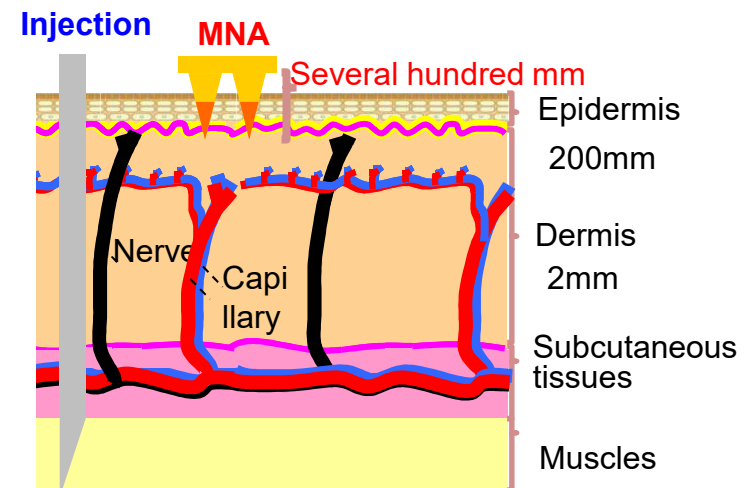


## MNA’s features (compared to traditional injections)

- More convenient and less pain
  - Reduced amount of antigen for vaccine administration
  - High level of stability (potentially stored at room temperature)
- New vaccine formulation of the future, creating new values

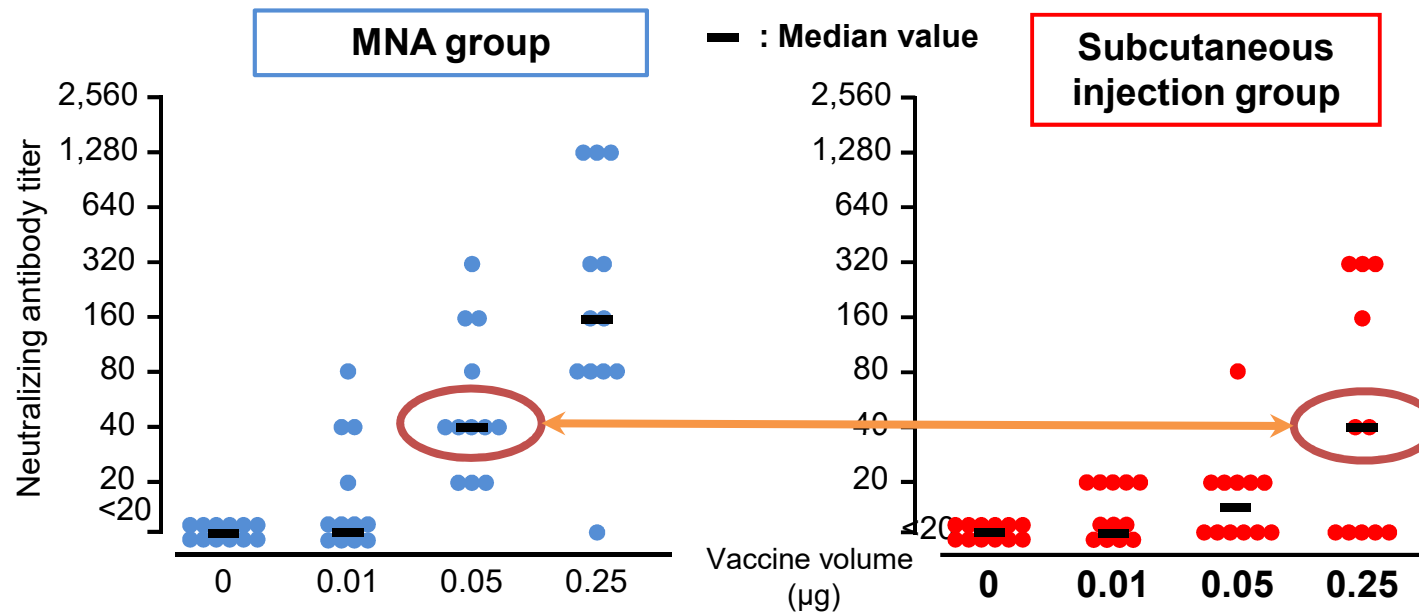
## Challenges in development

- Obtaining evidence from human trials
- Establishing mass-production technology

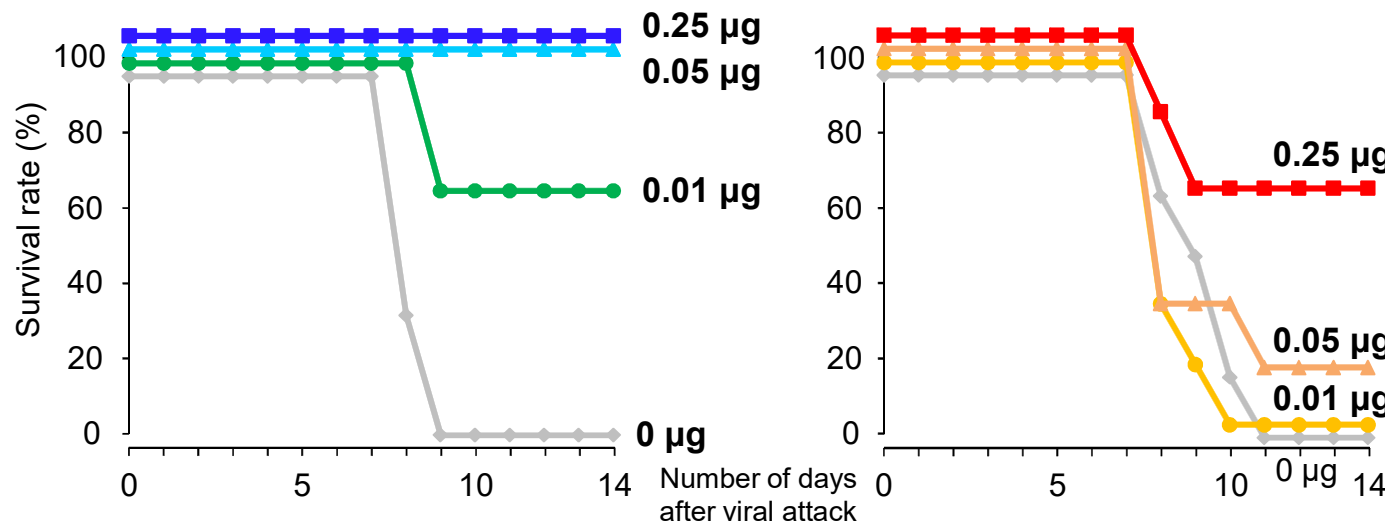


### 3-9. Serum Neutralizing Antibody Titer of mice injected with H5N1 vaccine and their survival rate when attacked with H5N1 virus

Vaccine Volume 35,  
Issue21, 15 May  
2017, Pages 2855-  
2861



The MNA group produced enough antibodies to neutralize viruses in blood with the amount of vaccine just one-fifth of what was given to the subcutaneous injection group.



When attacked by virus after vaccination, the MNA group achieved a high survival rate with the amount of vaccine lower than what was given to the subcutaneous injection group.

## 3-10. Status of MNA development

**Human clinical study results × Continuous aseptic manufacturing  
= Collaboration with large pharmaceutical companies**

### (1) Confirming efficacy and safety on humans (human clinical research)

- Completing sterile preparations for human clinical studies (placebo & vaccine formulation)
- Clinical study (on safety) initiated in July at Nara Medical University
- Clinical study (on efficacy and safety) using vaccine-containing MNA is planned.



After administration

### (2) Establishing manufacturing line for verifying mass production potential

- Completed and initiated operational in September 2018
- Preparing MNA containing influenza vaccine and conducting animal tests to obtain efficacy data
- Initiating partnership negotiations with global mega pharma and Japanese major pharmaceutical companies



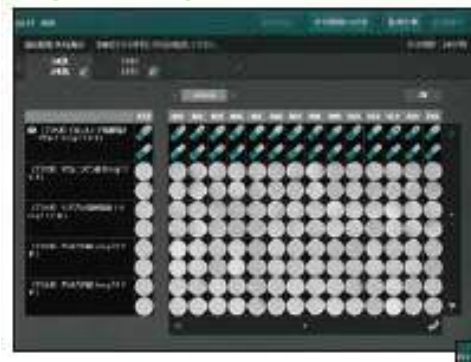
## 3-11. Pharmaceutical IoT solution business: Medication verification system



Reducing pharmacists' medication verification time  
→ Boosting pharmacies' productivity in areas such as pharmacists' personal care services



(1) Highly-accurate drug-type identification using Fujifilm's image recognition technology



(2) Easy-to-read printed labels  
Managed with 2D bar code



### ■ Visual medication verification and use of PROOFIT 1D to reduce / streamline workload

Conventional visual verification

Prescription input  
→ Dispensing and single-dose packaging

Visual verification of pouches

Usage instructions and other over-the-counter duties

With PROOFIT 1D

Prescription input  
→ Dispensing and single-dose packaging

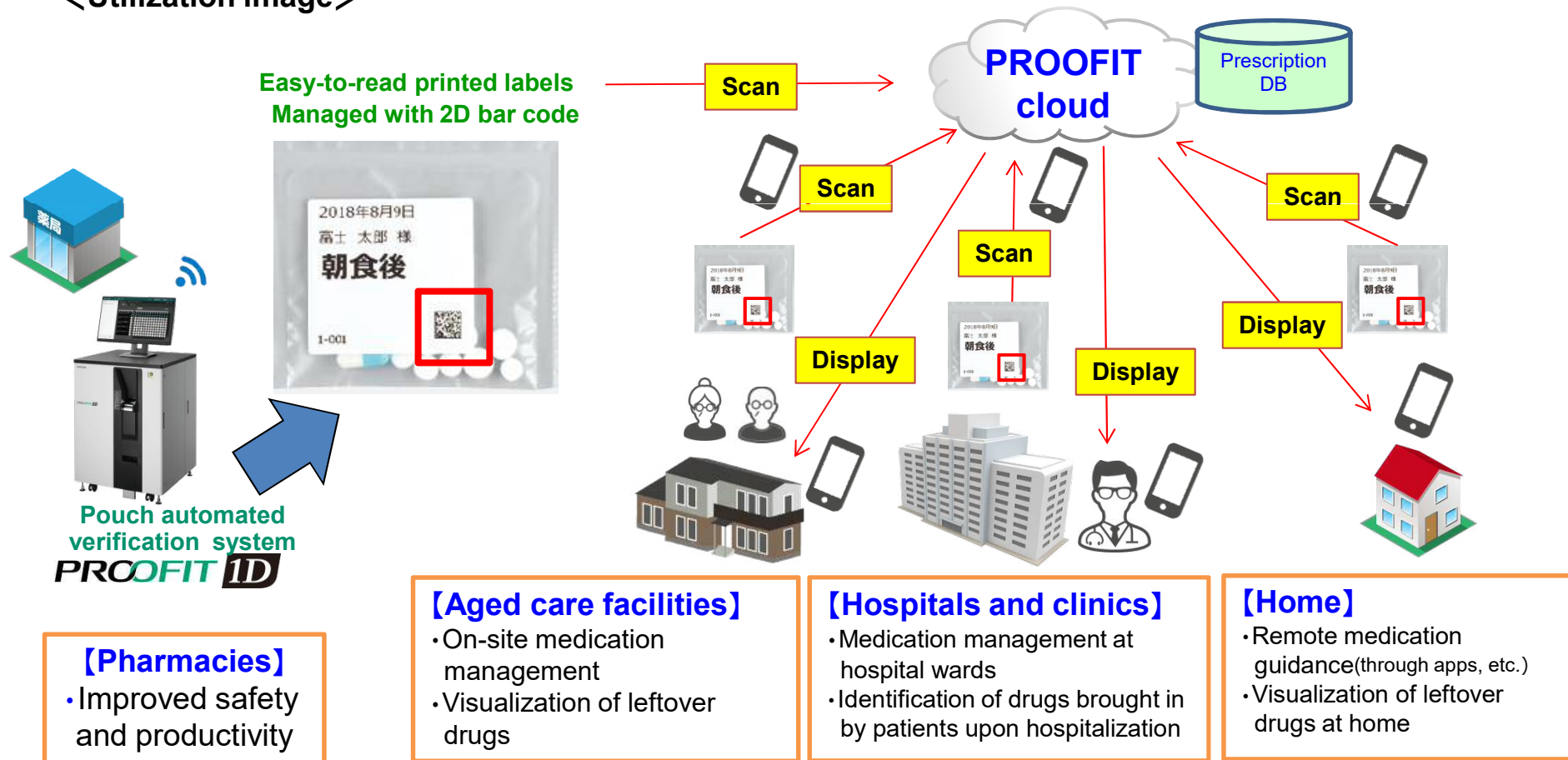
Verification support from PROOFIT 1D

Usage instructions and other over-the-counter duties

## 3-12. Pharmaceutical IoT solution business: Medication verification system

Using data obtained by PROOFIT 1D for continuous medication management and contributing medication adherence among patients

<Utilization image>





## 3-13. Pharmaceutical IoT solution business: Constant-temperature transportation systems

- ✓ Realized highly accurate constant temperature transport using the world's top level thermoelectric cooling technology and the newly-developed constant-temperature control technology.
- ✓ Centralized cloud system that centrally manages recorded data such as internal temperature and position information for providing high level transportation quality required for regenerative medicine, etc.

### Blood transportation system



ATR700-RC05/ATR705-RC05

- Maintaining temperature accurately and keeping extended temperature records
- Japan Red Cross Society is operating for blood products transport to the Ogasawara Islands

### Constant-temperature transportation system

**TS500-TSF**



- The internal temperature setting can be changed within 4°C~37°C.
- Application in the transportation of cells and tissues to be used in regenerative medicine, etc.

### Electronic refrigeration technology

Completely non-Freon cooling technology by using the high performance thermoelectric device.



Heavy-duty and high reliability thermoelectric cooling system. Durable cooling system for refrigerator of over 70,000 hours

## 4. Conclusions

### ➤ **Development of existing pipeline**

- Planning application for a manufacturing and marketing authorization of several drugs from 2019, through steady R&D progress of existing pipeline

### ➤ **Solutions using Fujifilm's original technologies**

- Focusing on DDS to apply to nucleic acid therapeutics, gene therapeutics, etc.
- Actualizing pharmaceutical IoT services

**Fujifilm will contribute to resolution of social issues including unmet medical needs and the improvement of patients QOL, through utilizing our original technologies and undertaking development of new drug and DDS technologies.**



**FUJIFILM**

**Value from Innovation**